Refinement of recurrent ischemic stroke patients with atrial fibrillation (beyond CHADS score with brain imaging and biomarkers)
Stroke recur during anticoagulation

- Stroke recur during anticoagulation

---

**Relative Risk Reduction (95% CI)**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Relative Risk Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFASAK-1 (N = 671)</td>
<td>[ ]</td>
</tr>
<tr>
<td>SPAF (N = 421)</td>
<td>[ ]</td>
</tr>
<tr>
<td>BAATAF (N = 420)</td>
<td>[ ]</td>
</tr>
<tr>
<td>CAFA (N = 378)</td>
<td>[ ]</td>
</tr>
<tr>
<td>SPINAF (N = 571)</td>
<td>[ ]</td>
</tr>
<tr>
<td>EAF (439)</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

All 6 Trials (N = 2900) 64%  

---

**Ischemic lesion pattern**

A

**Occusion of the corresponding artery**

B

---

**Ann inter med 2007**

**JSCVD 2014**
Results: Seven studies (including six entirely independent cohorts) were identified. Prior stroke/TIA (relative risk 2.5, 95% CI 1.8 to 3.5), increasing age (relative risk 1.5 per decade, 95% CI 1.3 to 1.7), a history of hypertension (relative risk 2.0, 95% CI 1.6 to 2.5), and diabetes mellitus (relative risk 1.7, 95% CI 1.4 to 2.0) were the strongest, most consistent independent risk factors. Observed absolute stroke rates for nonanticoagulated patients with single independent risk factors were in the range of 6 to 9% per year for prior stroke/TIA, 1.5 to 3% per year for history of hypertension, 1.5 to 3% per year for age >75, and 2.0 to 3.5% per year for diabetes. Female sex was inconsistently associated with stroke risk, whereas the evidence was inconclusive that either heart failure or coronary artery disease is independently predictive of stroke.
### CHADS2 score

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>H Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)</td>
<td>1</td>
</tr>
<tr>
<td>A Age ≥75 years</td>
<td>1</td>
</tr>
<tr>
<td>D Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S₂ Prior Stroke or TIA or Thromboembolism</td>
<td>2</td>
</tr>
</tbody>
</table>

1-point increase in the CHADS2 score was associated with a 1.5-fold higher hazard of stroke.

#### Annual Stroke Risk

<table>
<thead>
<tr>
<th>CHADS₂ Score</th>
<th>Stroke Risk %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9</td>
<td>1.2–3.0</td>
</tr>
<tr>
<td>1</td>
<td>2.8</td>
<td>2.0–3.8</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
<td>3.1–5.1</td>
</tr>
<tr>
<td>3</td>
<td>5.9</td>
<td>4.6–7.3</td>
</tr>
<tr>
<td>4</td>
<td>8.5</td>
<td>6.3–11.1</td>
</tr>
<tr>
<td>5</td>
<td>12.5</td>
<td>8.2–17.5</td>
</tr>
<tr>
<td>6</td>
<td>18.2</td>
<td>10.5–27.4</td>
</tr>
</tbody>
</table>

#### Table 2. One- and 5-year Incidence Rates per 100 Person-Years of Stroke, Death, and Cardiovascular Events, Stratified by the CHADS₂, VASc Score and the Essen Stroke Risk Score

<table>
<thead>
<tr>
<th>CHADS₂, VASc Score</th>
<th>1-y Rates</th>
<th>5-y Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke Events, n</td>
<td>Rate</td>
<td>Stroke Events, n</td>
</tr>
<tr>
<td>2</td>
<td>143</td>
<td>3.1</td>
</tr>
<tr>
<td>3</td>
<td>215</td>
<td>2.7</td>
</tr>
<tr>
<td>4</td>
<td>325</td>
<td>3.8</td>
</tr>
<tr>
<td>5</td>
<td>315</td>
<td>4.0</td>
</tr>
<tr>
<td>6</td>
<td>219</td>
<td>4.1</td>
</tr>
<tr>
<td>≥7</td>
<td>95</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Recurrent stroke

Stroke 2015
Among patients with incident HF with or without AF, the CHA2DS2-VASc score was associated with risk of ischemic stroke, thromboembolism, and death. But even better in those without AF.
CHADS2 score not specific

CHADS score also predicts stroke recur in those with Non-AF stroke

Neurology 2013
Am J Heart 2011
Can there be something more specific for CE

- What increases the risk of CE?
  - GWAS $\rightarrow$ AF polygenic risk scores

Genetic risk of AF is associated with cardioembolic stroke, independent of clinical risk factors.

