Novel Concepts in Left Atrial Appendage Closure Devices: Improving Safety and Efficacy

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Disclosures

• Consultant and/or Grant support:

  * I have an equity stake in these companies

• I will be discussing devices that are not FDA-approved or have CE-Mark, and are investigational.
• Can’t embolic strokes originate from outside the LAA?
• Issue of stroke severity
• Are there any new LAAC outcome data?
  ▶ What is forthcoming?
• Post-Implant Follow-Up Strategy (TEE Strategy)
• Advances in Technology & Techniques

**Non-Cardioembolic Stroke:** No evidence that (N)OACs provide any greater benefit than ASA

**TEE / CV Study**
- Non-valvular atrial fibrillation or flutter
  - n = 1,420
  - Atrial thrombosis = 87 patients (6.13%)
- 98% of left-sided thrombi are in the LAA

**Warfarin vs ASA**
- **WARSS / WASID** \( \triangleq \) ASA ≈ Warfarin
- **NAVIGATE-ESUS** \( \triangleq \) ASA ≈ Rivaroxaban 15mg
- **RESPECT-ESUS** \( \triangleq \) ASA ≈ Dabigatran
- **ATTICUS** (Compare Apixaban vs ASA)

**Stroke or SE**
**Stroke Severity in (N)OAC & LAAC Trials**

**Non-Disabling vs Disabling/Fatal**

### PROTECT-AF & PREVAIL:

- LAAC was non-inferior to VKAs for stroke

### Stroke Severity

- Warfarin & NOACs: ~50% disabling/fatal
- Post-LAAC strokes ~25% disabling/fatal

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**HR & p-value**

<table>
<thead>
<tr>
<th>Stroke Type</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stroke or SE</td>
<td>0.96</td>
<td>0.9</td>
</tr>
<tr>
<td>Ischemic stroke or SE</td>
<td>1.7</td>
<td>0.08</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.2</td>
<td>0.0022</td>
</tr>
</tbody>
</table>

**Hazard Ratio (95% CI)**

- Favors WATCHMAN (0.01-0.1)
- Favors warfarin (1-10)

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Ischemic Stroke Severity in LAAC vs OAC

Comparison of MRS Scores

LAAC

- European ACP multicenter registry (N=1,047, Dec 2008 – Nov 2013)
- Occurrence of stroke (N=24)

VKAs

- YONSEI Stroke Registry (N=429, Jan 2013 – Jan 2017)
- Occurrence of stroke (N=68)

Ischemic Strokes are more severe when occurring in the presence of Oral Anticoagulation

Mean MRS Score

Efficacy of LAAC in Stroke Prevention

Recent Registry Data: CAP (5 yr) / CAP2 (2 yr) & EWOLUTION (2 yr)

Ischemic Strokes in CAP

n = 566 pts

Ischemic Strokes in CAP2

n = 579 pts


Efficacy of LAAC in Stroke Prevention
LAAC FDA Studies & Large Multicenter Registries

Graph adapted from data from: Friberg. Eur Heart J (2012); NICE UK (2014)

TOTAL ~ 4,500 pts

- CAP
  - n=566; F/U = 5 yrs
- CAP2
  - n=579; F/U = 2 yrs
- EWOLUTION
  - n=1,021; F/U = 1 yr
- WASP
  - n=201; F/U = 1 yr
- ACP Registry
  - n=1,047; F/U = 1 yr
- AMULET Registry
  - n=1,088; F/U = 1 yr
Efficacy of LAAC in Stroke Prevention
CMS Claims Data (n=13,627)

Efficacy of LAAC in Stroke Prevention

**PRAGUE-17: RCT of LAAC vs NOACs**

- *PRAGUE-17* (NCT02426944) was an investigator-initiated, multicenter, open-label, randomized non-inferiority trial
  - Conducted in **10 Czech Cardiac Centers**
  - Funded by the Czech Ministry of Health

- RCT of NOACs vs LAAC

- Non-valvular AF + one of the following:
  1. History of **bleeding** requiring intervention or hospitalization, or
  2. History of a **cardioembolic event** while taking anticoagulation, or
  3. **CHA\textsubscript{2}-DS\textsubscript{2}-VASc ≥ 3** & **HAS-BLED ≥ 2**

- **Primary Endpoint**
  - Stroke / TIA, SE, CV Death, Major Bleed/CRNMB, Complications

