The Watchman FLX Pro Coating: Development of HEMOCOAT Technology
WATCHMAN FLX Pro Device

Built on the proven performance of the WATCHMAN FLX platform, the Next Gen WATCHMAN FLX is designed to improve the healing response, simplify placement, while further expanding the treatable patient population.

**Design Goals**

**Hemocompatible Coating**
Reduce the severity of acute foreign body response, encouraging controlled healing

**40mm Size**
Expand matrix to treat the largest range of patient anatomies

**Radiopaque Markers**
Increase fluoroscopic visibility for positioning & deployment

---

Meeting an Unmet Need:

HEMOCOAT™ Intro & Background
Why coat an LAAC device?

Thrombin Generation in LAAC patients

A


The HEMOCOAT Story...

‘What if we coated the WATCHMAN with PVDF?’

Yen-Lane Chen
Corporate Distinguished Fellow (Retired),
Boston Scientific

2019
HEMOCOAT™ Technology
A Teflon-like Polymer Coating

PVDF-HFP:
Poly(vinylidene-fluoride-co-
hexafluoropropylene)

A fluorinated copolymer

Stable
Non-active
Non-eluting

Established
A robust history of safe use on permanently implanted, blood-contacting medical devices

Effective?
Prior to FLX Pro, no data on PVDF-HFP coated devices without drug


The Development of HEMOCOAT

Coating Technology
How do we assess the coated device on the bench?

Animal Study Design
Does it heal differently?

Histology
Why does it heal differently?
How do we assess the coated device on the bench?

- Coated and uncoated fabric tested in bovine blood
  - Thrombus growth monitored over time
Human Blood Flow Loop Results

- PVDF-HFP-coated devices developed significantly less thrombus on the proximal surface of the device than uncoated devices.

Uncoated

PVDF-HFP-coated

![Graph showing % Thrombus Coverage over t = 4 hours](chart)

The Development of HEMOCOAT

Coating Technology: How do we assess the coated device on the bench?

Animal Study Design: Does it heal differently?
The Challenge In Vivo Experiment

“What if we implant in a thrombogenic animal for 3 days?”

Animal Study Design

3 Day Dog Study (Non-anticoagulated)

Uncoated

Coated

Mobile Thrombus

Thin, Laminar Thrombus Coverage
How does HEMOCOAT impact healing?

- Coating Technology
  - How do we assess the coated device on the bench?
- Animal Study Design
  - Does it heal differently?
- Histology
  - Why does it heal differently?

Is all thrombus created equal?

- Histology
  - “Is it good thrombus or bad thrombus?”
…first, back to the coating process...

Coating Technology

Why does the HEMOCOAT work so well with the WATCHMAN fabric?

Patented Interaction with Multifilament Polyester Fabric

United States Patent

Kangas et al.

Patent No.: US 11,484,320 B2

Date of Patent: Nov. 1, 2022

Reference Cited

U.S. PATENT DOCUMENTS

2016/0134642 A1
2010/0155417 A1
2010/0155417 A1
2015/0053809 A1
2012/0241372 A1
2013/0231472 A1

FOREIGN PATENT DOCUMENTS

EP

1440702 A2
1529165 A2

(Continued)
More Coated Surface with HEMOCOAT

~4x as much surface area with multifilament structure

Monofilament Structure

Multifilament Structure

FIG. 5

FIG. 6

HEMOCOAT Technology in Action

Multifilament PET Fabric Causes Coating to Wick In and Coat All Surfaces

Watchman Fabric

Dyed Coating Solution

FLX Pro Device with 0.007% Fluorescent Dye
Is all thrombus created equal?

“Is it good thrombus or bad thrombus?”

Uncoated vs Coated Histology at 3 days

3 day dog study, no OAC or APT

Uncoated

Inflammatory cell nuclei (purple dots) around uncoated fabric bundles

Coated

Minimal inflammatory cells around coated fabric bundles
Multifilament Structure Amplifies Benefits of HEMOCOAT

FIG. 6

Minimal inflammatory cells around coated fabric bundles

But wait, does it heal completely?

Animal Study Design

“A nonthrombogenic coating will never heal”
-Management
How did we test the coated device?

45 day In Vivo Challenge Animal Model

- N = 12 canines received an LAAC device
  - 6 Uncoated
  - 6 Coated
- No antiplatelets or anticoagulants given to dogs post-implant
- Intermediate TEE follow-ups at 14 and 28 days to image thrombus on device

<table>
<thead>
<tr>
<th>Implant</th>
<th>2 weeks</th>
<th>4 weeks</th>
<th>6 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEE</td>
<td>TEE</td>
<td>TEE</td>
<td>TEE</td>
</tr>
</tbody>
</table>

D-Dimer (baseline) → D-Dimer

2 week TEE Follow-Up

<table>
<thead>
<tr>
<th>Uncoated</th>
<th>Coated</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
</tr>
<tr>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
</tr>
<tr>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
</tr>
</tbody>
</table>
2-week TEE Follow-Up: Raised Thrombus Highlighted (red)

