ECG/Imaging Modalities for Stroke Risk Stratification in Patients with Atrial Fibrillation

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Agenda

1. ECG abnormalities and stroke incidence
2. LA remodeling and stroke in AF
3. Imaging of LAA for risk stratification of stroke
4. Emerging technique in intracardiac flow dynamics
AF-related stroke causes greater disability

- AF-related strokes usually present with severe strokes.
  - Higher bed-ridden presentation (41% vs. 24%)\(^1\)
  - Higher 30-day post-stroke mortality (25% vs 14%)\(^2\)

\(^1\) Dulli DA et al. Neuroepidemiology. 2003 Mar-Apr;22(2):118-23
How can we improve stroke prediction?

Clinical risk factors
• Chronic kidney disease (GFR <60 ml/min/1.73 m²)
• Untreated obstructive sleep apnoea
• AF burden >5.5 h on any given day

Echocardiographic parameters
• Left atrial volume index >32 ml/m²
• Abnormal left atrial longitudinal strain
• LAA pulse-wave velocity <0.2 m/s

Advanced imaging
Left atrial fibrosis on cardiac MRI

Serum biomarkers
• NT-proBNP >1,250 ng/l
• Troponin concentration (cTnT >16.7 ng/l or cTnl >10.1 ng/l)

Ziad Hijazi, Jonas Oldgren, Johan Lindbäck, John H Alexander, Stuart J Connolly, John W Eikelboom, Michael D Ezekowitz, Claes Held, Elaine M Hylek, Renato D Lopes, Agneta Siegbahn, Salim Yusuf, Christopher B Granger, Lars Wallentin, on behalf of the ARISTOTLE and RE-LY Investigators
Ambulatory Holter monitoring in evaluation of silent/asymptomatic atrial tachyarrhythmias in high-risk populations

- **Larsen et al. Copenhagen Holter Study**
  - 678 subjects w/o CVD/AF, 55-75 yrs.
  - 14.4 years follow up, 48-h Holter
  - ESVEA(+) 14.6%, HR=1.96 for ischemic stroke, p=0.02

- **Engstrom et al. ‘men born in 1914’**
  - 402 men, 68 y, 24-h Holter
  - APC>218/24hr: HR 1.9 for stroke, p=0.04
Excessive Atrial Ectopy and Short Atrial Runs Increase the Risk of Stroke Beyond Incident Atrial Fibrillation

Relationship between ESVEA & stroke remained significant despite of:

- Censoring at the time of AF
- Multivariate adjustment with AF as a time-varying exposure
- Fine-Gray Competing risk model with AF & death as competing risk.

J Am Coll Cardiol 2015;66:232–41
Excessive atrial ectopy and short atrial runs are associated with an increased risk of ischemic stroke beyond atrial fibrillation. However, the exact mechanism is not known and may be caused by undiscovered incident atrial fibrillation or an increased vascular risk profile.

J Am Coll Cardiol 2015;66:232–41
Recommendation in consensus document

- Excessive supraventricular ectopic activity (ESVEA): 30 premature supraventricular contractions (PSC) /hour (≥720 PCS /24 hours) or episode of PSC runs ≥20 beats.

ESVEA documented by Holter monitoring can be considered as a surrogate marker for paroxysmal AF.
Device detected AHRE & thromboembolic risk

• TRENDS study
  – Prospective, observational
  – 2486 pts
  – One or more stroke risk factor
  – PM or ICD
  – AT/AF burden was defined as the maximum number of hours of AT/AF on any day during the antecedent 30 days and may have included more than 1 episode of AT/AF on that day

AT/AF burden was divided into 3 subsets
- Zero AT/AF burden,
- Low AT/AF burden (<5.5 h)
- High AT/AF burden (≥5.5 h at least 1 day)
- Cut off was medial value of AF burden
- No EGM

<table>
<thead>
<tr>
<th>AT/AF Burden Subset</th>
<th>Annualized TE Rate (95% CI), %</th>
<th>Annualized TE Rate Excluding TIAs (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero AT/AF burden</td>
<td>1.1 (0.8–1.6)</td>
<td>0.5 (0.3–0.9)</td>
</tr>
<tr>
<td>Low AT/AF burden (&lt;5.5 h)</td>
<td>1.1 (0.4–2.8)</td>
<td>1.1 (0.4–2.8)</td>
</tr>
<tr>
<td>High AT/AF burden (5.5 h)</td>
<td>2.4 (1.2–4.5)</td>
<td>1.8 (0.9–3.8)</td>
</tr>
</tbody>
</table>

HR 2.2 (0.96-5.05, P=0.06)

