Left Atrial Appendage Occlusion – What is New in 2022?

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and CVC: CardioVascular Center Frankfurt, Frankfurt, Germany
Agenda

• Indications and Procedure
• The new Watchman FLX system
• Procedural outcomes/complications

• Data
  • Comparison to NOAC
  • Specific subsets
  • New trial available at Swedish (CHAMPION AF trial)
Indications

The WATCHMAN Device is indicated to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on CHADS$_2$ or CHA$_2$DS$_2$-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for warfarin; and
- Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

WATCHMAN is NOT intended to be a broad replacement for Oral Anticoagulants (OAC)
CMS will cover percutaneous LAAC implants when specific criteria are met:

- Eligible patients must have a CHADS<sub>2</sub> score ≥ 2 or a CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥ 3
- Patients must be suitable for short-term warfarin, but deemed unable to take long-term oral anticoagulation
- Documented evidence of a formal shared decision interaction between the patient and an independent non-interventional physician using an OAC evidence-based decision tool
- **LAA Registry**: Patients must be enrolled in a prospective national registry
- **Operator requirements**: IC or EP or cardiovascular surgeon must have performed at least 25 transseptal punctures (TSP) through intact septum
  - Must maintain at least 25 TSP over a two year period (at least 12 are LAAC)
- **Facility Requirements**: The procedure must be furnished in a hospital with an established structural heart disease (SHD) and/or electrophysiology (EP) program
Why does this work?

• Nonvalvular atrial fibrillation
  • Valvular = mechanical mitral valve or rheumatic mitral stenosis
    • 50% of clots from the left atrial appendage
    • 50% of clots from the left atrium

• Nonvalvular = anything else
  • 90-95% of clots come from the appendage
  • 5-10% from the left atrium

• So can closing the appendage decrease risk of stroke?
Who are people that likely can’t be on long-term blood thinners?

- Prior bleeding (melena, hematochezia, hematuria, orthopedic, CNS)
- Frailty (Falls, walker, unsteadiness)
- Anemia
- Use of other medications (antiplatelet agents)
Animation
Key aspects of the procedure

• Procedure under general anesthesia with TEE
• 14 Fr venous sheath (4.3 mm)
• Transseptal access, heparinize to ACT > 250
• Device closure
• Access site closure with perclose
• Recovery
  • Echo at 3 hours
  • End bedrest at 4 hours
  • Home same day majority of cases
• Followup
  • TEE evaluation at 45 days – check for leak or thrombus
Antiplatelet/Anticoagulation protocols
We use mostly PROTECT-AF or ASAP protocol
How do I decide?

- If patient is on anticoagulant prior to use same anticoagulant. DOAC preferred.

- If patient not on anticoagulant prior to use ASAP protocol

- This was confirmed in meta-analysis by Li et al. J Int Med Res 2020
  - 32 studies – 4474 patients
  - Adverse events – mortality, CV mortality, DRT formation,
  - Higher risk with single antiplatelet, then DAPT, then VKA, then DOAC
Watchman vs. Watchman FLX (new in 2020)

- **Watchman**
  - 10 Strut Frame (8%-20%)
  - Less Exposed Metal

- **Watchman FLX**
  - 18 Strut Frame (10%-30%)
  - Shorter Frame Length
  - Closed Distal End
What do these design changes mean

- Reduced height: Shallow/complex anatomies
- Closed distal end: Atraumatic Repositioning
- More hooks: Better anchoring
- More fabric: Better sealing
- Recessed screw: Less DRT

**Design Changes from WATCHMAN to WATCHMAN FLX**

- Two rows of 'J' shaped anchors
  - 18 total anchors (vs. 10)
- 'Straight' anchor
  - (WM Gen 2.5)
- 'J' anchor

**WATCHMAN 27mm**
- More distal PET fabric coverage

**WATCHMAN FLX 27mm**
- Recessed metal screw on proximal face
- 18 strut frame (vs. 10)
Outcomes: Efficacy and Safety
2002 Pilot
N=66
Non-randomized
Feasibility and Safety