**Uncoated**
- 6/6 with DRT > 3 mm

**Coated**
- 1/6 with DRT > 3 mm

45 Day Explants (Post-Fixation)

**Uncoated**
- 2/6 exhibit complete coverage/healing

**Coated**
- 6/6 exhibit complete coverage/healing
Coated Device: Faster Healing in Challenging In Vivo Model

Canine model (no OAC, no APT)

3 days 14 days 28 days 45 days

Uncoated

Coated

Thinner layer of provisional thrombus on coated device

Thrombus already resolving at 14 days in coated group

Near complete endothelial coverage at 30 days on coated device

Complete endothelialization on coated device in challenge in vivo model

Uncoated

Coated

~25% endothelialized

~70% endothelialized

~50% endothelialized

Faster, more complete healing may reduce DRT, simplify post-implant drug regimen

WATCHMAN FLX™ Pro Features HEMOCOAT™ Technology

Designed to Enhance Healing While Reducing DRT

~50% Increase in endothelial coverage at 45 days.

~50% endothelialized

~70% endothelialized

100% endothelialized

COATED

6/6 exhibit complete coverage/healing at 45 days

UNCOATED

2/6 exhibit complete coverage/healing at 45 days

*Challenged non-anticoagulated canine model. Not representative of clinical results
Device Related Thrombus After Left Atrial Appendage Occlusion

- Jai Parekh
• Left atrial appendage occlusion (LAAO) has emerged as an attractive alternative to oral anticoagulation in patients with non-valvular atrial fibrillation

• Although many studies have confirmed the safety and efficacy of LAAO, certain issues remain with the procedure

• Device-related thrombus (DRT) continues to represent a conundrum because of the uncertainties surrounding its prediction, detection and management

• There is no unified definition of DRT; a thorough review of the major LAAO trials’ protocols reveals no consensus definition of DRT underscoring the ambiguity of its interpretation in literature

• Accurate diagnosis of DRT is critical to avoid thromboembolic complications, whereas overdiagnosis might lead to irrelevant intensified anti-coagulation with an increased risk of bleeding

Imaging assessment of DRT

In a retrospective study of the PROTECT AF trial, an expert panel developed 5 criteria for the diagnosis of DRT on TEE. These included an echo density on the left atrial aspect of the device

• not explained by imaging artifact
• inconsistent with normal healing or device incorporation
• visible in multiple transesophageal echocardiographic planes
• in contact with the Watchman device
• exhibiting independent motion
### Device-Related Thrombus After Left Atrial Appendage Occlusion

**Table:**

<table>
<thead>
<tr>
<th>Grade 0</th>
<th>Subfibrous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Sessile ≤ 3 mm</td>
</tr>
<tr>
<td></td>
<td>+ LA wall continuity</td>
</tr>
<tr>
<td></td>
<td>+ Smooth surface</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Sessile &gt; 3 mm</td>
</tr>
<tr>
<td></td>
<td>+ LA wall continuity</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Pendunculated</td>
</tr>
</tbody>
</table>

**Cardiac CT following Watchman FLX implantation:**

- **Clinical results:** Hypoattenuated thinning (HAT) seen on 58/264 (22%) of all scans.
- **Study cohort:** 244 Watchman FLX patients.

**Preclinical results:** Successful Watchman FLX implantation in all coronary (48).
Incidence, Predictors & Clinical Impact of DRT

- The incidence of DRT varies considerably among published studies because of the variability in the frequency and standardization of post-LAAO surveillance imaging.

- In PROTECT AF and PREVAIL trials, the incidence of DRT was 3.7% (65 of 1,739) at 7,159 patient-years of follow-up.

- In the prospective PINNACLE FLX registry, DRT after LAAO with the second-generation Watchman FLX device was diagnosed within 12 months in 7 of 400 patients (1.7%).

- In a meta-analysis of 10,154 patients who underwent post-LAAO surveillance imaging in 66 studies, the pooled incidence of DRT was 3.8% (351 of 10,153).


In the meta-analysis by Alkhouli et al involving 66 studies, the DRT diagnosis was made at <90, 90 to 365, and >365 days in 42%, 57%, and 1% of patients, respectively.

- <90 days: 42%
- 90-365 days: 57%
- >365 days: 1%

The majority of DRTs (85%) were discovered after more than 45 days, suggesting that the currently recommended LAA surveillance at 45 days is inadequate.

In the 2 pivotal WATCHMAN RCTs and their nested registries, 29% of DRTs were detected on unscheduled TEE examinations conducted for other reasons, despite the robust LAA surveillance protocols (routine TEEs at 45, 180, and 365 days in the RCTs and at 45 and 365 days in the continuous access registries).

