Non-Embolic and Embolic Mechanisms of Stroke

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Declaration of Interests


- **Steering Committees/trials:** Includes steering committees for various Phase II and III studies, Health Economics & Outcomes Research, etc. Investigator in various clinical trials in cardiovascular disease, including those on antithrombotic therapies in atrial fibrillation, acute coronary syndrome, lipids, etc.

- **Editorial Roles:** Editor-in-Chief (clinical), Thrombosis & Haemostasis; Associate Editor, Europace; Guest Editor, Circulation, American Heart Journal.

- **Consultant/Advisor/Speaker:**
  - Consultant for Bayer/Janssen, BMS/Pfizer,Verseon, Boehringer Ingelheim, and Daiichi-Sankyo.
  - Speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo
Cardioembolic sources and embolic risk


Potential cardiac sources of emboli can be categorized into:

- a propensity for thrombus formation (AF, left atrial spontaneous echo contrast, mitral annular calcification, etc).
- masses (including LA/LV thrombi, atherosclerotic plaques, vegetations, and tumors)
- passageways for paradoxical embolism (patent foramen ovale, atrial septal defects, etc)

The most common are left atrial and left ventricular thrombi, left atrial spontaneous echo contrast, and aortic atherosclerosis...

High risk

Atrial
- Atrial fibrillation
- Sustained atrial flutter
- Sick sinus syndrome
- Left atrial thrombus
- Left atrial appendage thrombus
- Left atrial myxoma

Valvular
- Mitral stenosis
- Prosthetic valve
- Infective endocarditis
- Non-infective endocarditis

Ventricular
- Left ventricular thrombus
- Left ventricular myxoma
- Recent anterior myocardial infarct
- Congestive heart failure
- Dilated cardiomyopathy

Low/uncertain risk

- Patent foramen ovale
- Atrial septal aneurysm
- Atrial auto-contrast
- Mitral annulus calcification
- Mitral-valve prolapse
- Calcified aortic stenosis
- Fibroelastoma
- Giant Lambl’s excrescences

- Akinetic/dyskinetic ventricular wall segment
- Subaortic hypertrophic cardiomyopathy
- Congestive heart failure
- Dilated cardiomyopathy

Patent foramen ovale
- Atrial fibrillation
- Mitral stenosis
- Mechanical vegetation
- Cardiomyopathy

left ventricular contrast, and aortic
Transthoracic Echocardiography in Acute Ischemic Stroke Patients

de Abreu et al. Stroke. 2005;36:1565-1566

<table>
<thead>
<tr>
<th>Findings</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No findings suggesting need of anticoagulation</td>
<td>273 (62.8)</td>
</tr>
<tr>
<td>Dilated cardiopathy</td>
<td>83 (19.1)</td>
</tr>
<tr>
<td>Anterior wall dyskinesis</td>
<td>27 (6.2)</td>
</tr>
<tr>
<td>Left ventricle ejection fraction &lt;35%</td>
<td>16 (3.7)</td>
</tr>
<tr>
<td>Mitral valve stenosis with left atria &gt;55 mm</td>
<td>9 (2.1)</td>
</tr>
<tr>
<td>Intracardiac masses</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Valve prosthesis</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Mitral valve stenosis with left atria &gt;55 mm + dilated cardiopathy</td>
<td>7 (1.6)</td>
</tr>
<tr>
<td>Dilated cardiopathy + anterior wall dyskinesis</td>
<td>9 (2.1)</td>
</tr>
<tr>
<td>Dilated cardiopathy + left ventricle ejection fraction &lt;35%</td>
<td>8 (1.8)</td>
</tr>
<tr>
<td>Total</td>
<td>435 (100.1)</td>
</tr>
</tbody>
</table>
Overlap among cryptogenic stroke, ESUS, and cardioembolic stroke.

*Kamel and Healey
Circ Res. 2017;120:514-526*

... an imperfect but substantial overlap.