2008 CAP Registry
N=566
Non-randomized
Add'l patients and follow-up

2010 PREVAIL
N=407
Randomized
Comparison: warfarin

2005 PROTECT AF
N=707
Randomized
Comparison: warfarin

2009 ASAP
N=150
Non-randomized
Real-world, All comers

2012 CAP2 Registry
N=576
Non-Randomized
Add'l patients and follow-up

2013 EWOLUTION, WASP Registries
N=1020, N=201
Non-randomized
Real-world, All comers

2013 US NESTed NCDR LAAO Registry
N=2000
Post-approval statistical analysis

2016 SALUTE
N=42
Non-randomized
Japanese Approval Study

2017 WATCH-TAVR
N=312
Randomized
TAVR+WATCHMAN

2017 ASAP TOO
N= Up to 888
Randomized
US Indication Expansion
Worldwide study

2018 PINNACLE FLX
N=400
Non-randomized
FLX Device
US IDE

2019 OPTION
N=1600
Ongoing study in post-ablation patients
Randomized
Efficacy and Bleeding
Comparison: OAC
FLX Device

2019 FLXibility
N=300
Non-randomized
EU Post-Market Registry
FLX Device

2020 CHAMPION-AF
N= ~3000
Randomized,
WATCHMAN FLX vs.
NOACs in a broader NVAF population,
inclusive of lower risk patients

*Not US Indication

Ongoing DATA – 2.5 going to FLX
Expanding indications & continuing to evaluate WATCHMAN FLX

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Ongoing DATA – 2.5 going to FLX
Expanding indications & continuing to evaluate WATCHMAN FLX
Implant Success above 98%

Consistent with recent WATCHMAN studies, PINNACLE FLX showed favorable implant success.
OAC Discontinuation in Perspective

PINNACLE FLX

96%

WATCHMAN FLX device and DOAC 45-days post-procedure

CAP2
93%

PREVAIL
92%

CAP
96%

PROTECT AF
87%

WATCHMAN device and Warfarin 45-days post-procedure

Doshi, SK. Presented at HRS 2020.
## 12-Month CEC-Adjudicated Major Clinical Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of Events</th>
<th>12-Month Kaplan-Meier Event Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>25</td>
<td>6.6%</td>
</tr>
<tr>
<td>Cardiovascular/Unknown Death</td>
<td>16</td>
<td>4.4%</td>
</tr>
<tr>
<td>All Stroke</td>
<td>10</td>
<td>2.6%</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>10</td>
<td>2.6%</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Transient Ischemic Attack</td>
<td>1</td>
<td>0.3%</td>
</tr>
<tr>
<td>Systemic Embolism</td>
<td>1</td>
<td>0.3%</td>
</tr>
<tr>
<td>Device Embolization</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>PE Requiring Open Cardiac Surgery</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>PE Requiring Pericardiocentesis or Pericardial Puncture</td>
<td>4</td>
<td>1.0%</td>
</tr>
<tr>
<td>Major Bleeding (BARC 3 or 5)</td>
<td>31</td>
<td>7.9%</td>
</tr>
<tr>
<td>BARC 3 bleeding</td>
<td>29</td>
<td>7.4%</td>
</tr>
<tr>
<td>BARC 5 bleeding</td>
<td>2</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

*Secondary efficacy endpoint of ischemic stroke and systemic embolism will be evaluated at 24 months*

*Event rates from the PINNACLE FLX Trial are reported as Kaplan-Meier estimates, not rate per 100 patient years. This is different from previous WATCHMAN trials, due to the relatively small sample size (n=400) and limited duration of follow-up*
Timing of Pericardial Effusions and Ischemic Strokes

- Ischemic Stroke
- Pericardial Effusion Requiring Pericardiocentesis

Days Post-Implant:

- 0 45 90 135 180 225 270 315 360

PE resulted from AF ablation procedure

Successful Implant
Implant Attempt

Doshi, SK. Presented at HRS 2020.
Primary Safety Endpoint in Perspective

Major Procedural Complications within 7 Days Across Trials

Low event rates in the PINNACLE FLX trial demonstrated the safety of the WATCHMAN FLX device, when compared to the consistently low rates observed in previous WATCHMAN trials.

Major Procedural Complication defined as: death, ischemic stroke, systemic embolism, or device/procedure-related events necessitating cardiac surgery or major endovascular intervention within either 7-days post-implant or hospital discharge, whichever occurred later.

