
# Transcatheter LAA Occlusion: More than Anticoagulation-Title: Time to Intervene!

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# Disclosures

- Research Grants: St Jude Medical, Boston Scientific, Gore
- International Proctor: Boston Scientific, Gore Medical,  St Jude Medical
- EC Committee: CLOSURE I trial

# Introduction

- Thrombus arrising in the Left atrial appendage is the major cause of stroke in patients with atrial fibrillation (AF)
- Long term ntithrombotic therapy is the standard of care for prevention of stroke in AF patients
- Percutaneous closure of the left atrial appendage(LAA) is alternative to long term antithrombotic therapy
  - Lower LAA clot formation
  - Lower  long term risk of bleeding

# Prevention of stroke in AF: Treatment Options

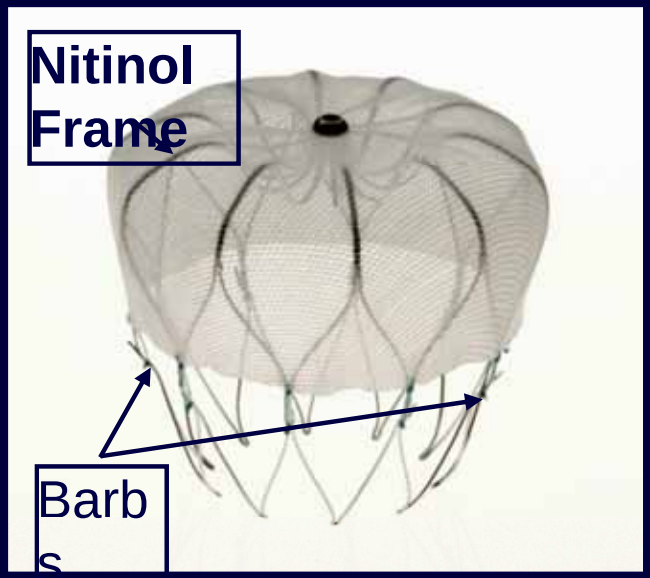
- Long Term antithrombotic therapy
  - Coumadin therapy
  - New oral anticoagulants: Dabigatran, Rivaroxaban, Apixaban
  - Antiplatelet agents
- Surgical Amputation or Ligation of LAA
- Percutaneous Occlusion of the LAA

# New Oral Agents versus Coumadin

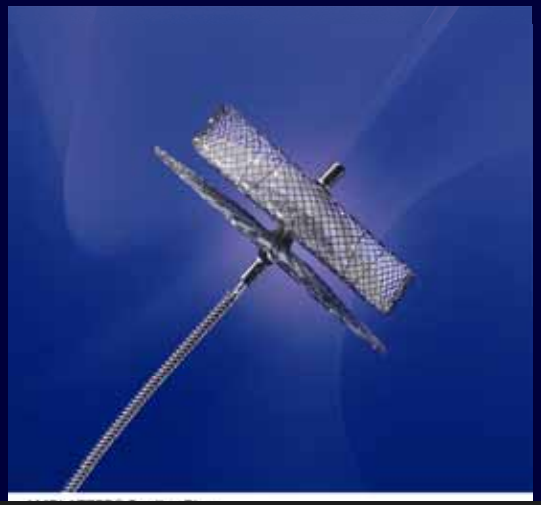
***There is no free lunch:***
***If it prevents clots, it will bleed***

- Overall bleeding risk is similar
  - IC bleed is lower than coumadin
- Does not require frequent monitoring
- Shorter half life
- Drug intolerance equivalent or higher than coumadin
- Drug dosing in extreme body weight or renal failure patients is problematic

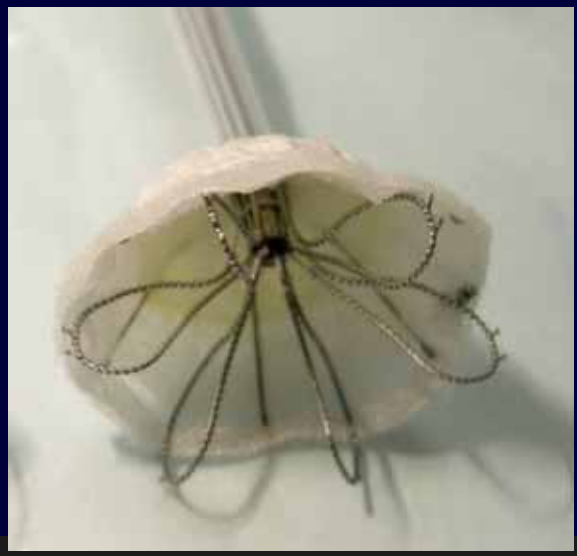
# LAA occlusion Devices (Endovascular approach)