## PRAGUE-17 Trial

### Baseline Characteristics (n = 402 pts)

<table>
<thead>
<tr>
<th></th>
<th>NOAC (n = 201)</th>
<th>LAAC (n = 201)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>73.2 ± 7.2</td>
<td>73.4 ± 6.7</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>130 (64.7%)</td>
<td>134 (66.7%)</td>
</tr>
<tr>
<td>AF type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal (%)</td>
<td>67 (33.3%)</td>
<td>53 (26.4%)</td>
</tr>
<tr>
<td>Persistent (%)</td>
<td>46 (22.9%)</td>
<td>47 (23.4%)</td>
</tr>
<tr>
<td>LS persistent (%)</td>
<td>16 (8.0%)</td>
<td>18 (9.0%)</td>
</tr>
<tr>
<td>Permanent (%)</td>
<td>72 (35.8%)</td>
<td>83 (41.3%)</td>
</tr>
<tr>
<td>CHA$_2$DS$_2$-VASc</td>
<td>4.7 ± 1.5</td>
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</tr>
<tr>
<td>CHA$_2$DS$_2$-VASc ≥ 6 (%)</td>
<td>54 (26.9%)</td>
<td>56 (27.9%)</td>
</tr>
<tr>
<td>HAS-BLED</td>
<td>3.0 ± 0.9</td>
<td>3.1 ± 0.9</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>90 (44.8%)</td>
<td>88 (43.8%)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>186 (92.5%)</td>
<td>186 (92.5%)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>90 (44.8%)</td>
<td>73 (36.3%)</td>
</tr>
<tr>
<td>History of cardioembolic event (%)</td>
<td>69 (34.3%)</td>
<td>73 (36.3%)</td>
</tr>
<tr>
<td>History of MI (%)</td>
<td>39 (19.4%)</td>
<td>30 (14.9%)</td>
</tr>
<tr>
<td>History of bleeding/bleeding predisposition</td>
<td>95 (47.3%)</td>
<td>109 (54.2%)</td>
</tr>
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Treatment characteristics

LAAC & NOAC Arms

**LAAC arm**
- 14 (7.0%) did not undergo the procedure
- Procedure was successful in **96.8%** (181/187) of procedure attempts
- Used: **Amulet-61%, Watchman-36%** or Watchman-Flex-3%
- Post-LAAC Antithrombotic regimen: **DAPT in 82%**
- **Complications**: in 9 pts **(4.8%)** including:
  - One procedure-related death (groin hematoma, vascular surgery, MI)
  - One device-related death (late pericardial tamponade)

[ **Operator experience**: 40% = 0 cases & Only 1 operator > 100 cases ]

**NOAC arm**
- **Apixaban** used in 192 patients **(95.5%)**
**PRAGUE-17: Primary Endpoint**

**Cumulative Incidence Function (mITT Population)**

**Gray’s test:** $p = 0.44$

**Subdistribution HR:** $0.84 \ (0.53 - 1.31), \ p = 0.44$

**Non-inferiority:** $p = 0.004$

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<td>$0.84 \ (0.53 - 1.31)$</td>
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<td>Per Protocol</td>
<td>$0.82 \ (0.52 - 1.30)$</td>
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<td>$0.75 \ (0.34 - 1.62)$</td>
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<td>$0.81 \ (0.44 - 1.52)$</td>
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<td>Non-Procedure Bleeding*</td>
<td>$0.53 \ (0.26 - 1.06)$</td>
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Mean follow-up: $20.8 \pm 10.8 \text{ mo (695 pt-yr)}$


PRAGUE-17: Primary Endpoint
Cumulative Incidence Function (Per Protocol Population)

Gray’s test: \( p = 0.40 \)
subdistribution \( HR = 0.82 \ (0.52-1.3) \)
Non-inferiority: \( p = 0.003 \)

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Mean follow-up: 20.8 ± 10.8 mo (695 pt-yr)
PRAGUE-17: Primary Endpoint
Cumulative Incidence Function (On-Treatment Population)

Gray’s test: $p = 0.31$
Subdistribution HR: 0.79 (0.49 – 1.25)
Non-inferiority: $p = 0.013$

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Mean follow-up: 20.8 ± 10.8 mo (695 pt-yr)
Secondary Endpoint: All Stroke/TIA
Cumulative Incidence Function (mITT Population)