This implies that even frequent routine surveillance will likely miss a non-negligible percentage of DRTs and highlights the challenges of determining an optimal surveillance protocol following LAAO.
### Table 1: Independent Predictors of DRT After LAOO

<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Population</th>
<th>Patient Factors</th>
<th>Procedural Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaneko et al. (2019)</td>
<td>Single-center analysis (n = 78)</td>
<td>CHA2DS2-VASC score</td>
<td>Deep device implantation</td>
</tr>
<tr>
<td>Dalpupiti et al. (2018)</td>
<td>Ad hoc analysis of PROTECT AF and PREVAIL (n = 1,729)</td>
<td>LAA orifice width, permanent AF, prior TIA, LVEF, vascular disease</td>
<td></td>
</tr>
<tr>
<td>Pracan et al. (2018)</td>
<td>Single-center analysis (n = 92)</td>
<td>Prior stroke/TIA, permanent AF, LVEF</td>
<td>Device size, deep device implantation</td>
</tr>
<tr>
<td>Fauchier et al. (2018)</td>
<td>Multicenter registry (France) (n = 469)</td>
<td>Age, prior stroke/TIA</td>
<td>No OAC or APT post-LAAO</td>
</tr>
<tr>
<td>Amnisio et al. (2019)</td>
<td>Prospective global Amulet registry (n = 1,016)</td>
<td>LAA orifice width</td>
<td></td>
</tr>
<tr>
<td>Simard et al. (2021)</td>
<td>Global DRT registry (n = 711)</td>
<td>Hypercoagulopathy, permanent AF, renal insufficiency</td>
<td>Percardial effusion, deep device implantation</td>
</tr>
<tr>
<td>Sedaghat et al. (2020)</td>
<td>EWOLUTION prospective Watchman registry (n = R35)</td>
<td>Permanent AF</td>
<td></td>
</tr>
<tr>
<td>Schmidt et al. (2022)</td>
<td>Ad hoc analysis of the Amulet IDE trial (n = 1,908)</td>
<td>Age, female, permanent AF</td>
<td></td>
</tr>
<tr>
<td>Vlij et al. (2022)</td>
<td>Multicenter registry (EUROC-DRT)</td>
<td>Age, prior stroke/TIA, HAS-BLED score, spontaneous echocardiographic contrast</td>
<td></td>
</tr>
<tr>
<td>Freixa et al. (2023)</td>
<td>Multicenter registry (Europe and Canada) (n = 1,317)</td>
<td></td>
<td>Deep device implantation, no or single APT post-LAAO</td>
</tr>
</tbody>
</table>

**Figure 1:** Risk Score

- **A:** Risk Score for Predicting Device-Related Thrombus (DRT) Formation
- **B:** Cardiac Risk Factors in DRT Score

**Major Risk Factors:**
- Hypercoagulable state
- Renal insufficiency

**Minor Risk Factors:**
- Deep LAOO implant (>10mm from pulmonary ridge)
- Non-paroxysmal AF

**Predictors of Device-Related Thrombus Following Percutaneous Left Atrial Appendage Occlusion.** Simard et al. JACC 2021
Antithrombotic therapy

The incidence of device-related thrombosis and the anticoagulation protocol in the key trials of the WATCHMAN device

<table>
<thead>
<tr>
<th>Trial/study</th>
<th>Population</th>
<th>Follow up</th>
<th>Anticoagulation</th>
<th>DRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROTECT-AF [8]</td>
<td>707</td>
<td>18 months</td>
<td>Warfarin and aspirin (81 mg) for 45 days, then aspirin (81-325 mg) &amp; Clopidogrel for 6 months followed by aspirin</td>
<td>4.2%</td>
</tr>
<tr>
<td>PREVAIL trial [9]</td>
<td>407</td>
<td>18 months</td>
<td></td>
<td>Not reported</td>
</tr>
<tr>
<td>CAP [10]</td>
<td>566</td>
<td>50 months</td>
<td></td>
<td>2.6%</td>
</tr>
<tr>
<td>CAP2 [10]</td>
<td>578</td>
<td>50 months</td>
<td></td>
<td>3.9%</td>
</tr>
<tr>
<td>Dukkipati, Srinivas R et al. [21]</td>
<td>1379</td>
<td>na</td>
<td></td>
<td>3.7%</td>
</tr>
<tr>
<td>Kubo, Shurosake et al. [22]</td>
<td>119</td>
<td>1,456±546 days</td>
<td></td>
<td>3.4%</td>
</tr>
<tr>
<td>EWOLUTION [13,14]</td>
<td>1020</td>
<td>24 months</td>
<td>warfarin (16%) DOACs (11%) DAPT (60%) SAPT (7%) no anticoagulation (62%)</td>
<td>4.1%</td>
</tr>
<tr>
<td>ASAP [12]</td>
<td>150</td>
<td>14.4±8.6 months</td>
<td>Clopidogrel for 6 months and aspirin for life</td>
<td>4%</td>
</tr>
<tr>
<td>Enomoto Y [16]</td>
<td>426</td>
<td>NOAC vs. Warfarin</td>
<td>0.9% vs. 0.5%, P=1</td>
<td>0%</td>
</tr>
<tr>
<td>Böösche, Leif I et al. [15]</td>
<td>45</td>
<td>417±323 days</td>
<td>NOAC vs. DAPT</td>
<td></td>
</tr>
</tbody>
</table>
Device-Related Thrombus After Left Atrial Appendage Occlusion. Alkhelf et al. JACC Nov 2023
Thank You!