8th Regional Teaching Course In Sub Saharan Africa

Cardiogenic stroke

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MOZAMBIQUE
Summary

• Embolic strokes
  – Origin
  – Clinical characterization

• Specific situations
  – Atrial fibrillation
    ▪ Primary prevention
    ▪ Secondary prevention
  – Heart failure

• Other issues
  – PFO
  – LAA
Ischaemic stroke

- 25% large artery atherosclerotic stenosis
- 25% small artery disease (lacunes)
- 25% cryptogenic
- 20% major-risk source cardiogenic embolism
- 5% unusual (e.g., dissections, arteritis)
Cardioembolic stroke: an update

José M Ferro
Cardioembolic sources and embolic risk

<table>
<thead>
<tr>
<th>High risk</th>
<th>Low/uncertain risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atrial</strong></td>
<td></td>
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<tr>
<td>Atrial fibrillation</td>
<td>Patent foramen ovale</td>
</tr>
<tr>
<td>Sustained atrial flutter</td>
<td>Atrial septal aneurysm</td>
</tr>
<tr>
<td>Sick sinus syndrome</td>
<td>Atrial auto-contrast</td>
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<tr>
<td>Left atrial thrombus</td>
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<tr>
<td>Left atrial appendage thrombus</td>
<td></td>
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<tr>
<td>Left atrial myxoma</td>
<td></td>
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<tr>
<td><strong>Valvular</strong></td>
<td></td>
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<tr>
<td>Mitral stenosis</td>
<td>Mitral annulus calcification</td>
</tr>
<tr>
<td>Prosthetic valve</td>
<td>Mitral-valve prolapse</td>
</tr>
<tr>
<td>Infective endocarditis</td>
<td>Calcified aortic stenosis</td>
</tr>
<tr>
<td>Non-infective endocarditis</td>
<td>Fibroelastoma</td>
</tr>
<tr>
<td><strong>Ventricular</strong></td>
<td></td>
</tr>
<tr>
<td>Left ventricular thrombus</td>
<td>Akinetic/dyskinetic ventricular wall segment</td>
</tr>
<tr>
<td>Left ventricular myxoma</td>
<td>Subaortic hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Recent anterior myocardial infarct</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td></td>
</tr>
</tbody>
</table>
Features suggestive of cardioembolic stroke

- Decreased consciousness at onset
- Rapid regression of symptoms (the spectacular shrinking syndrome)
- Sudden onset to maximal deficit (<5 min)
- Simultaneous or sequential strokes in different arterial territories (especially if bi-hemispheric or involving combined anterior and posterior, bilateral, or multi level posterior circulation)
- Haemorrhagic transformation of an ischaemic infarct
- Early recanalization of an occluded intracranial vessel
Specific Situations
Atrial Fibrillation

- Primary prevention
- When shall we introduce anticoagulants after a TIA or an Ischaemic stroke
- Secondary Prevention
Atrial Fibrillation – Primary Prevention

- Atrial Fibrillation, even in the absence of cardiac valvular disease, is associated with a 4- to 5-fold increased risk of ischemic stroke resulting from embolism of stasis-induced thrombi forming in the left atrial appendage (LAA).

- Embolism of appendage thrombi associated with AF accounts for ≈10% of all ischemic strokes and an even higher fraction in the very elderly in the United States.

- The absolute stroke rate averages≈3.5%/y for 70-year-old individuals with AF, but the risk varies 20-fold among patients, depending on age and other clinical features.

- AF is also an independent predictor of increased mortality.

- Paroxysmal AF increases stroke risk similar to sustained AF.

