Anticoagulation: From AF to CVD Risk Reduction

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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 20th 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)
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: 11286
No. with Atrial Fibrillation: 221 (1.96%)
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

Anticoagulant use in high risk patients:

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

Risk profile for thrombo-embolism:

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.
Marked under use of a cheap and effective intervention that cuts stroke risk by c60%

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

- Undertake a CHA2DS2-VASc score to define low risk patients
  - Score 0
  - Score 1
  - Score ≥2

- Discuss anticoagulation with the patient with AF, i.e. warfarin
- anticoagulation clinic with a target INR of 2.0

After 3 months consider a switch to a NOAC if the INR <3, OR 2 consecutive INRs <1.8, OR frequent INR testing required

Continue oral anticoagulation indefinitely with annual reassessment of FBC, U&E, LFTs, and renal function.

N.B. Poor compliance with any oral anticoagulant will reduce benefits but increase risks.

Contraindications to New Oral Anticoagulants

- Known large oesophageal varices
- Significant thrombocytopenia (platelet count < 50 x 10^9/L) - refer to haematology specialist
- Within 12 hours of major surgery with risk of severe bleeding - defer & assess
- 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
- Pregnancy or within 48 hours post partum - seek urgent haematology advice
- Severe renal impairment (GFR < 30 mL/min/1.73 m² or on dialysis)

Relative Contraindications

- Previous history intracranal haemorrhage
- Age > 75 years
- Recent major intracranial bleed within the last 6 months where the cause remains unclear
- Recent documented peptic ulcer (PU) within the last 6 months and decision for oral anti-thrombotic therapy should be deferred.
- Recent history of ischaemic heart disease
- Kidney disease (e.g. diabetes)
- Significant hypertension
- Cirrhosis
- Acute or chronic liver disease
- Chronic severe heart failure
- Recent cerebrovascular accident
- Systemic lupus erythematosus

N.B. A risk of falls is not a contraindication to initiating oral anticoagulants of 5% (CHA2DS2 score 2-3) would fail to take 285 lives for fall risk to outweigh benefits.

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

Anticoagulants for prevention of stroke and systemic embolism in NVAF

Drug use and dosing based on renal function estimation

<table>
<thead>
<tr>
<th>Warfarin (mg/day)</th>
<th>DOAC (dose)</th>
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<tr>
<td>CGi &gt;60 mg/min</td>
<td>Apixaban 5 mg or 2.5 mg bd if hef ≥ 2 of age &gt; 75 yrs, body weight ≥ 60 kg, serum creatinine ≥ 1.3 mmol/L</td>
</tr>
<tr>
<td>CGi 30-49 mg/min</td>
<td>Dabigatran 110 mg bd if 80 years and over or high risk of bleeding (HAS-BLED 3/3) or on warfarin</td>
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<tr>
<td>CGi 15-29 mg/min</td>
<td>Rivaroxaban 15 mg od.</td>
</tr>
<tr>
<td>CGi &lt;15 mg/min</td>
<td>Warfarin: PFR dependent dose adjustment.</td>
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Female 260kg+ creatinine clearance mL/min (NB do not use if weight lower than 60kg – see below)

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<th>Serum creatinine</th>
<th>Age</th>
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Male 270kg+ creatinine clearance mL/min (NB do not use if weight lower than 70kg – see below)

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AF QIP achievements

% of patients CHADS2 ≥ 1 and on Warfarin

65% of patients with CHADS2 ≥1 on Warfarin

6% absolute improvement
AFQIP Improvement by CHADS2

NNT = 13
NNT = 20
Apixaban in Patients with Atrial Fibrillation
Stuart J. Connolly, M.D., John Eikelboom, Hans-Christoph Diener, M.D., Ph.D., Robert Greg Flaker, M.D., Álvaro Avezum, M. Rafael Díaz, M.D., Mario Talajic, M.J., Andrea Budaj, M.D., Ph.D., Alexander Park, Patrick Commerford, M.B., Ch.B., Ru San Basu S. Lewis, M.D., Walter Van Meel, Joo Hyung Kim, M.D., Ph.D., Antonio González-Hermosillo, Muhammad Munawar, M.D., Ph.D., John Lawrence, M.D., Gayle and Salim Yusuf, for the AVERROES Steering Committee

Methods
In a double-blind study, we randomly assigned 5599 patients with atrial fibrillation who were at increased risk for stroke to receive either apixaban (at a daily dose of 20 mg) or dose-adjusted warfarin. The per-protocol, as-treated primary end point of stroke or systemic embolism was defined as occurring during the first 18 months of the study. The primary analysis was performed after 12 months of follow-up.