**Cryptogenic stroke** can be used to refer to a stroke with incomplete evaluation: if cryptogenic stroke is stringently defined, it essentially equals ESUS.
Distribution of Potential Etiologies of ESUS in the Athens Stroke Registry

Number of atherosclerotic risk factors and frequency of comorbid atherosclerotic disease in different stroke/TIA subtypes: OXVASC

Li et al. Lancet 2015

Cryptogenic group had fewer risk factors overall than the large artery disease (p=0·0001), small vessel disease (p=0·001), and cardioembolic (p=0·008) groups.
10-year absolute risks of acute coronary events, cardioembolic events, and recurrent ischaemic stroke: OXVASC

Li et al Lancet 2015

Patients with cryptogenic events had a lower risk of acute coronary events than large artery disease events (aHR 0.40, 95% CI 0.24–0.66; p=0.0003) and a similar risk to non-large artery disease events (0.76, 0.49–1.18; p=0.22)
Prevalence and Overlap of Potential Embolic Sources in Patients With Embolic Stroke of Undetermined Source

Ntaios et al
*J Am Heart Assoc* 2019;8:e012858.

Ten–year survival estimates of stroke recurrence in patients with embolic stroke of undetermined source, according to each potential embolic source (PES; top) and the number of PES per patient (bottom).
2-Year Age-Adjusted Incidence of Stroke per 1000


Risk factor
- HBP
- CHD
- CHF
- AF

Risk ratio
- HBP (3.4)
- CHD (2.4)
- CHF (4.3)
- AF (4.8)
Contribution of AF to Incidence and Outcome of Ischemic Stroke Population-Based L’Aquila Study

Kaplan–Meier estimates of the likelihood of recurrent stroke in patients with and without AF

Annual Mortality Rates in Patients With and Without AF:
At 1 year, AF 49.5% vs no AF, 27.5%
Increased mortality even up to 8 years
Atrial fibrillation and thrombosis: immunohistochemical differences between in situ and embolized thrombi

As fibrin is the major component of atrial thrombi (mean 68% in 22 thrombi) in AF …… pathophysiologic basis for why anticoagulation reduces thromboembolism in AF.

Thrombi from 22 patients with AF:
In atrial thrombi [black circles], fibrin-rich regions predominated (P<0.0001).
The platelet content of embolized thrombi [white circles] was nearly twice that of AF atrial thrombi (P=0.02).

‘Atrial thrombi in situ contain primarily fibrin and amorphous debris whereas embolized thrombi are comprised primarily of fibrin and platelets.’
Virchow’s triad and AF......

* Lip Lancet 1995; 346: 1313-14

Abnormalities of vessel wall
(endothelial dysfunction or damage)

Abnormalities of blood flow
(rheology, viscosity and flow reserve)

Abnormalities of blood constituents
(abnormal haemostatic factors, platelet activation and fibrinolysis)

......AF confers a prothrombotic or hypercoagulable state.
The prothrombotic state in AF

Khan and Lip
Cardiovasc Res 2019; 115, 31–45

Thomas and Lip.
Circ Res. 2017; 120:133-149

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Stroke/systemic embolism</th>
<th>Mortality</th>
<th>Major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac biomarkers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Troponin</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>+/++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Inflammation biomarkers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>IL-6</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>GDF-15</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Galectin-3</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Endothelial function</td>
<td>vWF</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Coagulation</td>
<td>D-dimer</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

Adapted from Hijazi et al.\textsuperscript{198}

\textsuperscript{198}+, outcomes in analysis unadjusted; ++, adjusted for clinical risk factors; ++++, adjusted for clinical risk factors and other biomarkers.
Altered fibrin clot structure in AF and worsening renal function.