Device-related thrombus: bark worse than bite

- **Risk factors**
  - Long-standing nonparoxysmal atrial fibrillation
  - Evidence of dense spontaneous echocontrast
  - Large LAA diameters at ostium

- **But not always associated with stroke/systemic embolism (Dukkipati Circulation 2018)**
  - 1739 patients, DRT in 65 pts (3.74%), Stroke/systemic embolism in 142 pts
  - DRT and SSE in 17/65 pts (26% of DRT population, 0.97% of total subset)
  - Showed up 47% of time at 1m, 63% by 6m. So 37% happened after 6m period
  - Rate of stroke/systemic embolism with DRT 7.46/100 py, w/o DRT 1.8/100py
  - Yet overall – most stroke/systemic embolism happened without DRT (87%)
A Favorable Outlook for Device Related Thrombus with FLX device

Note: In all cases of DRT detection, patients were on DAPT or ASA

Doshi, SK. Presented at HRS 2020.
**DRT – Detection and Timing**

All patients were on DAPT or ASA at time of DRT detection.

2 subjects with DRT experienced an ischemic stroke or SE.

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1. **DRT was identified during pre-ablation TEE for a planned PVI**
2. **Thrombus was identified on the device during post-mortem exam**

Doshi, SK. Presented at HRS 2020.
Causes of stroke after LAAO - my algorithm

• From left atrium
  • 90-95% from LAA, but 5-10% of clots from left atrium itself
• Leak around device
  • Leak of > 5 mm associated with stroke, can consider closure
• Transseptal puncture
  • If residual leak present, was there a R to L shunt?
• Device-related thrombus
  • TEE or CT, consider 2-3m course of anticoagulation
Comparison to NOAC
# PRAGUE-17
A randomized trial of percutaneous LAAC versus DOAC agents in high-risk atrial fibrillation patients

<table>
<thead>
<tr>
<th>Study Objective</th>
<th>To compare LAAC with DOAC in high risk AF patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>Prospective, multicenter, open-label, randomized non-inferiority trial</td>
</tr>
</tbody>
</table>
| Primary Endpoint| Composite of:  
* Stroke or TIA  
* Systemic embolism  
* Clinically-significant bleeding*  
* Cardiovascular death, or  
* Significant peri-procedural or device-related complications |
| Patient Population | 415 |
| Number of Sites | 10 Cardiac Centers in the Czech Republic |
| Follow-up | 6 weeks, 3 months, 6 months, 9 months, 12 months, then every 6 months |
| Status | Enrolling Complete |

### LAAC
Amulet or Watchman/Watchman FLX**

- **Post-implant antithrombotic treatment:**
  - DAPT for 3 months: aspirin (100 mg/day) + clopidogrel (75 mg/day)
  - 3 month TEE; discontinue clopidogrel
  - Continue aspirin indefinitely

*Regimen could be individualized if needed*

### DOAC
Rivaroxaban, Apixaban, or Dabigatran at manufacturer-recommended dose.

*Apixaban preferred*

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61% of LAAC procedures in this trial were performed with Abbott's Amulet LAA occlude
**The WATCHMAN FLX devices used in this study were of an older generation than what is currently available in the European market**
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>DOAC (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>Average CHA₂DS₂-VASc</td>
<td>4.7 ± 1.5</td>
<td>4.7 ± 1.5</td>
</tr>
<tr>
<td>HAS-BLED</td>
<td>3.0 ± 0.9</td>
<td>3.1 ± 0.9</td>
</tr>
<tr>
<td>Paroxysmal AF</td>
<td>67 (33.3%)</td>
<td>53 (26.4%)</td>
</tr>
<tr>
<td>History of cardioembolic event (%)</td>
<td>69 (34.3%)</td>
<td>73 (36.3%)</td>
</tr>
<tr>
<td>History of bleeding/bleeding predisposition</td>
<td>95 (47.3%)</td>
<td>109 (54.2%)</td>
</tr>
</tbody>
</table>

*61% of LAAC procedures in this trial were performed with Abbott’s Amulet LAA occluder
**The WATCHMAN FLX devices used in this study were of an older generation than what is currently available in the European market*
LAAC Non-Inferior to DOAC for Primary Endpoint

Results of this trial show that LAAC is non-inferior to DOACs for the treatment of NVAF.

*61% of LAAC procedures in this trial were performed with Abbott’s Amulet LAA occluder

Specific subsets

- CKD and Dialysis patients
  - HD: avoid coumadin, consider rivaroxaban 10 or apixaban 2.5 (De Vriese Nephrol Dial Transplant 2021)
  - HD: LAAO patients had reduced bleeding (HR 6.5) and mortality (HR 2.0).