Results
Before enrollment, 40% of the patients had used a vitamin K antagonist. The data were analyzed as of February 12, 2010. Among the 5599 patients who were randomly assigned, 5521 were included in the intention-to-treat analysis and the per-protocol analysis. The rate of the primary outcome was 1.13% per year in the apixaban group, as compared with 1.21% per year in the warfarin group (hazard ratio, 0.96; 95% confidence interval [CI], 0.81 to 1.14; P<0.001 for noninferiority; P<0.001 for superiority). The treatment effects were consistent among important subgroups.

Conclusions
In patients with atrial fibrillation who were at increased risk for stroke and who were considered to be unsuitable candidates for or unwilling to receive vitamin K antagonist therapy, apixaban was noninferior to warfarin for the primary end point of stroke or systemic embolism. (Funded by Bristol-Myers Squibb and Pfizer; ClinicalTrials.gov number, NCT00403767.)

Rivaroxaban versus Warfarin
Methods
In a double-blind trial, we randomly assigned 14,264 patients with nonvalvular atrial fibrillation who were at increased risk for stroke to receive either rivaroxaban (at a daily dose of 20 mg) or dose-adjusted warfarin. The per-protocol, as-treated primary end point of stroke or systemic embolism was defined as occurring during the first 18 months of the study. The primary analysis was performed after 12 months of follow-up.

Results
In the primary analysis, the primary end point occurred in 188 patients in the rivaroxaban group (hazard ratio in the rivaroxaban group, 0.79; 95% confidence interval [CI], 0.66 to 0.96; P<0.001 for noninferiority; P<0.001 for superiority). The rates of death were 4.8% per year in the rivaroxaban group and 6.8% per year in the warfarin group (hazard ratio in the rivaroxaban group, 0.71; 95% CI, 0.58 to 0.89; P<0.001 for noninferiority; P=0.005 for superiority). The rates of major bleeding were 2.7% per year in the rivaroxaban group and 3.7% per year in the warfarin group (hazard ratio, 0.73; 95% CI, 0.56 to 0.98; P=0.04 for noninferiority; P=0.04 for superiority). The rates of gastrointestinal bleeding were 1.1% per year in the rivaroxaban group and 1.7% per year in the warfarin group (hazard ratio, 0.68; 95% CI, 0.46 to 1.00; P=0.05 for noninferiority; P=0.05 for superiority). In a sensitivity analysis, the results were consistent except for a lower rate of gastrointestinal bleeding in the rivaroxaban group.

Conclusions
In patients with atrial fibrillation who were at increased risk for stroke and systemic embolism and who were considered to be unsuitable candidates for or unwilling to receive vitamin K antagonist therapy, rivaroxaban was noninferior to warfarin for the primary end point of stroke or systemic embolism. (Funded by Bristol-Myers Squibb and Pfizer; ROCKET AF ClinicalTrials.gov number, NCT00496769.)

Atrial Fibrillation
Atrial fibrillation: the management of atrial fibrillation

Clinical guideline
Methods, evidence and recommendations
January 2014

Draft for Consultation
Commissioned by the National Institute for Health and Care Excellence

M. WRIGHT (Chair)
## Atrial Fibrillation-Stroke risk: CHA$_2$DS$_2$VASc

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<th>CHA$_2$DS$_2$VASc risk criteria</th>
<th>Score</th>
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<td>Cardiac failure</td>
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<td>Hypertension</td>
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<td>Diabetes mellitus</td>
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<td>Stroke or TIA (previous history)</td>
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<td>Vascular disease (IHD, PAD)</td>
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# AF Bleeding Risk: HASBLED

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<th>HAS-BLED risk criteria</th>
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<td>Hypertension (i.e. Uncontrolled BP)</td>
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<tr>
<td>Abnormal renal and liver function (1 point each)</td>
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<tr>
<td>Stroke</td>
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<td>Bleeding</td>
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<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>

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

*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

**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 & reassess 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.
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
PIONEER AF-PCI
Rationale for Dual and Triple Therapy Arms

<table>
<thead>
<tr>
<th>Study group 1</th>
<th>Study group 2</th>
<th>Study group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>1, 6 or 12 months</td>
<td>1, 6 or 12 months</td>
</tr>
<tr>
<td>Rivaroxaban 15 mg OD plus P2Y&lt;sub&gt;12&lt;/sub&gt;</td>
<td>Rivaroxaban 2.5 mg BID plus ASA plus P2Y&lt;sub&gt;12&lt;/sub&gt;</td>
<td>VKA plus ASA plus P2Y&lt;sub&gt;12&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

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.<sup>1</sup>

This strategy has not yet been tested in a large study.

