The Role of the Left Atrial Appendage

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Stroke in AF patients ≈ Appendage-related stroke

Prognostic Implications

Stroke, Mortality

Risk Ratio

Stroke

Mortality

- Whitehall Regional Heart Study
- Framingham
- Whitehall Framingham (no Heart Disease)
- Framingham Manitoba

Hersi and Wyse Curr Probl Cardiol. 2005 Apr;30(4):175-233
Prognostic Implications

Dementia

Bunch TJ et al Heart Rhythm 2010 Apr;7(4):433-7
Understanding LAA Anatomy

Understanding LAA physiology

LAA and ANP/BNP production

Autonomic cardiac nerves
Vein of Marshall Anatomy and Histology

Cabrera JA Eur Heart J 2008 29(3):356-362

Left Atrial Cardiac Innervation

Vaitkevicius et al. *Heart Rhythm*. 2009 Feb;6(2):221-8
Role of LAA in atrial fibrillation

• **Source of thromboembolic events**
• **Source of atrial fibrillation triggers/substrate**
  – Autonomic innervation
  – Reentrant circuits
  – AF Triggers
• **Source of atrial natriuretic peptide**
  – Potential role in fluid retention post-ligation or post-ablation
Goal #1: Stroke Prevention
Not all patients have equal risk

- CHADS<sub>2</sub>-CHA<sub>2</sub>DS<sub>2</sub>-VASc Scores

### Adjusted Stroke Rate (% per y)

<table>
<thead>
<tr>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt;</th>
<th>CHA&lt;sub&gt;2&lt;/sub&gt;DS&lt;sub&gt;2&lt;/sub&gt;-VASc&lt;sup&gt;0&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive HF</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 y</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disease (prior MI, PAD, or aortic plaque)</td>
<td>2</td>
</tr>
<tr>
<td>Age 65–74 y</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (i.e., female sex)</td>
<td>1</td>
</tr>
<tr>
<td>Maximum score</td>
<td>9</td>
</tr>
</tbody>
</table>

J Am Coll Cardiol. 2014;64(21):2246-2280. doi:10.1016/j.jacc.2014.03.021
Validation of CHADS-VASc

1. Risk of LAA-related stroke

**CHA\textsubscript{2}DS\textsubscript{2}-VASc Scores: Not specific**

- **CHA\textsubscript{2}DS\textsubscript{2}-VASc** predicts risk of ischemic stroke in the ABSENCE of AF. *(Atherosclerosis. 2014 Dec;237(2):504-13.)*

- An assessment of LAA-related risk of stroke is necessary to decide on its closure.

When to anticoagulate patients with AF

- Benefits of stroke risk reduction must outweigh risks of bleeding.
- CHADS2 > 1
- CHADS-VASc ≥ 1 for men and ≥ 2 for women
Stroke prevention strategies

• Systemic anticoagulation
  – Warfarin
  – NOACs

• LAA closure
  – Watchman and other devices
  – Lariat
  – Atri-clip

• Selecting the right strategy requires individualization of risks/benefits!
# Novel Oral Anticoagulants (NOACs)

This chart is not based on a head-to-head trial and is not intended to suggest head-to-head comparisons of the separate trials or the therapies under study.


<table>
<thead>
<tr>
<th>Comparator</th>
<th>Dadigatran&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Rivaroxaban&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Apixaban&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Edoxaban&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total enrolled subjects</td>
<td>18,113</td>
<td>14,264</td>
<td>18,201</td>
<td>21,105</td>
</tr>
<tr>
<td>Trial design</td>
<td>Randomized, controlled, non-inferiority (doses of dabigatran were blinded)</td>
<td>Randomized, controlled, double-blind, non-inferiority</td>
<td>Randomized, controlled, double-blind, non-inferiority</td>
<td>Randomized, double-blind, double-dummy</td>
</tr>
<tr>
<td>Median duration of follow-up</td>
<td>2 years</td>
<td>1.94 years</td>
<td>1.8 years</td>
<td>2.8 years</td>
</tr>
<tr>
<td>Average CHADS&lt;sub&gt;2&lt;/sub&gt; score</td>
<td>2.1</td>
<td>3.5</td>
<td>2.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Results (primary outcome = stroke or systemic embolism)</td>
<td>Reduction in primary outcome compared with warfarin</td>
<td>Reduction in primary outcome compared with warfarin</td>
<td>Reduction in primary outcome compared with warfarin</td>
<td>Noninferior to warfarin</td>
</tr>
</tbody>
</table>
Preventing Strokes in AF patients
Individualizing Risk: 4 questions

• 1. What are the causes of stroke risk in this patient?
  • AF-related vs AF unrelated stroke
  • LAA-related vs LAA unrelated

• 2. What are the risks of stroke prevention strategies?
  • Bleeding risk
  • Hemorrhagic stroke risk
  • Procedural risk

• 3. Are there benefits of anticoagulation besides preventing LAA thrombus in AF?