- Cerebral Amyloid Angiopathy
  - Schrag Transl Stroke Res 2021 – safe and tolerable

- No issues with cardioversion (Sharma et al. JACC 2019)
What else is new?

• Same day discharge is feasible and safe (a byproduct of Covid)

• Use of CT and intracardiac echocardiography can avoid transesophageal echocardiography and general anesthesia

• Combined procedure trials – LAA and TAVR, LAAO and ablation

• Expanded indication to CHADSVASc 2 in men using DOAC
CHAMPION-AF

Global Head-to-Head RCT comparing the safety & efficacy of WATCHMAN FLX to NOACs in a broader NVAF population, inclusive of lower risk patients

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<tr>
<th>Study Design</th>
<th>Prospective, randomized 1:1 (WATCHMAN FLX vs NOAC), multi-center, global</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrollment</td>
<td>3,000 NVAF patients at 150 global sites</td>
</tr>
</tbody>
</table>
| Primary Endpoints* | • 1st Primary Endpoint: Occurrence of stroke (including ischemic and/or hemorrhagic), cardiovascular (CV) death (including unexplained death), and systemic embolism at 36 months. (non-inferiority)  
• 2nd Primary Endpoint: Non-procedural bleeding (ISTH major bleeding and clinically relevant non-major bleeding) at 36-months. (superiority)  
• 3rd Primary Endpoint: Occurrence of ischemic stroke and systemic embolism at 60 months (non-inferiority) |
| Imaging      | Intraprocedural: TEE or ICE**  
Follow-Up: TEE or CT at 4-month follow-up*** |
| Follow-Up    | 3 months, 4 months (Imaging), 12 months, 24 months, 36 months, 48 months, 60 months |
| Study Duration | 36-month and 60-month primary endpoints; 5-year study follow-up |
| Status       | Enrolling                                                               |

* If a NOAC patient meets a primary endpoint, there is an option to cross over from NOAC to WATCHMAN FLX

**If ICE is used, TEE or CT pre-planning is required and operator must have performed ≥ 25 WM/WM FLX procedures with ICE

***TEE is recommended. If findings suspicious for significant DRT or PDL is noted on CT, a TEE must be performed to determine therapy required
Patient has documented non-valvular atrial fibrillation (i.e., atrial fibrillation in the absence of moderate or greater mitral stenosis or a mechanical heart valve)

CHA$_2$DS$_2$-VASc score of $\geq 2$ or for men and $\geq 3$ or for women

Patient is deemed to be suitable for long-term NOAC

Notable changes compared to commercially implanted patients

Patient is not required to have a reason to seek a non-pharmacologic alternative to NOAC

There is no requirement for documented shared decision-making

Device patients should not be included in the NCDR-LAAO Registry
CHAMPION-AF
Expanding post-implant drug regimen options – we modify these as well

Post Procedure Therapy

<table>
<thead>
<tr>
<th>Current US</th>
<th>CHAMPION-AF</th>
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</thead>
<tbody>
<tr>
<td>OAC +/- ASA</td>
<td>NOAC + ASA or DAPT</td>
</tr>
<tr>
<td>Clopidogrel + ASA daily</td>
<td>ASA (80-110mg) daily</td>
</tr>
</tbody>
</table>

Destination Therapy

<table>
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<tr>
<th>Current US</th>
<th>CHAMPION-AF</th>
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<tr>
<td>ASA (80-110mg) daily</td>
<td>ASA (80-110mg) daily</td>
</tr>
</tbody>
</table>

45 days* 

6 months

3-Months

*discontinue OAC only if 45-day TEE shows seal ≤ 5mm
Key Points - I

• Indication: for patients with CHADSVASc 3 or more with problems with anticoagulation (falls/frailty/anemia/bleed)
• Anticoagulation regimen can be modified based on risk
• LAAO Is safe ‡ 0.5% risk of major adverse event
• LAAO Is effective ‡ 98% ability to come off of anticoagulation
Key Points - II

• LAAO Watchman FLX device is true iteration that improves safety
• Subsets of CKD, cerebral amyloid, cardioversion, gender, low LVEF, prior bleed, all benefit
• CHAMPION-AF trial for expanded indication of CHADSVASc 2 and NOAC use.