Where US guidelines recommend triple therapy with a VKA,<sup>2,3</sup> recent European guidelines suggest that a NOAC may be used in triple and dual therapy after PCI.<sup>4,5</sup>

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.<sup>2,3</sup>

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

- VKA (INR 2.0–3.0) plus DAPT§
- VKA plus low-dose ASA

- **DAPT duration** (1, 6 or 12 months)
- **End of treatment** (12 months)

**DAPT 1 m: 15%**
- 6 m: 35%
- 12 m: 50%

**DAPT 1 m: 16%**
- 6 m: 35%
- 12 m: 49%

---

*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
• 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%

- **CV death, MI or stroke**
- **Major bleeding**

### Medical intervention in studies
- TRITON trial
- PLATO trial

### Event rate (%) at 12 months post event

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CV death, MI or stroke</th>
<th>Major bleeding*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA + Clopidogrel³</td>
<td>12.1</td>
<td>1.8*</td>
</tr>
<tr>
<td>ASA + Prasugrel³</td>
<td>9.9</td>
<td>2.4*</td>
</tr>
<tr>
<td>ASA + Clopidogrel⁴</td>
<td>11.7</td>
<td>2.2*</td>
</tr>
<tr>
<td>ASA + Ticagrelor⁴</td>
<td>9.8</td>
<td>2.8*</td>
</tr>
</tbody>
</table>

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%)

Rivaroxaban 5.0 mg bd + Aspirin 100 mg od
Rivaroxaban 2.5 mg bd + Aspirin 100 mg od
Aspirin 100 mg od

30-day run-in, ASA 100mg

1:1:1

N=27,395

Final washout period visit
Final follow-up visit

Average follow up: 23 months at early termination of study

Factorial Design ± pantoprazole*

* 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

<table>
<thead>
<tr>
<th>Key inclusion criteria*</th>
<th>Key exclusion criteria‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>• PAD</td>
<td>• Stroke ≤1 month or any haemorrhagic or lacunar stroke</td>
</tr>
<tr>
<td>• CAD with ≥1 of:</td>
<td>• Severe HF with known ejection fraction &lt;30% or NYHA class III or IV symptoms</td>
</tr>
<tr>
<td>• Age ≥65 years</td>
<td>• Need for dual antiplatelet therapy, other non-aspirin antiplatelet therapy, or oral anticoagulant therapy</td>
</tr>
<tr>
<td>• Age &lt;65 years plus atherosclerosis in ≥2 vascular beds or ≥2 additional risk factors</td>
<td>• eGFR &lt;15 ml/min</td>
</tr>
<tr>
<td>• Current smoker</td>
<td></td>
</tr>
<tr>
<td>• Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>• Renal dysfunction (eGFR&lt;60 ml/min)</td>
<td></td>
</tr>
<tr>
<td>• Heart failure</td>
<td></td>
</tr>
<tr>
<td>• Non-lacunar ischaemic stroke ≥1 month ago</td>
<td></td>
</tr>
</tbody>
</table>

*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

Bosch J *et al*, *Can J Cardiol* 2017;33:1027–1035
## Dual Pathway Inhibition with Rivaroxaban Vascular Dose

2.5mg bd + Aspirin Reduced Stroke, CV Death and MI

<table>
<thead>
<tr>
<th></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>
</tr>
<tr>
<td>Rivaroxaban 5mg bd</td>
<td>4.9</td>
<td>0.90 (0.79-1.03)</td>
<td>0.12</td>
</tr>
<tr>
<td>Rivaroxaban 2.5mg bd + Aspirin 100 mg OD</td>
<td>4.1</td>
<td>0.76 (0.66-0.86)</td>
<td>&lt;0.001</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

![Graph showing the natural history survival of claudication patients over 10 years with different outcomes: survival, MI, intervention, and amputation.](image-url)

### 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>Clopidogrel*</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>
</tbody>
</table>

**Combination of therapies**
- Antiplatelet agent and Beta-blocker (BB) | 76.69 |
- Antiplatelet agent, BB and Statin | 72.64 |
- Antiplatelet agent, BB, Statin, ACEI/ARB | 70.61 |
- Antiplatelet agent and Statin | 77.03 |
- Antiplatelet agent, statin and ACE-I/ARB | 74.32 |

**Other indices**
- Smokers | 19.70 |
- Systolic blood pressure< 131mmHg | 61.15 |
- Systolic blood pressure< 141mmHg (QOF target) | 76.35 |

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

Type 2 Diabetes
Using:
- SGLT2 inhibitors
- Metformin
- Other agents

Blood pressure control
Using:
- ACE-I/ARB
- DHP
- Thiazides

Anti-Platelet/Anticoagulant
Acute CAD/PAD
- DAPT
- Acute CVA/TIA
- Clopidogrel 75mg

CAD/PAD
After 12 months switch to
- Rivaroxaban 2.5mg bd
- Aspirin 75mg

Smoking
Supporting smoking withdrawal

Lifestyle
Encourage smoking cessation at every contact

Continue healthy lifestyle

Atrovastatin 80mg
HbA1c <58mmol
Systolic Blood Pressure Target 130mmHg

Westcliff Cardiology Service  August 2018
Thank you for your attention

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