SEM of fibrin clots in worsening CKD (5,000x magnification).
Biomarkers in atrial fibrillation: a clinical review
Hijazi et al Eur Heart J 2013

Various biomarkers have been used to aid risk stratification in AF..
- D-dimer, vWF, BNP, CRP, troponin, etc

Cumulative hazard rates for stroke or systemic embolism, according to Troponin I levels at randomization in an anticoagulated cohort from RE-LY trial
Protein Biomarkers of CVD and Mortality in the Community
Ho et al
JAHA 2018;7:e008108

Figure. Heatmap of biomarkers associated with all-cause mortality (FDR q < 0.05) are also associated with other concomitant fatal and non-fatal cardiovascular outcomes, including atherosclerotic CVD, heart failure, and CVD death. ASCVD indicates atherosclerotic cardiovascular disease; CVD, cardiovascular disease; FDR, false discovery rate; HF, heart failure; HR, hazard ratio.
Refining Stroke and Bleeding Prediction in AF by Adding Consecutive Biomarkers to Clinical Risk Scores

Rivera-Caravaca .. Lip, Roldan. Stroke 2019
DOI:10.1161/STROKEAHA.118.024305

By adding consecutive biomarkers, the predictive ability of CHA₂DS₂-VASc for ischemic stroke was not increased, whereas the predictive ability of HAS-BLED for major bleeding was only slightly enhanced.

The net benefit and clinical usefulness of the biomarker-based models were marginal in comparison to the original scores based on clinical factors.
2-Year Age-Adjusted Incidence of Stroke per 1000


Risk factor
- HBP
  - Absent
  - Present
- CHD
  - Absent
  - Present
- CHF
  - Absent
  - Present
- AF
  - Absent
  - Present

Risk ratio
- HBP (3.4)
- CHD (2.4)
- CHF (4.3)
- AF (4.8)
Kaplan–Meier estimate of the cumulative stroke rate among patients in the SAVE trial


Over 5 years, the rate of stroke was 1.5%/year. LV function, older age, and non-use of aspirin and/or anticoagulants were independent risk factors for thromboembolism.

For each 5% decrease in EF, there was an 18% increase in stroke rate.

Patients with EF ≤28% had a 5-year cumulative stroke risk of 8.1% [vs 4.1% for those with EF >35%]
OAC versus antiplatelet or placebo in patients with heart failure and sinus rhythm: Systematic review and meta-analysis

Ntaios .. Lip
Int J Stroke. 2019 Dec; 14(9):856-861

OAC vs antiplatelet or placebo for stroke (top) and major bleeding (bottom)
2-Year Age-Adjusted Incidence of Stroke per 1000


Risk factor
- HBP (3.4)
- CHD (2.4)
- CHF (4.3)
- AF (4.8)

Incidence of stroke (per 1000)

Risk ratio
- Absent
- Present

KDIGO
Stroke after Myocardial Infarction: A Meta-Analysis


Summary estimates (fixed effects)

In-hospital
Komrad
Longstreth
Nakaoka
Puletti
Spencer
Thompson
Wienberger
Angeja
Becker
Behar
O’Neill
30 days
Brodie
Pullicino
Mooe
1 year
Heller
Ng

Summary estimates (model)

In-hospital
30 days
1 year

Stroke rate/1000
Clopidogrel 75mg and Aspirin (75=162mg) vs Aspirin Alone for the Prevention of Atherothrombotic Events

<table>
<thead>
<tr>
<th>End Point</th>
<th>Clopidogrel plus Aspirin (N=7802)</th>
<th>Placebo plus Aspirin (N=7801)</th>
<th>Relative Risk (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction (nonfatal)</td>
<td>147 (1.9)</td>
<td>159 (2.0)</td>
<td>0.92 (0.74–1.16)</td>
<td>0.48</td>
</tr>
<tr>
<td>Ischemic stroke (nonfatal)</td>
<td>132 (1.7)</td>
<td>160 (2.1)</td>
<td>0.82 (0.66–1.04)</td>
<td>0.10</td>
</tr>
<tr>
<td>Stroke (nonfatal)</td>
<td>149 (1.9)</td>
<td>185 (2.4)</td>
<td>0.80 (0.65–0.997)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Safety end points