Mean follow-up: 20.8 ± 10.8 mo (695 pt-yr)
Secondary Endpoint: Cardiovascular Death
Cumulative Incidence Function (mITT Population)

Mean follow-up: 20.8 ± 10.8 mo (695 pt-yr)

* Incorporates the 2 LAAC deaths
Secondary Endpoint: Bleeding
Cumulative Incidence Function (mITT Population)

sHR: 0.53, p = 0.07

Primary Endpoint
mITT 0.84 (0.53 – 1.31) 0.44
Per Protocol 0.82 (0.52 – 1.30) 0.40
On-Treatment 0.79 (0.49 – 1.25) 0.31
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CV Death 0.75 (0.34 – 1.62) 0.46
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* Major + CRNM Bleeding

Mean follow-up: 20.8 ± 10.8 mo (695 pt-yr)
PRAGUE-17

Conclusions

• Among high-risk AF patients, LAAC was noninferior to NOACs in preventing major cardiovascular or neurological events.

• Safety issues remain with LAAC, warranting further refinements in operator technique and device technology.

• Limitation: PRAGUE-17 was insufficiently powered to separately evaluate differences in the “safety” and “efficacy” components of the primary endpoint (e.g., stroke/death, bleeding).
LAA Closure
Randomized Clinical Trials

- “Absolute” Contraindications to OACs
  - ASAP-TOO: FDA Trial
  - STROKECLOSE

- “Relative” Contraindications to OACs
  - PROTECT-AF / PREVAIL
  - PRAGUE-17
  - CLOSURE-AF / OCCLUSION-AF
  - WATCH-TAVR: TAVR vs TAVI

- No Contraindications (LAA Closure as an alternative to OAC)
  - OPTION: After AF ablation, LAAC vs NOAC
  - CATALYST (Abbott): FDA Trial of LAAC
  - CHAMPION-AF (BSCI): FDA Trial of Watchman vs OAC

**ASAP-TOO**

CH\(A_2\)DS\(_2\)-VASc \(\geq 2\)

Contraindication to OAC

Randomization (2:1)

- Watchman (DAPT x 3 mo)
- Control (ASA)

**Endpoint:** Isch Stroke / SE

Goal Enrollment = 888
Current Enrollment = 428
LAAC vs NOAC

**CATALYST:** FDA Randomized Clinical Trial

- Multicenter, multinational RCT
- Randomization, 1:1 Amulet vs NOACs
- Key Inclusion Criterion
  - \( \text{CHA}_2\text{DS}_2\text{-VASc} \geq 3 \) (tentative)
- Total sample size \( \sim 2650 \) patients (tentative)
- Enrollment at \( \sim 150 \) centers

- Primary Endpoints (tentative):
  - Isch Stroke / SE / CV Mortality (non-inferiority)
  - Major Bleed / CRNMB (non-superiority)
  - Non-procedure MB / CRNMB (superiority)

- Trial enrollment expected in \( \sim 2 \) months
What is the Optimal Time for the Follow-Up TEE?

Results of a Two-Center Analysis

- What is the purpose of the TEE?
  - Assess for closure to determine whether to continue OAC
  - Assess for device-related thrombus (DRT)

- 2-Center retrospective study: Strategy of TEE at 4 months
  - 521 Patients: Warfarin – 26%, NOACs – 55%, DAPT – 19%
  - Median f/u = 12mo 17 ischemic strokes / 6 TIs

Peri-Device Leaks After LAAC

Obliteration with Coils □ In whom should this be employed?
Novel LAAC Devices for Stroke Prevention
Status in the United States

- **PINNACE-FLX** (Watchman-FLX): Data to be presented soon (HRS)
- **E** (Amulet vs Watchman): In follow-up
- **IDE** (Watchman vs Watchman-FLX): Recruiting
- **EF**

18 strut frame (vs 10)

Recessed metal screw on proximal face
Novel LAAC Devices for Stroke Prevention
Status in the United States

- **PINNACE-FLX** (Watchman-FLX): Data to be presented soon (? HRS)
- **AMULET IDE** (Amulet vs Watchman): In follow-up
- Wavecrest IDE (Wavecrest vs Watchman): Recruiting
- Conformal: EFS IDE Ongoing
Novel LAAC Devices for Stroke Prevention
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The Transeptal Puncture
Making the Difficult Case Easy ... or *Vice Versa*

Windsock
Chicken Wing

Low-Posterior
Low-Anterior

Low-Posterior
Low-Anterior