Subclinical Atrial Fibrillation and the Risk of Stroke

• ASSERT
• 2580 pts, ≥65 years, No AF Hx. 2.5 year-f/u.
• AHRE: ≥190 bpm, >6 min.
• AHRE occurred 10% in 3 month.
• HR=3.9 in CHADS score >2 and 3 month-AHRE(+) group

Stroke risk of SCAF was generally lower than clinical AF

<table>
<thead>
<tr>
<th>CHADS$_2$ Score</th>
<th>Subclinical Atrial Tachyarrhythmias between Enrollment and 3 Months</th>
<th>Hazard Ratio for Ischemic Stroke or Systemic Embolism with Subclinical Atrial Tachyarrhythmias (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>Present</td>
</tr>
<tr>
<td></td>
<td>no. of patients</td>
<td>no. of events</td>
</tr>
<tr>
<td>1</td>
<td>600</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>1129</td>
<td>119</td>
</tr>
<tr>
<td>&gt;2</td>
<td>848</td>
<td>72</td>
</tr>
</tbody>
</table>

Silent AF related to silent brain ischemia

- 109 pts
- AHRE > 5 min.
- AHRE was found in 25% of pts.
- AHRE independently predicted silent ischemic lesion on brain CT performed at inclusion

Europace (2015) 17, 364–369
## Thromboembolic risk of AF in patients with CIED

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Number</th>
<th>F/U</th>
<th>Rate cut-off</th>
<th>Duration cut-off</th>
<th>HR</th>
<th>Event rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>MOST</td>
<td>312</td>
<td>27 months</td>
<td>&gt;220 bpm</td>
<td>5 min</td>
<td>6.7</td>
<td>5% vs. 1.3%</td>
</tr>
<tr>
<td>2005</td>
<td>Italian AT500 registry</td>
<td>725</td>
<td>22 months</td>
<td>&gt;174 bpm</td>
<td>24 hour</td>
<td>3.1</td>
<td>Annual 1.2%</td>
</tr>
<tr>
<td>2009</td>
<td>Botto et al.</td>
<td>568</td>
<td>1 year</td>
<td>&gt;174 bpm</td>
<td>CHADS+ burden</td>
<td></td>
<td>Overall 2.5%</td>
</tr>
<tr>
<td>2009</td>
<td>TRENDS</td>
<td>2486</td>
<td>1.4 years</td>
<td>&gt;175 bpm</td>
<td>5.5 h</td>
<td>2.2</td>
<td>2.4% vs. 1.1%</td>
</tr>
<tr>
<td>2012</td>
<td>Home Monitor CRT</td>
<td>560</td>
<td>370 days</td>
<td>&gt;180 bpm</td>
<td>3.8 h</td>
<td>9.4</td>
<td>Overall 2.0%</td>
</tr>
<tr>
<td>2012</td>
<td>ASSERT</td>
<td>2580</td>
<td>2.5 years</td>
<td>&gt;190 bpm</td>
<td>6 min</td>
<td>2.5</td>
<td>1.69% vs 0.69%</td>
</tr>
<tr>
<td>2014</td>
<td>SOS AF</td>
<td>10016</td>
<td>2 years</td>
<td>&gt;175 bpm</td>
<td>1 h</td>
<td>2.11</td>
<td>Annual 0.39%</td>
</tr>
</tbody>
</table>
There is still uncertainty regarding the duration of device-detected AF that increases TE risk.

Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT

Isabelle C. Van Gelder\textsuperscript{4*}, Jeff S. Healey\textsuperscript{2}, Harry J.G.M. Crijns\textsuperscript{3}, Jia Wang\textsuperscript{2},

Longest single episode of SCAF>24h was related to stroke

Limitation: have no data of AF burden

Eur Heart J. 2017 May 1;38(17):1339-1344
Recommendations (2017 consensus)

- For patients with two additional CHA2DS2-VASc risk factors (≥2 in males, ≥3 in females) oral anticoagulation is recommended for AF burden >5.5 h/day (TRENDS)

- AHRE > 5 min may merit OAC if multiple risk factors are present. (MOST, ASSERT)
Area of terminal inverted P portion independently predicted ischemic stroke. Had an incremental value in addition to CHADSVASc score.
P wave signal-averaged ECG for AF/stroke risk evaluation

68 pts, post stroke, no AF.

Presence of atrial late potential (risk ratio 11.15; p = 0.002) and frequent PACs (>100/24 h) (risk ratio 4.53; p = 0.007) had significant correlation to the occurrence of AF.

Fig. 1. Representative P-wave signal-averaged electrocardiography in each group. It is notable that the filtered P-wave duration (FPD) is longer and the root-mean-square voltage for the last 20 ms (RMS20) is lower in the atrial fibrillation (AF) patient than in the non-AF patient.