*Neurology 2018*
Focusing on afib itself

**ACTIVE W**

- **Cumulative Hazard Rates**
  - No. at Risk: 1999, 1121, 862, 304
  - Years: 0.0, 0.5, 1.0, 1.5

**ENAGAGE AF TIMI 41**

**Event Rate, %/y**

<table>
<thead>
<tr>
<th>Event</th>
<th>Paroxysmal</th>
<th>Persistent</th>
<th>Permanent</th>
<th>HR (95% CI)</th>
<th>P Value</th>
<th>HR (95% CI)</th>
<th>P Value</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/SEE (Figure 1)</td>
<td>1.49</td>
<td>1.83</td>
<td>1.95</td>
<td>0.79 (0.66–0.96)</td>
<td>0.015</td>
<td>0.79 (0.67–0.93)</td>
<td>0.004</td>
<td>0.99 (0.85–1.16)</td>
<td>0.95</td>
</tr>
<tr>
<td>Stroke/SEE/CV death (Figure 2)</td>
<td>3.16</td>
<td>4.57</td>
<td>4.49</td>
<td>0.73 (0.64–0.82)</td>
<td>&lt;0.001</td>
<td>0.78 (0.70–0.87)</td>
<td>&lt;0.001</td>
<td>1.07 (0.97–1.18)</td>
<td>0.18</td>
</tr>
<tr>
<td>All-cause death (Figure 3)</td>
<td>2.99</td>
<td>4.41</td>
<td>4.41</td>
<td>0.73 (0.64–0.83)</td>
<td>&lt;0.001</td>
<td>0.78 (0.69–0.87)</td>
<td>&lt;0.001</td>
<td>1.06 (0.96–1.17)</td>
<td>0.23</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2.86</td>
<td>2.65</td>
<td>2.73</td>
<td>1.07 (0.91–1.25)</td>
<td>0.42</td>
<td>1.01 (0.88–1.16)</td>
<td>0.87</td>
<td>0.95 (0.82–1.09)</td>
<td>0.45</td>
</tr>
<tr>
<td>Major or clinically relevant nonmajor bleeding</td>
<td>12.17</td>
<td>10.68</td>
<td>10.37</td>
<td>1.08 (0.99–1.17)</td>
<td>0.070</td>
<td>1.08 (1.01–1.16)</td>
<td>0.035</td>
<td>1.00 (0.93–1.08)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>MACE (Ml/stroke/SEE/CV death)</td>
<td>3.90</td>
<td>5.09</td>
<td>5.04</td>
<td>0.79 (0.71–0.89)</td>
<td>&lt;0.001</td>
<td>0.84 (0.76–0.93)</td>
<td>&lt;0.001</td>
<td>1.06 (0.96–1.16)</td>
<td>0.23</td>
</tr>
<tr>
<td>Death/stroke/SEE</td>
<td>4.08</td>
<td>5.68</td>
<td>5.68</td>
<td>0.75 (0.68–0.84)</td>
<td>&lt;0.001</td>
<td>0.80 (0.72–0.88)</td>
<td>&lt;0.001</td>
<td>1.06 (0.97–1.16)</td>
<td>0.21</td>
</tr>
</tbody>
</table>
Overall, there is a growing consensus that the risk of thromboembolism increases as patients progress from paroxysmal to sustained to permanent AF.
Table 2. Sensitivity, Specificity, and Predictive Ability (C-Statistics and Their 95% CIs) for the CHADS₂ and CHA₂DS₂-VASc Stroke Risk Stratification Schema in Relation to Atrial Fibrillation Burden