Meschia et al Stroke December 2014
Once the diagnosis of AF is established, the next step is to estimate an individual’s risks:

- For cardioembolic stroke
- For haemorrhagic complications of antithrombotic therapy.
# Stroke Risk Stratification Schemes for Patients With AF

## CHA2DS2-VASc

<table>
<thead>
<tr>
<th>Scoring system</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure—1 point</td>
<td></td>
</tr>
<tr>
<td>Hypertension—1 point</td>
<td></td>
</tr>
<tr>
<td>Age 65–74 y—1 point</td>
<td></td>
</tr>
<tr>
<td>≥75 y—2 points</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus—1 point</td>
<td></td>
</tr>
<tr>
<td>Stroke/TIA—2 points</td>
<td></td>
</tr>
<tr>
<td>Vascular disease (eg, peripheral artery disease, myocardial infarction, aortic plaque)—1 point</td>
<td></td>
</tr>
<tr>
<td>Female sex—1 point</td>
<td></td>
</tr>
<tr>
<td>Risk scores range: 0–9 points</td>
<td></td>
</tr>
</tbody>
</table>

Levels of risk for thromboembolic stroke

- Low risk=0 points
- Moderate risk=1 point
- High risk ≥2 points

## HAS-BLED

<table>
<thead>
<tr>
<th>Risk factor</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension—1 point</td>
<td></td>
</tr>
<tr>
<td>Abnormal renal function—1 point</td>
<td></td>
</tr>
<tr>
<td>Abnormal liver function—1 point</td>
<td></td>
</tr>
<tr>
<td>Prior stroke—1 point</td>
<td></td>
</tr>
<tr>
<td>Prior major bleeding or bleeding predisposition—1 point</td>
<td></td>
</tr>
<tr>
<td>INR in therapeutic range &lt;60% of time—1 point</td>
<td></td>
</tr>
<tr>
<td>Age &gt;65 y—1 point</td>
<td></td>
</tr>
<tr>
<td>Use of antiplatelet or nonsteroidal drugs—1 point</td>
<td></td>
</tr>
<tr>
<td>Excessive alcohol use—1 point</td>
<td></td>
</tr>
</tbody>
</table>

Risk scores range: 0–9 points

Score >2 associated with clinically relevant and major bleeding.382

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Stroke prevention in atrial fibrillation.

1. Mechanical heart valves or moderate or severe mitral stenosis
   - Yes
   - No

2. Estimate stroke risk based on number of CHA$_{2}$DS$_{2}$-VASc risk factors$^a$
   - 0$^b$
     - No antplatelet or anticoagulant treatment (IIIB)
   - 1
     - OAC should be considered (IIB)
   - ≥2
     - Oral anticoagulation indicated
       - Assess for contra-indications
       - Correct reversible bleeding risk factors

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

4. NOAC (IA)$^c$
5. VKA (IA)$^{cd}$

European Heart Journal (2016) 37, 2893–2962
What to Choose

• Vit K anticoagulants
• NOAC
• Aspirin
Adjusted-dose warfarin has generally been the treatment of choice for patients at high risk for cardioembolic stroke and acceptably low risk of hemorrhagic complications, particularly intracranial haemorrhage. Treatment with adjusted-dose warfarin (target INR, 2 to 3) robustly protects against stroke (RR reduction, 64%; 95% CI, 49–74).

Paroxysmal AF increases stroke risk similar to sustained AF.

Meschia et al Stroke December 2014
The bleeding risk on aspirin is not different to the bleeding risk on VKA or NOAC therapy, while VKA and NOACs, but not aspirin, effectively prevent strokes in AF patients.

Compared with aspirin, adjusted-dose warfarin reduces stroke by 39% (95% CI, 22–52)
Ischaemic and haemorrhagic stroke associated with non-vitamin K antagonist oral anticoagulants and warfarin use in patients with atrial fibrillation: a nationwide cohort study

