Controversies in Risk Stratification

There are more questions than answers
So---Let me pose the questions

Banff 2016
Triggers vs Substrate in Pathophysiology of AF

Paroxysmal?
Persistent?
Permanent

AF burden

Triggers (“lone” AF)
Triggers & diseased substrate

P vein isolation/ WACA pts
Trials of pharmacologic rhythm vs rate control Incl AFFIRM and RACE

Relative importance

Modulating factors

Genetics?  \(\uparrow\) vagal tone

Age  Obesity  Atherosclerotic risk factors

Wyse & Gersh: Circ, 2004
The Epidemic of Atrial Fibrillation – is It a Vascular Disease?

Hypothesis

Role of inflammation

- Obesity
- Hypertension
- Age
- Atherosclerosis
- Increased arterial stiffness

- Diastolic dysfunction
- LVH

- Increased LA volume
- Electrical heterogeneity

A fibrillation

Myasaka: Circ, 2007
AFib as a Vascular Disease
Suggestive Evidence

- Obesity
- Hypertension
- Metabolic syndrome
- Sleep apnea

↑ Arterial stiffness
Diastolic dysfunction
↑ LA volume

Atrial fibrillation

Diastolic dysfunction
↑ LA volume

- Neurohormonal factors
  - Ang II
  - TGFβ1

- Tissue factors
  - CTGF
  - MMPs
  - PDGF
  - Endothelin-I

- Vascular and hemostatic factors
- Oxidative stress and inflammation
- Galactin

Cause
Surrogate

Tsang and Gersh: EHJ 2008; JACC 2008; AJC 2008; AJC 2006; JACC 2006; JACC 2003; JACC 2002
Meta-Analysis of Stroke – 5 Randomized Trials
Placebo Stroke Rate – 4.5%/yr

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous stroke/TIA</td>
<td>2.5</td>
</tr>
<tr>
<td>Hx of HTN</td>
<td>1.6</td>
</tr>
<tr>
<td>Advanced age (continuous)</td>
<td>1.4/10 yr</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.7</td>
</tr>
<tr>
<td>Hx of CHF</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Age related
Pt aged ≤60 yr +
No risk factors
Stroke rate ≤1%/yr

Collaborative Analysis – AFib Investigators
Arch Intern Med, 1994
Kopecky: NEJM, 1987
Performance of Contemporary Risk Stratification Schemes

<table>
<thead>
<tr>
<th>Study</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
<th>C statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFI, 94</td>
<td></td>
<td></td>
<td>80</td>
<td>0.573</td>
</tr>
<tr>
<td>SPAF, 95</td>
<td></td>
<td></td>
<td>60</td>
<td>0.549</td>
</tr>
<tr>
<td>CHADS&lt;sub&gt;2&lt;/sub&gt;</td>
<td></td>
<td></td>
<td>80</td>
<td>0.561</td>
</tr>
<tr>
<td>CHADS&lt;sub&gt;2&lt;/sub&gt; revised</td>
<td></td>
<td></td>
<td>80</td>
<td>0.586</td>
</tr>
<tr>
<td>Framingham</td>
<td></td>
<td></td>
<td>80</td>
<td>0.638</td>
</tr>
<tr>
<td>NICE, 2006</td>
<td></td>
<td></td>
<td>80</td>
<td>0.598</td>
</tr>
<tr>
<td>ACC/AHA/ESC, 2006</td>
<td></td>
<td></td>
<td>80</td>
<td>0.571</td>
</tr>
<tr>
<td>ACCP, 2008</td>
<td></td>
<td></td>
<td>80</td>
<td>0.571</td>
</tr>
<tr>
<td>Birmingham, 2009</td>
<td></td>
<td></td>
<td>80</td>
<td>0.606</td>
</tr>
</tbody>
</table>

Range 0.549-0.638

Lip: Chest, 2010
CHADS$_2$ Score and Left Atrial Thrombi in AF

- Case control study

Cases
- 110 pt
- NVAF
- LAA thrombus
- TEE

Distribution of Scores

Wysosinski: AHJ, 2010
## Atrial Fibrillation Guidelines

<table>
<thead>
<tr>
<th>Risk</th>
<th>Recommended therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ESC 2012</td>
</tr>
<tr>
<td>Risk factors (no.)</td>
<td>No antithrombotic therapy</td>
</tr>
<tr>
<td>CHA$_2$DS$_2$-VASc = 0</td>
<td></td>
</tr>
<tr>
<td>CHA$_2$DS$_2$-VASc = 1</td>
<td><strong>NOAC &gt; VKA (IIa A)</strong></td>
</tr>
<tr>
<td>CHA$_2$DS$_2$-VASc ≥ 2</td>
<td><strong>NOAC &gt; VKA (IA)</strong></td>
</tr>
<tr>
<td>Mechanical prosthetic valve</td>
<td>VKA: INR 2.0-3.0 (AVR)</td>
</tr>
<tr>
<td></td>
<td>VKA: INR 2.5-3.5 (MVR)</td>
</tr>
</tbody>
</table>
Stroke and TE Rates Based on CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>–VASc Scores