• 4. What is the prior patient’s experience on anticoagulation?
1. Risk of LAA-related stroke
CHA$_2$DS$_2$-VASc Scores: Not specific

<table>
<thead>
<tr>
<th>CHA$_2$DS$_2$-VASc score</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 year-old (1)</td>
<td></td>
</tr>
<tr>
<td>Female (1)</td>
<td></td>
</tr>
<tr>
<td>Diabetic (1)</td>
<td></td>
</tr>
<tr>
<td>Hypertensive (1)</td>
<td></td>
</tr>
<tr>
<td>Ca score of 450 (1)</td>
<td></td>
</tr>
<tr>
<td>Persistent AF for 2 years</td>
<td></td>
</tr>
<tr>
<td>TEE prior to cardioversion showing LAA thrombus, resolved 1 month later</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHA$_2$DS$_2$-VASc score</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 year-old (1)</td>
<td></td>
</tr>
<tr>
<td>Prior strokes (2)</td>
<td></td>
</tr>
<tr>
<td>Ischemic cardiomyopathy with CHF (1)</td>
<td></td>
</tr>
<tr>
<td>Extensive, mobile atheromatous plaque in the aortic arch (1)</td>
<td></td>
</tr>
<tr>
<td>Persistent AF post CABG, cardioverted without recurrence</td>
<td></td>
</tr>
</tbody>
</table>

Only patients with high LAA-related risk of stroke would benefit from closure
1. Risk of LAA-related stroke

CHA$_2$DS$_2$-VASc Scores: LAA vs Aortic plaque

- SPAF-TEE study: Of 332 High-risk AF patients with CHF, prior stroke, female sex, Age >75. (One or more)

```
10
20
30
40
50
60
70
80
75.3
74.7

30
3
4.5
18.2

35
4
4
15.8

LAA thombus/contrast  Complex aortic plaque
```

Prevalence  RR  Stroke Risk  Warfarin  Reduction

LAA-related stroke risk?

Extreme LAA Features

LA appendage closure

Endovascular

Epicardial

Courtesy of Randall Lee, MD
Risks of Stroke Prevention
Warfarin vs Watchman

Risks of Stroke Prevention
Bleeding on Warfarin vs Watchman

Definition of bleeding: Serious bleeding event that required intervention or hospitalization according to adjudication committee

HR = 0.29
p<0.001
71% Relative Reduction In Major Bleeding after cessation of anti-thrombotics

Are there benefits of anticoagulation beyond the LAA?

  - 65% of strokes in atrial fibrillation classified as cardioembolic.
  - Up to 25% of strokes can be related to intrinsic cerebrovascular disease

- AF associations “procoagulant systemic state”:

- 4. Are there other diagnoses: DVT, PE
Making decisions

- Extreme risk: LAA thrombus, other diagnoses requiring anticoagulation
- First choice
  - Financial constraints
  - Stable INRs
  - No bleeding
  - Good tolerance
- Bleeding
- Stroke on anticoagulation
- Poor tolerance
- Hemorrhagic stroke
- Procedural candidacy
- High LAA-risk

NOACs  Warfarin  Watchman
Role of LAA in atrial fibrillation

- Source of thromboembolic events
- Source of atrial fibrillation triggers/substrate
  - Autonomic innervation
  - Reentrant circuits
  - AF Triggers
- Source of atrial natriuretic peptide
  - Potential role in fluid retention post-ligation or post-ablation
LAA automaticity
Yamada *Heart Rhythm* 2008 5:766-767
Localized LAA reentry
VOM bypassing Mitral Isthmus
Briceño D, Valderrábano M. Circ Arrhythmia Electrophysiol 2014
LAA AF triggers
Circulation. 2009;120:S690–S691

- Up to 30% of recurrent AF patients with persistent AF had LAA triggers
- LAA isolation—but not focal ablation—effective.
LAA triggers were observed in 21 (0.3%) subjects (age 60 ± 9 years; 57% males; 52% persistent AF). Twenty (95%) patients were undergoing repeat ablation. The LAA was the only nonpulmonary vein trigger in 3 patients; the remaining 18 patients had both LAA and other nonpulmonary vein triggers.
Longstanding Persistent AF: Left atrial appendage isolation?