<table>
<thead>
<tr>
<th>End Point</th>
<th>Clopidogrel plus Aspirin (N=7802)</th>
<th>Placebo plus Aspirin (N=7801)</th>
<th>Relative Risk (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe bleeding</td>
<td>130 (1.7)</td>
<td>104 (1.3)</td>
<td>1.25 (0.97–1.61)</td>
<td>0.09</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>26 (0.3)</td>
<td>17 (0.2)</td>
<td>1.53 (0.83–2.82)</td>
<td>0.17</td>
</tr>
<tr>
<td>Primary intracranial hemorrhage</td>
<td>26 (0.3)</td>
<td>27 (0.3)</td>
<td>0.96 (0.56–1.65)</td>
<td>0.89</td>
</tr>
<tr>
<td>Moderate bleeding</td>
<td>164 (2.1)</td>
<td>101 (1.3)</td>
<td>1.62 (1.27–2.10)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**CI, 0.77 to 0.998; P = 0.046.**
Diagnostic Evaluation of Ischemic Stroke to Determine Stroke Mechanism

Yaghi et al Circ Res. 2017;120:527-540

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Suggested Algorithm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain imaging</td>
<td>Brain MRI in patients with cryptogenic stroke</td>
</tr>
<tr>
<td></td>
<td>Brain CT when stroke mechanism is known</td>
</tr>
<tr>
<td>Vascular imaging</td>
<td>Intracranial and extracranial vascular imaging on all patients with ischemic stroke</td>
</tr>
<tr>
<td></td>
<td>MRA with fat-suppressed images when clinical suspicion for cervical artery dissection</td>
</tr>
<tr>
<td>Cardiac imaging</td>
<td>TTE on all patients with ischemic stroke to look for evidence of cardiac disease (evidence of prior myocardial infarction warranting ischemic cardiac</td>
</tr>
<tr>
<td></td>
<td>evaluation or systolic heart failure</td>
</tr>
<tr>
<td></td>
<td>TEE with bubble study on patients &lt;50 y old to look for cardiac shunts/cardiac tumors if TEE was nonrevealing</td>
</tr>
<tr>
<td>Cardiac monitoring</td>
<td>Thirty-day noninvasive cardiac monitoring on patients with cryptogenic stroke and ≥40 y</td>
</tr>
<tr>
<td></td>
<td>Implantable cardiac monitor if 30-day monitor does not reveal AF or flutter</td>
</tr>
<tr>
<td>Hypercoagulable testing</td>
<td>Serum hypercoagulable workup in patients with no or minimal risk factors</td>
</tr>
<tr>
<td>Screening for malignancy</td>
<td>Age appropriate screening</td>
</tr>
<tr>
<td></td>
<td>CT chest/abdomen/pelvis when systemic symptoms suggestive of cancer are present such as unexplained weight loss or unexplained fever</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; CT, computed tomography; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography.

Figure 1. A and B. Multiple small infarcts in the posterior circulation in a patient with proximal basilar artery stenosis. C. Small infarcts in multiple vascular territories suggestive of a cardioaortic source.
Embolic Stroke of Undetermined Source and Detection of AF on Follow-Up: How Much Causality Is There

Ntaios ... Lip et al J Stroke Cerebrovasc Dis 2016 http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.08.015

- Among 275 ESUS patients, AF was detected during follow-up in 80 (29.1%).
- NIHSS score was similar between the two groups (5 [2-13] versus 5 [2-14], P = .998).
- More recurrent strokes or peripheral embolisms occurred in the AF group compared with the non-AF group (42.5% versus 13.3%, P = .001).

Cumulative probability of recurrent stroke or peripheral embolism in the AF and non-AF ESUS patients.
Diagnosis of AF after stroke and transient ischaemic attack: a systematic review and meta-analysis
*Sposato et al Lancet Neurology 2015; 14: 377-87*

<table>
<thead>
<tr>
<th>4 sequential phases of screening:</th>
<th>cardiac monitoring methods</th>
<th>%dx with poststroke AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 (emergency room) -</td>
<td>admission electrocardiogram (ECG)</td>
<td>7.7% (95% CI 5.0–10.8)</td>
</tr>
<tr>
<td>Phase 2 (in hospital)</td>
<td>serial ECG, continuous inpatient ECG monitoring, continuous inpatient cardiac telemetry, and in-hospital Holter monitoring</td>
<td>5.1% (3.8–6.5)</td>
</tr>
<tr>
<td>Phase 3 (first ambulatory period)</td>
<td>ambulatory Holter;</td>
<td>10.7% (5.6–17.2)</td>
</tr>
<tr>
<td>Phase 4 (second ambulatory period)</td>
<td>mobile cardiac outpatient telemetry, external loop recording, and implantable loop recording</td>
<td>16.9% (13.0–21.2)</td>
</tr>
</tbody>
</table>