Table 2
Multivariate Cox proportional hazard analysis for the identification of patients at risk for AF.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>p-Value</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 70 (years)</td>
<td>0.188</td>
<td>2.06 (0.7–6.1)</td>
</tr>
<tr>
<td>ALP</td>
<td>0.002</td>
<td>11.15 (2.5–49.7)</td>
</tr>
<tr>
<td>PAC &gt; 100 (beats/day)</td>
<td>0.007</td>
<td>4.53 (1.5–13.6)</td>
</tr>
<tr>
<td>LAD ≥ 41 (mm)</td>
<td>0.111</td>
<td>2.29 (0.8–6.3)</td>
</tr>
<tr>
<td>BNP ≥ 80 (pg/ml)</td>
<td>0.557</td>
<td>1.36 (0.5–3.8)</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; ALP, atrial late potentials; BNP, brain natriuretic peptide; CI, confidence interval; LAD, left atrial dimension; PAC, premature atrial contractions.

Journal of Cardiology 61 (2013) 49–52
LA imaging and stroke risk

- LA volume shows stronger association with CV outcome than LA diameter (d/t asymmetrical remodeling?)
- Marker of diastolic dysfunction, LA pressure elevation.
- Associated with
  - Incidence of AF
  - Stroke
  - Overall mortality (after MI)
  - Death and hospitalization (DCMP)

317 pts, NSR at baseline, 3.5 yrs f/u
LAVI predicted MACE (AUC=0.71)

>300 patients with AMI
LA volume index was a powerful predictor of mortality

Prediction of AF by **LA volume & function** in normal population

**AF-risk** being highest for subjects with concomitant LA emptying fractions \(<49\%\) and LA volume \(>38\ \text{ml/m}^2\) (hazard ratio \(9.3\), \(p=0.003\))

574 subjects with NSR, mean 74 yrs old, 2 yr f/u

![Bar chart showing age-adjusted associations between LA emptying fraction and indexed maximum LA volume for the prediction of AF or atrial flutter.](image)

Figure 3. Age-adjusted associations between LA emptying fraction and indexed maximum LA volume for the prediction of AF or atrial flutter.

Am J Cardiol 2008;101:1626 –1629
Of 538 patients, 61 (11%) developed AF, and this occurred within 2 years in 85% of patients. with a 13-fold greater hazard of AF (p < 0.001) in patients with increased clinical risk and reduced reservoir strain (AUC=0.85).
Left Atrial Strain Provides Incremental Value for Embolism Risk Stratification over CHA2DS2-VASc Score
AF with systemic embolism(82), Japanese AF without embolism(204)
Cut off: Global LA strain <12%

Decreased LASp and LASRr were independently associated with stroke in patients with permanent AF.
(J Am Soc Echocardiogr 2011;24:513-9.)
Prediction of stroke by LA imaging (2)

PA-TDI:
Distance from
P wave to A’ wave
=electro-mechanical delay

>1300 pts, 7.9 yrs f/u
LA reservoir strain & PA-TDI provides additional risk stratification for stroke

LA strain correlated with fibrosis

Global PALS showed the best diagnostic accuracy to detect LA fibrosis (area under the curve 0.89) than LAVI, LAEF, E/E’ (46 pts, OP for MR)
LA Fibrosis Assessment From LGE-MRI

Steps to identify LA fibrosis

- Step 1: Acquire axial views of left atrium
- Step 2: Isolate and identify left atrial wall
- Step 3: Quantify enhancement
- Step 4: Render 3D model of left atrium

Stage 1~4 fibrosis (Utah group)

272 of 329 pts (57 pts (17%) excluded due to poor MRI quality)

The addition of fibrosis to a recurrence prediction model \(\rightarrow\) C statistic increasing from 0.65 to 0.69
LA fibrosis and stroke risk

1,228 pts with AF.
62 stroke or TIA
Retrospective.
LA fibrosis well correlated with stroke

- Total 111 pts.
- ESUS a higher LA fibrosis ($p=0.03$)
- AF and ESUS showed a similar value of atrial fibrosis.
- an atrial disease may be associated with stroke.

J Am Coll Cardiol 2017;70:1311–21

Stroke. 2018;49:734–737
Value of cardiac MRI in stroke prediction

169 PAF pts.
LA strain measured by MRI had additive value in stroke prediction.

Low strain region = LA fibrosis region


Figure 4. Incremental value of left atrial (LA) strain for diagnosis of stroke. The addition of the LA minimum volume ($V_{min}$) to the model on the basis of the CHA$_2$DS$_2$-VASC score resulted in significant improvement in the diagnostic value for stroke. The value was further increased by adding the LA global longitudinal maximum strain ($S_{max}$).