47,574 Subjects – Danish Registries

Olesen: Thromb and Hemostasis, 2012

Olesen: Thromb and Hemostasis, 2012
Comparisons of Scores for Stroke Prediction in a Taiwanese Population

- 186,570 AF pts.
- Follow-up 3.4 years mean

12.1% ischemic stroke

<table>
<thead>
<tr>
<th>CHA2DS2-VASc score</th>
<th>No.</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score = 0 (reference group)</td>
<td>9,416</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Score = 1</strong></td>
<td>12,137</td>
<td>1.695 (1.547-1.857)</td>
</tr>
<tr>
<td>Score = 2</td>
<td>3,464</td>
<td>2.609 (2.338-2.912)</td>
</tr>
<tr>
<td>Score = 3</td>
<td>269</td>
<td>3.998 (3.115-5.130)</td>
</tr>
</tbody>
</table>
## Risk Factors for Thromboembolic Events in Atrial Fibrillation Patients

### Are all 1 pointers equal

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard ratio estimates</th>
<th>CHA$_2$DS$_2$-VASc Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥75 years (reference &lt;65 years)</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Age 65-74 years (reference &lt;65 years)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Previous Ischemic Stroke</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Female Gender</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Vascular Disease</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>History of heart failure</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>History of intracranial bleeding</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Reference</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Annual Stroke Rates in Different Cohort Studies
Patients With CHADS\textsubscript{2}-VASc of 1

Annual Stroke Rates

<table>
<thead>
<tr>
<th>Registry</th>
<th>Men (‰/yr)</th>
<th>Women (‰/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denmark*</td>
<td>2.01</td>
<td></td>
</tr>
<tr>
<td>Sweden**</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Taiwan***</td>
<td>2.75</td>
<td>2.55</td>
</tr>
</tbody>
</table>

- \* Hospital admission and death due to TE
- \** Ischemic stroke only
- \*** Other thromboembolic events and TIA

Refs:
- Oleson BMJ 2011
- Friberg JACC 2015
- Chao JACC 2015
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 Terent, MD, PhD

JACC, 2015

- 140,420 patients
- Swedish nationwide health registry

Exclusions
- Valvular AF
- Warfarin exposure
- 4 week quarantine period after diagnosis

Annual Event Rates

“Tipping point”
1.7%/yr – Warfarin
0.9%/yr – NOAC

- +TIA
- +Pulmonary Embolism
- +Unspecified Stroke/+Systemic Embolism
- Ischemic stroke only
Adherence to Warfarin and NOAC – Clinical Outcomes
Insurance Administrative Claims Database
(USA – 100 Million Enrollees Over 20 Yr Period)

- 64,661 pt
- 2000-2014
- AF (OAC)
  - Warfarin
  - Dabigatran
  - Rivaroxatan
  - Apixiban

Adherence (≥80 days covered by OAC)
43.2%

Cumulative time off OACs
(≤1 wk as reference)

<table>
<thead>
<tr>
<th>CHA2DS2VASC</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, 1</td>
<td>HR 2.73</td>
</tr>
<tr>
<td>2, 3</td>
<td>HR 3.36</td>
</tr>
<tr>
<td>≥4</td>
<td>HR 3.36</td>
</tr>
</tbody>
</table>

Noseworthy P (In Press)
Comparison of Stroke and Bleeding Scores in Patients on NOACS

- 39,539 patients
- U.S. commercial insurance database

**Stratification of Bleeding Risk**

<table>
<thead>
<tr>
<th>Score</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>HA(_2)DS(_2)-VASc</td>
<td>35%</td>
<td>11%</td>
<td>28%</td>
</tr>
<tr>
<td>CHADS(_2)</td>
<td>20%</td>
<td>40%</td>
<td>40%</td>
</tr>
<tr>
<td>HAS-BLED</td>
<td>25%</td>
<td>50%</td>
<td>25%</td>
</tr>
<tr>
<td>ORBIT</td>
<td>30%</td>
<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>ATRIA</td>
<td>30%</td>
<td>40%</td>
<td>30%</td>
</tr>
</tbody>
</table>

