Role of biomarkers for stroke risk in AF: Should ABC *trump* CHA₂DS₂-VASc?
No financial disclosures or conflicts of interest for this presentation

European Society of Cardiology Guidelines Task Force for AF & ESC Education Committee
Case:
74 year old lady
Sinus rhythm; no history of AF
TOE to plan aortic valve surgery
In AF on day of admission six weeks later
On-table TOE
AF and stroke

- 20-30% of patients with an ischaemic stroke have AF diagnosed before, during or after admission.
- Silent cerebral events are common.
- Cognitive impairment and dementia are increased in AF.

Stagnant blood flow

Thrombus formation in AF

Pro-thrombotic milieu

Endothelial dysfunction
Management of AF: 2016 ESC Guidelines

**Treatment**

- Acute rate and rhythm control
  - (e.g., β-blockers, cardioversion)
- Manage precipitating factors
  - Lifestyle changes, treatment of underlying cardiovascular conditions
- Assess stroke risk
  - Oral anticoagulation in patients at risk for stroke
- Assess heart rate
  - Rate control therapy
- Assess symptoms
  - Antiarrhythmic drugs, cardioversion, catheter ablation, AF surgery

**Desired outcome**

- Haemodynamic stability
- Cardiovascular risk reduction
- Stroke prevention
- Symptom improvement, preservation of LV function
- Symptom improvement

**Patient benefit**

- Improved life expectancy
  - Improved quality of life, autonomy, social functioning

Stroke prevention strategies

1. Oral anticoagulants – warfarin & other VKA versus NOACs.
   • Ease of use of NOACs, their efficacy and the lower rate of intracranial haemorrhage shift the balance towards use in patients at lower stroke risk.

2. Percutaneous left atrial appendage (LAA) devices.
   • Typical indication (contraindication to anticoagulation) untested.

3. Thoracoscopic LAA clipping and open surgery approaches.
   • Becoming more available; current stroke prevention data limited.
Patient selection

Approach has changed…

• NOT to select those at highest risk of stroke
• Instead, identify those at lowest risk of stroke who do not require stroke prevention strategies (everyone else anticoagulated)

Clinical risk scores developed initially in small cohort studies and subsequently validated in larger populations

• Advantages: Easy to use; no waiting for blood results
• Disadvantages: At best, modest prediction of stroke & embolus
### CHA\textsubscript{2}DS\textsubscript{2}-VASc

<table>
<thead>
<tr>
<th>CHA\textsubscript{2}DS\textsubscript{2}-VASc risk factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Congestive heart failure</strong>&lt;br&gt;Signs/symptoms of heart failure or objective evidence of reduced LVEF</td>
<td>1</td>
</tr>
<tr>
<td><strong>Hypertension</strong>&lt;br&gt;Resting blood pressure &gt;140/90 mmHg on at least two occasions or current antihypertensive treatment</td>
<td>1</td>
</tr>
<tr>
<td><strong>Age 75 years or older</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong>&lt;br&gt;Fasting glucose &gt;125 mg/dL (7 mmol/L) or current treatment</td>
<td>1</td>
</tr>
<tr>
<td><strong>Previous stroke, transient ischaemic attack, or thromboembolism</strong></td>
<td>2</td>
</tr>
<tr>
<td><strong>Vascular disease</strong>&lt;br&gt;Previous myocardial infarction, peripheral artery disease, or aortic plaque</td>
<td>1</td>
</tr>
<tr>
<td><strong>Age 65–74 years</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Sex category (female)</strong></td>
<td>1</td>
</tr>
</tbody>
</table>
### CHA$_2$DS$_2$-VASc derivation

<table>
<thead>
<tr>
<th>Description</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Original cohort:</strong></td>
<td>n=1,084 without anticoagulation, mitral stenosis or valve surgery in the EuroHeart Survey on AF.</td>
</tr>
<tr>
<td><strong>Validation:</strong></td>
<td>n=73,538 without anticoagulation, any mitral or aortic valve disease or surgery from the Danish national patient registry.</td>
</tr>
<tr>
<td><strong>Validation:</strong></td>
<td>n=140,420 without anticoagulation or any valve disease from the Swedish nationwide registries.</td>
</tr>
</tbody>
</table>
Management of AF: 2016 ESC Guidelines