J Am Heart Assoc. 2015:4:e001844
LAA as a more important embolic source in NVAF

- 20% of ischemic stroke has cardiac embolic source
- AF is most common cardiac abnormality associated with stroke
- NVAF with stroke: ~90% have LAA thrombus
- 57% of thrombi in rheumatic heart disease

Imaging of LAA and stroke risk

1. Spontaneous echocontrast/thrombus
2. LAA peak emptying velocity
3. LAA orifice size/LAA volume
4. LAA morphologic type/trabeculation
5. Flow pattern of LAA
LAA flow in NSR vs. AF

NSR: Decreased LAA flow → Late diastolic contraction flow

AF: Spontaneous echocontrast/thrombus → increased stroke

Decreased LAA peak velocity and SEC/thrombus/stroke

A lot of observation data demonstrated the association between low LAA velocity and SEC/thrombus/stroke

- Various cut off value
- SEC increased when LAAV < 35 cm/s
  - (J Am Coll Cardiol 1994;23:961-9)
- Thrombus/SEC increased significantly at an LAAV < 55 cm/s
  - (JASE 2005;18:1366-72)
- LAA peak velocity < 20 cm/s
  - RR 1.7 for stroke
  - SPAF III data, J Am Coll Cardiol 1998;31:1622–6
  - OR 4.48 for stroke in age <70
  - CHEST 2001; 120:840 - 846
LAA size and stroke

• Longer duration of AF $\rightarrow$ enlarged LAA

• Larger LAA $\rightarrow$ thrombus/stroke
  – LAA area by TEE (circulation 1991;84:223-231)
  – CT/MRI: LAA orifice size/depth/volume was associated to stroke (JCE 2011;22:10-15)
    • OR:LAA os size $>>$ depth $>$ volume in this study.
Relationship between LAA orifice size and emptying flow velocity

Small LAA with preserved LAA velocity

Large LAA with decreased LAA velocity

Bernoulli's principle

\[ R = -0.48 \]
\[ P < 0.001 \]

Additional value of LAA for Stroke prevention in low risk patients (CHA$_2$DS$_2$VASc <2)

Patients with both large LAA os and low LAA velocity showed very high odds ratio of stroke (OR 10.9, 95% CI 3.0-40.0, p<0.001)

LAA morphology and stroke

Non-Chicken wing morphology was associated with Higher Hx of stroke/TIA

932 pts with AF
CT or MRI before RFCA
Retrospective, cross sectional design (odds ratio)
Anticoagulation status – unknown
LAA velocity and size were not associated to stroke, in this data.

L. Di Biase, et al. J Am Coll Cardiol 2012:60;531-8
LAA morphology may associated with LAA flow: Computational flow dynamics of LA

“Lowest washout of contrast agent was observed for the Cauliflower morphology”

LAA morphology is associated to LAA flow velocity by TEE.

Chicken Wing LAA of patient showing normal LAA flow velocity.

Cauliflower type LAA with decreased LAA flow velocity

Lee JM, Seo J et al. J Cardiovasc Electrophysiol, 2015;26;922-927
Particle image velocimetry: Comparison of LA vortex between SR and AF

Multiple, pulsatile, compact and elliptical-shaped vortices were seen in the periphery of the LA. These vortices were persistently maintained and vectors were directed toward the atrioventricular inflow.

A large, merged, lower pulsatile and round-shaped vortex was observed in the center of the LA.

KH Park, GR Hong et al. Ultrasound Med Biol 2013
Particle image velocimetry by TEE

- More ERAF in lower pulsatility (RS: relative strength) group
- Impaired LA flow might be associated with electrical remodeling and recurrent AF

JM Lee, GR Hong, HN Pak et al. IJC imaging 2015;31:1139-1148
MRI-measured LAA flow velocity
Correlated with TEE-measured velocity

Flow velocity was lower in AF than NSR

M Markl et al.
Circ Cardiovasc Imaging. 2016 Sep;9(9):e004984
EHJ – Cardiovascular Imaging (2016) 17, 1259–1268
Summary

• ESVEA on Holter, AHRE on CIED, SAECG P wave duration can predict AF and stroke.
• Increased LA volume, increased LA fibrosis, and impaired LA function are the main hallmarks of LA remodeling, and showed increased risk of stroke.
• LAA is particularly associated with risk of stroke.
• Decreased LAA flow, enlarged LAA, some morphologic characteristics of LAA can predict stroke risk.
• Intracardiac flow studies are emerging, but need more data for clinical application.
Thank you for attention