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>C-Statistic</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS₂</td>
<td></td>
<td></td>
<td>0.653 (0.50–0.81)</td>
<td>0.051</td>
</tr>
<tr>
<td>CHADS₂ ≥1</td>
<td>86</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHADS₂ ≥2</td>
<td>43</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[CHADS₂ ≥3]+[CHADS₂=2 except AF-free]+[CHADS₂=1 with AF ≥24 h]</td>
<td>79</td>
<td>63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHADS₂+AF burden</td>
<td></td>
<td></td>
<td>0.713 (0.56–0.86)</td>
<td>0.007</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc</td>
<td></td>
<td></td>
<td>0.898 (0.84–0.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc ≥1</td>
<td>100</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA₂DS₂-VASc ≥2</td>
<td>100</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[CHA₂DS₂-VASc ≥3]+[CHA₂DS₂-VASc=2 except AF-free]</td>
<td>100</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[CHA₂DS₂-VASc ≥3]+[CHA₂DS₂-VASc=2 with AF ≥24 h]</td>
<td>93</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHA₂DS₂-VASc+AF burden</td>
<td></td>
<td></td>
<td>0.910 (0.86–0.93)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation.
MI vs. stroke

- Serologic biomarker....
Troponin I

- Marker of myocardial damage
- Prognostic marker of poor outcome and increased mortality

Factors associated with TpI elevation:
- previous ischemic heart disease
- congestive heart failure,
- comorbid atrial fibrillation
- active cancer

Distribution of troponin levels

2nd tertile (0.012 ng/mL) and 3rd tertile (0.025 ng/mL) of a detectable troponin

99th percentile (0.04 ng/mL)

Number at risk
Elevated Non-elevated
166 1,526
97 51 15 152
0.01

Cumulative mortality

Number at risk
Elevated Non-elevated
166 1,526
97 51 15 152
0.01

Cumulative mortality

Troponin I in NOAC trials

- RELY trial
- N=6189 patients

Adding high-sensitivity cTnT to the CHA2DS2-VASc score improved the C statistic from 0.63 to 0.65.

*Circulation.* 2012;125:1605-1616
**Elevated NT proBNP**

- Elevated NT-ProBNP
  - Prognostic marker for hospital mortality in **heart failure** patients
  - Prediction of mortality and **MI in unstable angina**
  - Long term mortality on **stable CAD**

- Elevated NT-ProBNP in AF
  - More elevated in patients with AF
  - Detection of **major structural heart disease** in patients with AF
  - **Prognosis** after ablation
NT Pro-BNP in NOAC trials

- **ARISTOTLE TRIAL**
- **N = 14892 of 18201 with NT Pro-BNP data**

Increased risk of Stroke/SE in those with elevated Pro-BNP (by quartile)

**J Am Coll Cardiol. 2013**
NT Pro-BNP in NOAC trials

- RELY trial
- N=6189 patients

The addition of NT-proBNP level to the CHA2DS2-VASc score improved its C statistic from 0.62 to 0.65
Renal function

- Impairment of renal function
  - Associated with AF
  - Increased thromboembolic risk
  - More bleeding events

| Table 2. Clinical Factors Associated with Stroke or Systemic Embolism in the ROCKET AF Trial |
|---------------------------------|--------|---------------|-----------|
|                                 | LR $\chi^2$ | HR            | 95% CI    | LR $P$ Value |
| History of stroke or TIA       | 40.77    | 1.825         | 1.514–2.199 | <0.0001      |
| CrCl (Cockcroft/Gault; HR for a 10-ml/min decrease) | 26.38    | 1.115         | 1.068–1.164 | <0.0001      |
| Diastolic for 10-n increase    |          |               |           |              |
| Paroxysmal (versus persistent)  |          |               |           |              |

Risk Stratification Model C-Index (95% CI)*

- CHADS$_2$ 0.575 (0.55–0.60)
- CHA$_2$DS$_2$VASc 0.578 (0.55–0.60)
- R$_2$CHADS$_2$ 0.587 (0.56–0.61)
- Age, HR for 10-yr increase 0.04
- Heart failure 0.59

LR = Likelihood Ratio; HR = Hazard Ratio; CI = Confidence Interval; CHADS$_2$ = Congestive Heart Failure, Hypertension, Age $\geq$ 75, Diabetes, Stroke; CHA$_2$DS$_2$VASc = Congestive Heart Failure, Hypertension, Atrial Fibrillation, Age $\geq$ 75, Diabetes, Stroke, Vascular Disease; R$_2$CHADS$_2$ = Risk Stratification Model.
Inflammation and coagulation