Stroke prevention in atrial fibrillation

Mechanical heart valves or moderate or severe mitral stenosis

Yes

No

Estimate stroke risk based on number of CHA\textsubscript{2}DS\textsubscript{2}-VASc risk factors

0\textsuperscript{a}

No antiplatelet or anticoagulant treatment (IIIB)

1

OAC should be considered (IIaB)

≥2

Oral anticoagulation indicated

Assess for contra-indications

Correct reversible bleeding risk factors

LAA occluding devices may be considered in patients with clear contra-indications for OAC (IIbC)

NOAC (IA)\textsuperscript{b}

VKA (IA)\textsuperscript{c}

\textsuperscript{a} Includes women without other stroke risk factors
\textsuperscript{b} IIaB for women with only one additional stroke risk factor
\textsuperscript{c} IB for patients with mechanical heart valves or mitral stenosis

How well do they predict stroke?

### Ischaemic stroke

<table>
<thead>
<tr>
<th>Method</th>
<th>C-statistic</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHA²DS²-VASc (cont.)</td>
<td>0.67</td>
<td>0.66–0.68</td>
</tr>
<tr>
<td>CHA²DS²-VASc</td>
<td>0.56</td>
<td>0.56–0.57</td>
</tr>
<tr>
<td>CHADS² (cont.)</td>
<td>0.66</td>
<td>0.66–0.67</td>
</tr>
<tr>
<td>CHADS² revised</td>
<td>0.62</td>
<td>0.61–0.62</td>
</tr>
<tr>
<td>CHADS² classic</td>
<td>0.65</td>
<td>0.64–0.65</td>
</tr>
<tr>
<td>Framingham (cont.)</td>
<td>0.67</td>
<td>0.66–0.68</td>
</tr>
<tr>
<td>Framingham</td>
<td>0.64</td>
<td>0.64–0.65</td>
</tr>
<tr>
<td>SPAF 1999</td>
<td>0.63</td>
<td>0.62–0.64</td>
</tr>
<tr>
<td>ACC/AHA/ESC 2006</td>
<td>0.62</td>
<td>0.61–0.62</td>
</tr>
<tr>
<td>NICE 2006</td>
<td>0.61</td>
<td>0.60–0.62</td>
</tr>
<tr>
<td>AFI 1994</td>
<td>0.58</td>
<td>0.58–0.59</td>
</tr>
</tbody>
</table>

**Receiver operator curves**

![Graph showing sensitivity vs. 1-specificity with different C-statistics: CHA²DS²-VASc (cont.) C-statistic 0.67, CHA²DS²-VASc C-statistic 0.56, CHADS² (cont.) C-statistic 0.66, CHADS² revised C-statistic 0.62, CHADS² classic C-statistic 0.65, Framingham (cont.) C-statistic 0.67, Framingham C-statistic 0.64, SPAF 1999 C-statistic 0.63, ACC/AHA/ESC 2006 C-statistic 0.62, NICE 2006 C-statistic 0.61, AFI 1994 C-statistic 0.58.]
Other known risk factors for stroke and embolus…

- Unstable INR and low time in therapeutic range
- Previous bleed or anaemia
- Alcohol excess and other markers for decreased adherence
- Chronic kidney disease
- Biomarkers…

But… more factors does not necessarily mean a better fit for the statistical model!
### The ABC (age, biomarkers, clinical history) stroke risk score

<table>
<thead>
<tr>
<th>Original cohort:</th>
<th>n=14,701 anticoagulated in the ARISTOTLE trial, excluding mod+ mitral stenosis/prosthetic valves</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validation:</td>
<td>n=1,400 with and without anticoagulation in the STABILITY coronary heart disease trial</td>
</tr>
<tr>
<td>Validation:</td>
<td>n=8,356 anticoagulated in the RE-LY trial, excluding mod+ mitral stenosis/prosthetic valves</td>
</tr>
</tbody>
</table>

Hijazi; Eur Heart J. 2016;37:1582-90
Oldgren; Circulation. 2016;134:1697-1707
ABC stroke risk score