Laila Staerk¹, Emil Loldrup Fosbøl²,³, Gregory Y.H. Lip⁴, Morten Lamberts¹,², Anders Nissen Bonde¹, Christian Torp-Pedersen⁵, Brice Ozenne⁶, Thomas Alexander Gerds⁶, Gunnar Hilmar Gislason¹,³,⁷,⁸, and Jonas Bjerring Olesen¹,⁹
<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of events</th>
<th>Adjusted HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke/thromboembolism</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VKA</td>
<td>419</td>
<td>reference</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>336</td>
<td>0.97 [0.84-1.13]</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>128</td>
<td>0.91 [0.74-1.12]</td>
</tr>
<tr>
<td>Apixaban</td>
<td>171</td>
<td>1.07 [0.87-1.31]</td>
</tr>
<tr>
<td><strong>Ischemic stroke</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VKA</td>
<td>219</td>
<td>reference</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>163</td>
<td>0.89 [0.72-1.09]</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>68</td>
<td>0.89 [0.67-1.19]</td>
</tr>
<tr>
<td>Apixaban</td>
<td>86</td>
<td>0.98 [0.74-1.30]</td>
</tr>
<tr>
<td><strong>Intracranial bleeding</strong>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VKA</td>
<td>150</td>
<td>reference</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>48</td>
<td>0.37 [0.27-0.52]</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>34</td>
<td>0.66 [0.45-0.98]</td>
</tr>
<tr>
<td>Apixaban</td>
<td>29</td>
<td>0.53 [0.34-0.83]</td>
</tr>
</tbody>
</table>
Conclusions

Among anticoagulant-naïve patients with AF, treatment with dabigatran, rivaroxaban, and apixaban was not associated with significant lower risk of stroke/TE, but only treatment with dabigatran and apixaban was associated with significant lower risk of intracranial bleeding, compared with VKA.
Patient with an acute TIA or Ischaemic Stroke

When shall we Initiate anticoagulation after transient ischaemic attack or ischaemic stroke?
• Embolism of cardiac origin accounts for about one fifth of ischaemic strokes.
• Strokes due to cardioembolism are generally severe and prone to early recurrence. The risk of long term recurrence and mortality are also high after a cardioembolic stroke.
• About 20–40% of all patients with stroke, experience haemorrhagic transformation within the first week of symptom onset.
• Haemorrhagic transformation happens in up to 71% of cardioembolic strokes. As many as 95% of haemorrhagic infarcts are caused by cardioembolism.

• The traditional recommendation is to start anticoagulation early in mild cardioembolic strokes and to begin heparin therapy in severe cases with a major cardioembolic source, after the exclusion of haemorrhagic transformation with a repeated CT 3–5 days after onset.

• The time to start anticoagulation for secondary prevention is unclear. It is our practice to start it immediately in transient ischaemic attacks and minor strokes with a high-risk source of cardioembolism and nonhaemorrhagic infarcts and to delay it for 5–15 days in disabling strokes and large or haemorrhagic infarcts.
This approach is based on consensus rather than prospective data.
Atrial Fibrillation – Secondary Prevention

Secondary stroke prevention

- The most important risk factors for stroke in patients with AF are advanced age and previous cardioembolic stroke or TIA, emphasizing the need for OAC in these patients.
- The highest risk of recurrent stroke is in the early phase after a first stroke or TIA.
Initiation of anticoagulation after intracranial haemorrhage

- The available evidence indicates that anticoagulation in patients with AF can be reinitiated after 4–8 weeks, especially when the cause of bleeding or the relevant risk factor has been treated, and that such treatment leads to fewer recurrent (ischaemic) strokes and lower mortality.
- If anticoagulation is resumed, it seems reasonable to consider anticoagulants with a low bleeding risk.
Patient with AF suffering from an intracranial bleed on OAC
If acute event: establish intensity of anticoagulation (see bleeding flow chart)

Contra-indication for OAC

Consider further information to allow informed judgement

Factors supporting withholding of OAC:
- Bleeding occurred on adequately dosed NOAC or in setting of treatment interruption or underdosing
- Older age
- Uncontrolled hypertension
- Cortical bleed
- Severe intracranial bleed
- Multiple microbleeds (e.g., >10)
- Cause of bleed cannot be removed or treated
- Chronic alcohol abuse
- Need for dual antiplatelet therapy after PCI

Factors supporting reinitiation of OAC:
- Bleeding occurred on VKA or in setting of overdose
- Traumatic or treatable cause
- Younger age
- Well controlled hypertension
- Basal ganglia bleed
- No or mild white matter lesions
- Surgical removal of subdural haematoma
- Subarachnoid bleed: aneurysm clipped or coiled
- High-risk of ischaemic stroke