- **CRP**
  - Without AF: Log rank $p = 0.001$
  - With AF: Log rank $p = 0.67$
  - $p < 0.005$
  - $p < 0.01$
  - $p < 0.005$

- **D-dimer**
  - $D$-dimer $< 0.5\mu g/ml$ (n = 206)
  - $D$-dimer $\geq 0.5\mu g/ml$ (n = 63)
  - $p < 0.01$ (Log-rank test)
  - $r = 0.318$
  - $p < 0.001$
Pathophysiology of AF-stroke

- Atrial tissue changes
  - Myocytic hypertrophy
  - Sclerosis
  - Fibroelastosis
  - Extracellular matrix abnormal changes

- Re-entry foci formation

- Atrial fibrillation

- Inflammation
  - vWF, interleukin 6

- Endothelial damage/dysfunction

- Coagulation cascade activation
  - ↑ D-dimer
  - ↑ Prothrombin 1 and 2
  - ↑ Thrombin-antithrombin complex

- Platelet activation
  - ↑ β-thromboglobulin

- Hemocoagulation
  - ↑ Hematocrit

- Blood stasis

- Thrombus formation

- Thromboembolism and stroke

- Atrial tissue

- Atrium

- Atrial tissue

- Wall motion abnormalities
Left atrial enlargement

- NVAF patients with acute ischemic stroke
- N=1611 patients
- Left atrium diameter index = LAD / body surface

LA diameter >45 mm was associated with the risk of ischemic stroke even after adjustment for the CHA$_2$DS$_2$-VASc score (HR, 1.74; 95% CI, 1.25–1.83)
Lower flow velocity in LAA in those with thrombus or history of TIA or stroke
Can be extended to ESUS to find atrioptathy
Crime science
Stroke pattern of CE

Multiple territory infarction
Large cortico-subcortical infarction
JOS 2014
AJNR 2006
Fresh red clot rich of RBCs and fibrin → Susceptible vessel sign
Imaging characteristics of CE

Cardioembolism

But difference in mechanism → Difference in embolic pattern
High risk

Needs to define high risk stroke patients

- **Image**
  - Multiple lesions in multiple vascular territory
  - Multistage lesions (different ADC value)
  - Silent ischemic lesion at follow-up image

Higher risk of stroke
But no data among AF-stroke patients
May be high risk patients and need appropriate management. MRA data may be considered for stratifying the subsequent stroke risk.
Conclusion

• CHADS2 score is effective and acceptable evaluating the risk

• However simple methods with serological biomarkers may enhance the predictability of stroke in AF
  – Cardiac markers, coagulation, inflammation and renal markers

• May be focusing on the AF and structure of LA may be the best choice
  – Burden of AF
  – Structure of LAA
  – Function of LAA

• Neuroimaging may have a potential role in predicting subsequent ischemic stroke also in AF patients.
Other scores

- **STAF score**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥62 y</td>
<td>2</td>
</tr>
<tr>
<td>Age ≤62 y</td>
<td>0</td>
</tr>
<tr>
<td>Baseline NIHSS score ≥8</td>
<td>1</td>
</tr>
<tr>
<td>Baseline NIHSS score &lt;8</td>
<td>0</td>
</tr>
<tr>
<td>Left atrial dilatation Yes</td>
<td>2</td>
</tr>
<tr>
<td>Left atrial dilatation No</td>
<td>0</td>
</tr>
<tr>
<td>Absence of vascular etiology Yes</td>
<td>2</td>
</tr>
<tr>
<td>Absence of vascular etiology No</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>0-8</td>
</tr>
</tbody>
</table>

![ROC curve and bar graph showing STAF score vs BNP](image)
• ABC score
  – age, biomarker, clinical history
  – N=8705 ENGAVE AF TIMI 48 study

Higher c indexes than the CHA2DS2-VASc score for stroke or systemic embolic events (0.67 [95% CI, 0.65–0.70] versus 0.59 [95% CI, 0.57–0.62]; P<0.001) and HAS-BLED score for major bleeding (0.69 [95% CI, 0.66–0.71] versus 0.62 [95% CI, 0.60–0.64]; P<0.001)