Disadvantages:
- Anticoagulated/selected
- More complex
- Ideally need computer/app
- Await blood results
- Cost of biomarkers

Advantages:
- Based on high quality trial data and adjudicated outcomes
- ‘Minor’ factors removed

Hijazi; Eur Heart J. 2016;37:1582-90
<table>
<thead>
<tr>
<th>Cohort</th>
<th>Time</th>
<th>ABC (trop T)</th>
<th>CHA$_2$DS$_2$-VASc</th>
</tr>
</thead>
<tbody>
<tr>
<td>STABILITY trial (n=1,400)</td>
<td>3.4 years</td>
<td>0.66 (0.58-0.74)</td>
<td>0.58 (0.49-0.67)</td>
</tr>
<tr>
<td>RE-LY trial (n=8,356)</td>
<td>1.9 years</td>
<td>0.65 (0.61-0.69)</td>
<td>0.60 (0.57-0.64)</td>
</tr>
<tr>
<td>Spanish cohort (n=1125)</td>
<td>3.5 years</td>
<td>0.66 (0.63-0.69)</td>
<td>0.60 (0.57-0.63)</td>
</tr>
<tr>
<td></td>
<td>6.5 years</td>
<td>0.66 (0.63-0.69)</td>
<td>0.62 (0.59-0.65)</td>
</tr>
</tbody>
</table>
### Prediction of stroke and bleeding risk

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>The CHA\textsubscript{2}DS\textsubscript{2}-VASc score is recommended for stroke risk prediction in patients with AF.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Bleeding risk scores should be considered in AF patients on oral anticoagulation to identify modifiable risk factors for major bleeding.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Biomarkers such as high-sensitivity troponin and natriuretic peptide may be considered to further refine stroke and bleeding risk in AF patients.</td>
<td>IIb</td>
<td>B</td>
</tr>
</tbody>
</table>
1. Treatment decisions in difficult patients

How and where to use?

- Stroke risk
- Bleeding risk

2. Age is the major driving risk factor

3. Be aware that biomarkers can be raised for other (acute) reasons
## Bleeding risk on anticoagulation

### Modifiable bleeding risk factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (especially systolic BP &gt; 160mmHg)</td>
<td>a, b, c</td>
</tr>
<tr>
<td>Labile INR or time in therapeutic range &lt; 60%</td>
<td>a</td>
</tr>
<tr>
<td>Medication predisposing to bleeding</td>
<td>a, d</td>
</tr>
<tr>
<td>Excess alcohol (≥ 8 drinks/week)</td>
<td>a, b</td>
</tr>
</tbody>
</table>

### Potentially modifiable bleeding risk factors

### Non-modifiable bleeding risk factors

### Biomarker-based bleeding risk factors

- a Derived from the HAS-BLED score.
- b Derived from the HEMORR2HAGES score.
- c Derived from the ATRIA score.
- d Derived from the ORBIT score.
- e Derived from the ABC bleeding score.
Role of biomarkers for stroke risk in AF:

Should ABC trump CHA₂DS₂-VASc? 

- Hopefully not!

- Can be complementary – additional information from biomarkers can be useful to risk stratify beyond clinical risk factors

- Reminder that all risk scores have at best a modest ability to predict outcomes and that clinical decision-making and patient involvement are key
# Patient involvement, education and self-management

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tailored patient education is recommended in all phases of AF management to support patients’ perception of AF and to improve management.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Patient involvement in the care process should be considered to encourage self-management and responsibility for lifestyle changes.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Shared decision making should be considered to ensure that care is based on the best available evidence and fits the needs, values and preferences of the patient.</td>
<td>IIa</td>
<td>C</td>
</tr>
</tbody>
</table>

[www.escardio.org/guidelines](http://www.escardio.org/guidelines)
ESC / CATCH ME apps for atrial fibrillation

Download now for free!

Android

[Google Play Store][Android]

Apple iOS

[App Store][iOS]

Search for “My AF” (patient app)

“AF Manager” (healthcare app)

Kotecha & Kirchhof; Eur Heart J. 2017;38:2643-2645

Kotecha et al; Europace. 2017; in press