Patient or next of kin choice informed by multidisciplinary team advice

No stroke protection (no evidence)

LAA occlusion (IIbC)

Initiate or resume OAC, choosing an agent with low intracranial bleeding risk, after 4–8 weeks (IIbB)
What to do in Patients with heart failure as primary prevention?
Thrombo-embolism and antithrombotic therapy for heart failure in sinus rhythm. A Joint Consensus Document from the ESC Heart Failure Association and the ESC Working Group on Thrombosis

Gregory Y.H. Lip\textsuperscript{1*}, Piotr Ponikowski\textsuperscript{2}, Felicita Andreotti\textsuperscript{3}, Stefan D. Anker\textsuperscript{4}, Gerasimos Filippatos\textsuperscript{5}, Shunichi Homma\textsuperscript{6}, Joao Morais\textsuperscript{7}, Patrick Pullicino\textsuperscript{8}, Lars H. Rasmussen\textsuperscript{9}, Francisco Marin\textsuperscript{10}, and Deirdre A. Lane\textsuperscript{1}
Heart Failure and Sinus Rythm

HEART FAILURE

Blood flow abnormalities
- Impaired contractility
- LV aneurysm
- Low cardiac output

Vessel wall abnormalities
- Endothelial dysfunction
- Vascular remodeling

Abnormal blood constituents
- Coagulation abnormalities
- Platelet abnormalities
- Rheological abnormalities
- Activation of neuroendocrine system

THROMBOSIS
Until more evidence becomes available, clinical decisions to treat patients with HF in sinus rhythm with anticoagulants must be made on a patient-by-patient basis, balancing the individual benefits against the risks of treatment, especially amongst high risk patients.
2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC
Primary Prevention

• Other than in patients with AF (both HFrEF and HFpEF), there is no evidence that an oral anticoagulant reduces mortality/morbidity compared with placebo or aspirin.

• Studies testing the nonvitamin K antagonist oral anticoagulants (NOACs) in patients with HFrEF are currently ongoing.

• Patients with HFrEF receiving oral anticoagulation because of concurrent AF or risk of venous thromboembolism should continue anticoagulation.

• Similarly, there is no evidence on the benefits of antiplatelet drugs (including acetylsalicylic acid) in patients with HF without accompanying CAD, whereas there is a substantial risk of gastrointestinal bleeding, particularly in elderly subjects, related with this treatment.
• NOACs are preferred for patients with HF with non-valvular AF, as NOACs compared with vitamin K antagonists seem to be at least similarly effective and even safer (less intracranial haemorrhage) in patients with HF than in subjects without HF, although concerns exist about their safety in older patients with HF and poor renal function.

• A left atrial occlusion device could be considered in a patient with AF as an alternative to an oral anticoagulant who is at high-risk both of thromboembolism and of bleeding in order to avoid the risk of haemorrhage due to anticoagulation risk
• Patient values and preferences are important determinants when balancing the risk of thrombo-embolism against bleeding.
• All antithrombotic drugs carry an intrinsic risk of bleeding complications and, at this point, there is still uncertain benefit for their use in HF patients in sinus rhythm. Discussions regarding treatment options need to actively involve the patient, with consideration of their preferences when making antithrombotic treatment decisions.
• Clinical trials are needed to see if the new oral anticoagulants that may offer a different risk–benefit profile compared with warfarin could offer the reduction in ischaemic stroke with less risk of major bleeding.
• Anticoagulation may potentially be considered by some clinicians in the following HF patient groups:
  • HFrEF with previous thrombo-embolism
  • newly diagnosed intracardiac thrombus
  • right heart failure with pulmonary hypertension
but evidence is limited and more research is needed to ascertain the long-term risk–benefit ratio.
Patent Foramen Ovale
• Patent foramen ovale is present in a third of all patients with stroke, and is normally between 2–8 mm in diameter, is found in up to 40% of patients with ischaemic stroke who are younger than 55 years of age.