**C-statistic**

<table>
<thead>
<tr>
<th>Score</th>
<th>Major bleeding</th>
<th>Intracranial bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>HA(_2)DS(_2)-VASc</td>
<td>0.65</td>
<td>0.61</td>
</tr>
<tr>
<td>CHADS(_2)</td>
<td>0.64</td>
<td>0.66</td>
</tr>
<tr>
<td>HAS-BLED</td>
<td>0.64</td>
<td>0.63</td>
</tr>
<tr>
<td>ORBIT</td>
<td>0.60</td>
<td>0.55</td>
</tr>
<tr>
<td>ATRIA</td>
<td>0.60</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Yao and Noseworthy in press
Excessive Atrial Ectopy and Short Runs Increase the Risk of Stroke Beyond Incident AF

- Copenhagen Holter Study Cohort
- 678 pt (age 55-75)
- No history of CVD, stroke or AF

Excessive supraventricular ectopic activity (ESVEA)
- 30 PAC’s/hour daily
- Any runs of 20 PACs

Adjusted analysis for risk of ischemic stroke (pt censored at home of AF)

ESVEA – H Ratio 1.96 (1.10-3.49)

Larsen: JACC, 2015
Outcomes in Patients With AF Stratified by CHA₂DS₂-VASc Score and hs-TnT

12,892 Patients ARISTOTLE Trial

Stroke and Systemic Embolism

Cardiac Death

Hijazi: JACC
Outcomes in Patients With AF Stratified by CHA$_2$DS$_2$-VASc Score and hs-TnT
12,892 Patients ARISTOTLE Trial

Major Bleeding

<table>
<thead>
<tr>
<th>CHA$_2$DS$_2$VASc score</th>
<th>hs-Troponin-T (ng/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥5</td>
<td>≤1.5</td>
</tr>
<tr>
<td></td>
<td>&gt;1.5-6.8</td>
</tr>
<tr>
<td></td>
<td>&gt;6.8-13</td>
</tr>
<tr>
<td></td>
<td>&gt;13</td>
</tr>
</tbody>
</table>

Major bleeding (%)
Stroke and Systemic TE and NT-proBNP in Patients With AFib

18,201 Patients – ARISTOTLE Trial
Stratified by CHA$_2$DS$_2$VASc Score

Hijazi: JACC, vol. 2013

Stroke or systemic embolism (%)

NT-proBNP (ng/L)

CHA$_2$DS$_2$VASc score
Independent Relationship Between hs Troponin and Events

Multifactorial

Myocyte stress

Apoptosis  Necrosis

Aging  Tissue vulnerability  Comorbidities  ↑ or variable heart rates  Ischemia  Myocardial dysfunction and remodeling

Possible contributory mechanisms

• Inflammation
• Fibrosis
• Hypercoagulable state
• Endothelial dysfunction
• ↑ myocyte turnover
• Cellular integrity and permeability
BNP as a Prognostic Marker for Stroke in Atrial Fibrillation

Potential Mechanisms

BNP secreted by myocytes
NT-proBNP

Reflects

LV size and function
LV filling pressures
Renal function
Age
Sex

Levels of BNP ↑ in AFib vs SR

Reflects

Atrial function and pressure
Atrial Fibrillation and the Risk of Stroke
Potential Role of Biomarkers

- Dilatation/fibrosis \( \rightarrow \) AFib
- Stasis \( \downarrow \) LA & LAA flow velocity

Risk marker? Surrogate?

Risk factor

Hypertension

eGFR
Cystatin

- \( \downarrow \) compliance
- Dilatation/fibrosis \( \rightarrow \) AFib
- Stasis \( \downarrow \) LA & LAA flow velocity

Risk marker? Surrogate?

LVH
Diastolic dysfunction

Prothrombotic state
- Strept clotting factors
- Inflammation?

Inflammation?
- Aortic plaque
- Cerebrovascular disease

CRP
IL-6

Troponins
BNP
D-dimer
Von Willebrand factor

BNP
IL-6
D-dimer

CRP
D-dimer

IL-6
D-dimer

eGFR
Cystatin

↑ Stroke risk
Appendage Morphology and Stroke Risk

Limitations of Risk Stratification Scores for Atrial Fibrillation

The AF population is very heterogeneous regarding stroke risk

- Different classifications in measuring stroke rates lead to overestimates
- Incorporation of other embolic episodes into determinants of stroke risk
- Current risk stratification schema are based primarily upon clinical risk factors

- Differential weight of individual risk factors
- Performance varies according to baseline risk of stroke which is variable among populations

What will be the role of biomarkers and imaging