Overall AF detection yield after all phases of sequential cardiac monitoring was 23.7% (95% CI 17.2–31.0).
## Diagnostic Evaluation of Ischemic Stroke to Determine Stroke Mechanism

*Yaghi et al Circ Res. 2017;120:527-540*

<table>
<thead>
<tr>
<th>Cause</th>
<th>Diagnostic Tests</th>
<th>Therapeutic Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac causes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal occult AF</td>
<td>Noninvasive cardiac monitoring, and if no AF or flutter detected, then implantable cardiac monitoring</td>
<td>Anticoagulation therapy</td>
</tr>
<tr>
<td>Atrial cardiopathy</td>
<td>Serum NT-proBNP, echocardiography, ECG</td>
<td>Treatment with antiplatelet vs anticoagulation is unknown, but empirical treatment with anticoagulation may be reasonable</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>Echocardiography (TEE superior to TTE)</td>
<td>Venous imaging if atrial septal defect detected</td>
</tr>
<tr>
<td><strong>Atherosclerotic causes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic arch disease</td>
<td>Echocardiography (TEE superior to TTE)</td>
<td>Antiplatelet and statin therapy</td>
</tr>
<tr>
<td>Substenotic atherosclerosis</td>
<td>Vessel wall imaging, plaque MRI</td>
<td>Antiplatelet and statin therapy</td>
</tr>
<tr>
<td><strong>Other causes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>CT chest, abdomen, and pelvis</td>
<td>Antiplatelet vs. anticoagulation treatment of underlying cancer</td>
</tr>
<tr>
<td>Hypercoagulable state</td>
<td>Hypercoagulable work-up, including antiphospholipid antibodies</td>
<td>Anticoagulation therapy based on findings</td>
</tr>
<tr>
<td>Arterial dissection</td>
<td>MRA with fat-suppressed images</td>
<td>Antiplatelet therapy</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; CT, computed tomography; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TEE, transesophageal echocardiography; and TTE, transthoracic echocardiography.
Comparison Between Oral Anticoagulation and Antiplatelet Rx in Patients With ESUS/Cryptogenic Stroke and Underlying Potential Embolic Source


<table>
<thead>
<tr>
<th>Condition</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid atherosclerosis</td>
<td>1.20 (0.86-1.68)</td>
</tr>
<tr>
<td>Aortic arch atherosclerosis</td>
<td>0.80 (0.40-1.62)</td>
</tr>
<tr>
<td>Enlarged left atrial diameter</td>
<td>0.26 (0.07-0.94)</td>
</tr>
<tr>
<td>Patent foramen ovale</td>
<td>0.68 (0.32-1.48)</td>
</tr>
<tr>
<td>Left ventricular disease</td>
<td>0.60 (0.46-0.78)</td>
</tr>
</tbody>
</table>

HRs and 95% CIs are obtained from exploratory subgroup analyses of the NAVIGATE ESUS trial
Significantly fewer cardioembolic strokes (hazard ratio [HR], 0.40 [95% CI, 0.20-0.78]; P = .005) and embolic strokes of undetermined source (HR, 0.30 [95% CI, 0.12-0.74]; P = .006) in the combination therapy group compared with the aspirin-only group.

For patients with systemic atherosclerosis, low-dose rivaroxaban plus aspirin was associated with large, significant reductions in cardioembolic strokes and embolic strokes of undetermined source.
Non-Embolic and Embolic Mechanisms of Stroke

• Cardioembolic stroke accounts for roughly 15% of all strokes.

• The risk profile for a potential cardiogenic source of embolism needs to be stratified.

• Common causes are AF, heart failure, CAD, hypertension…

• Evidence to guide long term medical management is …
  – strong in some areas eg. atrial fibrillation.
  – limited in some areas – large trials of longer duration are needed.