**CENTRAL ILLUSTRATION:** Lesion Set With and Without Empirical LAA Electrical Isolation

Group 1: LAA Empirical Electrical Isolation

Group 2

Group 1: LAA Empirical Electrical Isolation

Group 2

Of the 93 patients who had transesophageal echocardiography (TEE), preserved left atrial appendage (LAA) function was reported in 45 (48.4%) patients, whereas an impaired contractile pattern was observed in 48 (51.6%).
Unexpectedly High Incidence of Stroke and Left Atrial Appendage Thrombus Formation After Electrical Isolation of the Left Atrial Appendage for the Treatment of Atrial Tachyarrhythmias

Andreas Rillig, MD*; Roland R. Tilz, MD, FHR*; Tina Lin, MBBS, BMedSci, FRACP; Thomas Fink, MD; Christian-H. Heeger, MD; Anita Arya, PhD, MBBS; Andreas Metzner, MD; Shibu Mathew, MD; Erik Wissner, MD, FHR; Hisaki Makimoto, MD, PhD; Peter Wohlmuth, PhD; Karl-Heinz Kuck, MD, FESC, FHR; Feifan Ouyang, MD

Background—Electric left atrial appendage (LAA) isolation (LAAI) may occur during catheter ablation of atrial tachyarrhythmias. Data regarding the risk of thromboembolic events and stroke after LAAI are sparse. This study evaluated the incidence of LAA thrombus formation and thromboembolic events after LAAI.

Methods and Results—Fifty patients had LAAI (age=71 years; female=56%; CHA₂DS₂-VASc score before ablation =3 [2;3]). LAAI patients were compared with matched patients with comparable baseline characteristics who underwent atrial fibrillation ablation without LAAI (n=50). Ablation strategies in the LAAI group included pulmonary vein isolation in 50 (100%), left atrial isthmus line in 47 (94%), anterior line in 45 (90%), complex atrial fractionated potentials in 24 (48%), and roofline in 14 (28%) patients. Transesophageal echocardiography was performed during follow-up in 47/50 (94%) patients in the LAAI group and in all patients of the control group. Oral anticoagulation (OAC) independent of CHA₂DS₂-VASc score was strongly recommended in all patients. During a median follow-up of 6.5 (4–12) months, stroke occurred in 2 patients on OAC and transient ischemic attack in one without OAC in the LAAI group. In the remaining 47 patients, LAA thrombus was identified on transesophageal echocardiography in 10 (21%) patients (OAC=9; no OAC=1). In the control group, no LAA thrombus was detected and no stroke occurred (P<0.001). Stable sinus rhythm was maintained in 32 patients (64%) of the LAAI group after a median follow-up of 6.5 months (4–12), including 17/32 patients on antiarrhythmic drugs.

Conclusions—After LAAI, an unexpectedly high incidence of LAA thrombus formation and stroke was observed despite OAC therapy. (Circ Arrhythm Electrophysiol. 2016;9:e003461. DOI: 10.1161/CIRCEP.115.003461.)
The price of LAA isolation

- 50 patients with LAA isolation
- 2 CVA, 1 TIA
- In remainder 47 patients, LAA thrombus was identified on transesophageal echocardiography in 10 (21%) patients (OAC=9; no OAC=1).
After LAA isolation

• If TEE shows LAA velocity >40 cm/s
  – No CVA
• If LAA velocity < 40
  – Off anticoagulation
  CVA risk 16.7%
  – Reduced by LAA closure

Does ablation reduce stroke?

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>Disabling Stroke*</th>
<th>Any Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ablation Group (n=1108)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30 days after ablation</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>&gt;30 days after ablation</td>
<td>51</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td>Never ablated (n=102)</td>
<td>7</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>58</td>
<td>3</td>
<td>27</td>
</tr>
</tbody>
</table>

| **Drug Therapy Group (n=1096)**|       |                   |            |
| ≤30 days after initiating drug | 0     | 1                 | 3          |
| >30 days after initiating drug | 67    | 6                 | 35         |
| Never started drug therapy (n=4)| 0     | 0                 | 1          |
| **Total**                      | 67    | 7                 | 39         |

| **Drug Group Patients Who Crossed Over to Ablation (n=301) **|       |                   |            |
| Patients with event prior to crossover | --    | 0                 | 5          |
| Patients with event after crossover    | 7     | 0                 | 7          |
Amaze trial

PVI + LARIAT

PVI
Conclusions

• The LAA is a critical structure in atrial fibrillation
  • As a source of thromboembolism
    • Not the only one
    • Treated with OAC
    • Treated with LAA exclusion
  • As a source of AF maintenance
    • Triggers
    • Reentry
    • Innervation
    • Treated with LAA isolation
      • Increased risk of OAC dependence
      • Requires LAA occlusion