PFO as visualized on biplane transesophageal echocardiography

Sun YP, Circ J 2016; 80: 1665–1673
• A patent foramen ovale is common and found in nearly 25% of healthy individuals.
• The presence of PFO has been found to be higher in patients with cryptogenic stroke.
• Patients with cryptogenic stroke and PFO are generally treated with antiplatelet therapy in the absence of another condition for which anticoagulation is necessary.
• Based on the findings of 3 large randomized clinical trials, current consensus guidelines do not recommend percutaneous closure, though this is an area of controversy.

Sun YP, Circ J 2016; 80: 1665–1673
Comments and Opinions

Left Atrial Appendage Function and Stroke Risk

Shadi Yaghi, MD; Christopher Song, MD; William A. Gray, MD; Karen L. Furie, MD, MPH; Mitchell S.V. Elkind, MD, MS; Hooman Kamel, MD
• About 30% to 40% of ischemic stroke is of unknown cause.

• Recently, biomarkers of atrial dysfunction, or atrial cardiopathy, have been associated with embolic stroke risk even in the absence of atrial fibrillation (AF), suggesting that the presence of AF is not required for left atrial thromboembolism to occur.

• Most left atrial thrombi occur in the left atrial appendage (LAA), but there is limited use of LAA dysfunction parameters, such as LAA low velocity and morphology, to predict ischemic stroke risk.

Yaghi et al Stroke. 2015;46:3554-3559
Atrial cardiopathy: evidence of markers of atrial dysfunction such as elevated N-terminal proBNP, evidence of p-wave dispersion on ECG, increased left atrial size, and paroxysmal supraventricular tachycardia.
N-terminal pro-brain natriuretic peptide has been shown to be a marker of atrial dysfunction, risk of incident AF, and cardiac embolism. ECG signs related to the left atrium, such as paroxysmal supraventricular tachycardia and P-wave terminal force in lead V1 (PTFV1), have been associated with the risk of incident stroke, particularly of nonlacunar sub-types even in the absence of AF.

Yaghi et al Stroke. 2015;46:3554-3559
<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Ref&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>After surgical occlusion or exclusion of the LAA, it is recommended to continue anticoagulation in at-risk patients with AF for stroke prevention.</td>
<td>I</td>
<td>B</td>
<td>461, 462</td>
</tr>
<tr>
<td>LAA occlusion may be considered for stroke prevention in patients with AF and contra-indications for long-term anticoagulant treatment (e.g. those with a previous life-threatening bleed without a reversible cause).</td>
<td>IIb</td>
<td>B</td>
<td>449, 453, 454</td>
</tr>
<tr>
<td>Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery.</td>
<td>IIb</td>
<td>B</td>
<td>463</td>
</tr>
<tr>
<td>Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients undergoing thoracoscopic AF surgery.</td>
<td>IIb</td>
<td>B</td>
<td>468</td>
</tr>
</tbody>
</table>
• Many questions remain about LAA closure, including whether it is as effective if compared with non-vitamin K antagonist oral anticoagulant drugs that have a lower risk of intracranial hemorrhage.

• However, the Watchman trials are nevertheless consistent with a protective effect against thromboembolism, which again supports the role of the LAA as the origin of thrombus formation in left atrial disease.
• Given the substantial benefit of anticoagulant therapy in patients with atrial disease in the form of AF, such therapy may ultimately prove beneficial for patients without AF but compelling evidence of LAA dysfunction.

• Future research is needed to identify optimal methods to assess patients for LAA dysfunction and to test the benefit of anticoagulant therapy in stroke prevention in these patients.
The ABC (age, biomarkers, clinical history) stroke risk score: a biomarker-based risk score for predicting stroke in atrial fibrillation
Take Home Messages

- Cardioembolic stroke is frequent and preventable.
- AF should be actively diagnosed and risk stratification should be done to start anticoagulation soon for primary prevention of Stroke.
- We must be careful when starting anticoagulation after a TIA or an embolic stroke.
- The NOACs are still very expensive and their benefit is not what we were expecting.
- Prevention in heart failure and PFO or LAA are still areas that need further data for decision.