*Watchman Device Gen II (Atritech) §*



*Amplatzer Cardiac Plug §*



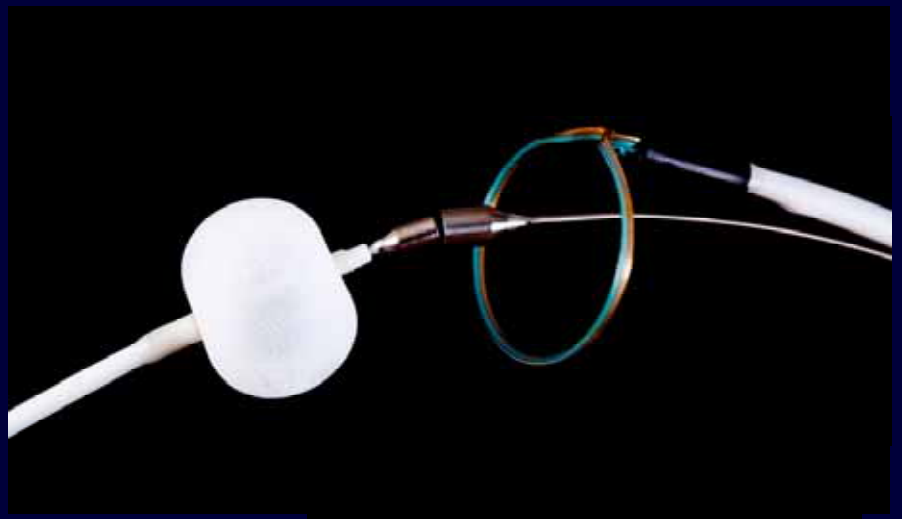
*WaveCrest Device (Coherex)#*

§ Investigational in US

# Investigational in Europe

# LAA occlusion Devices

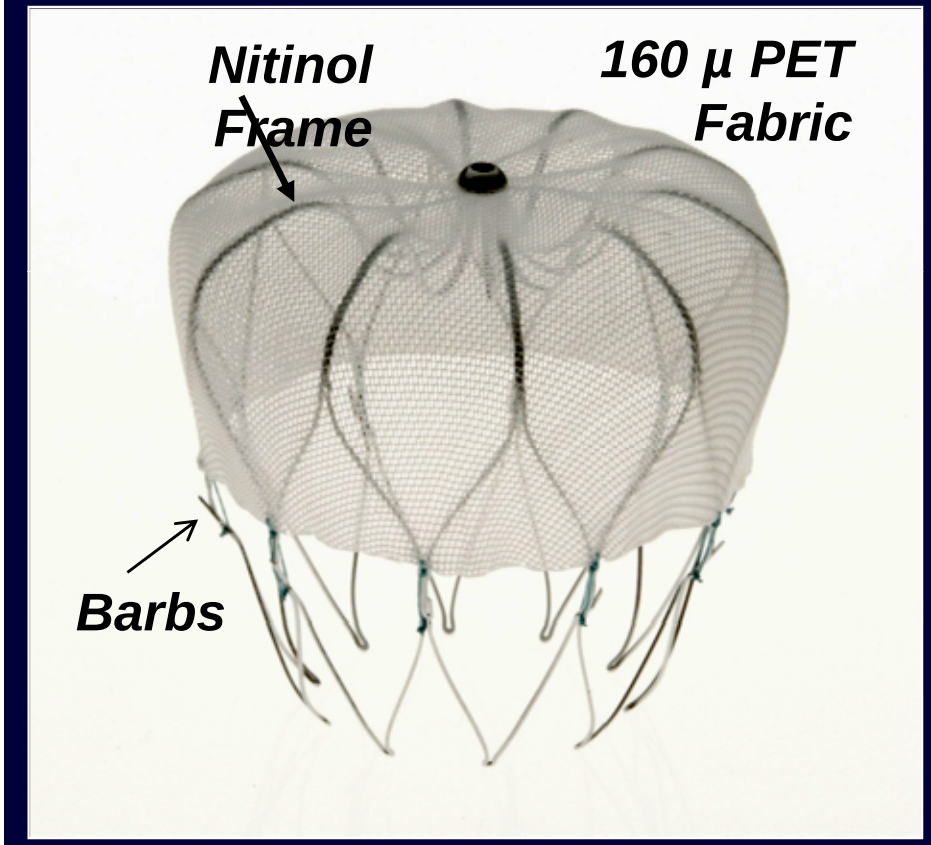
*Transpericardial approach*

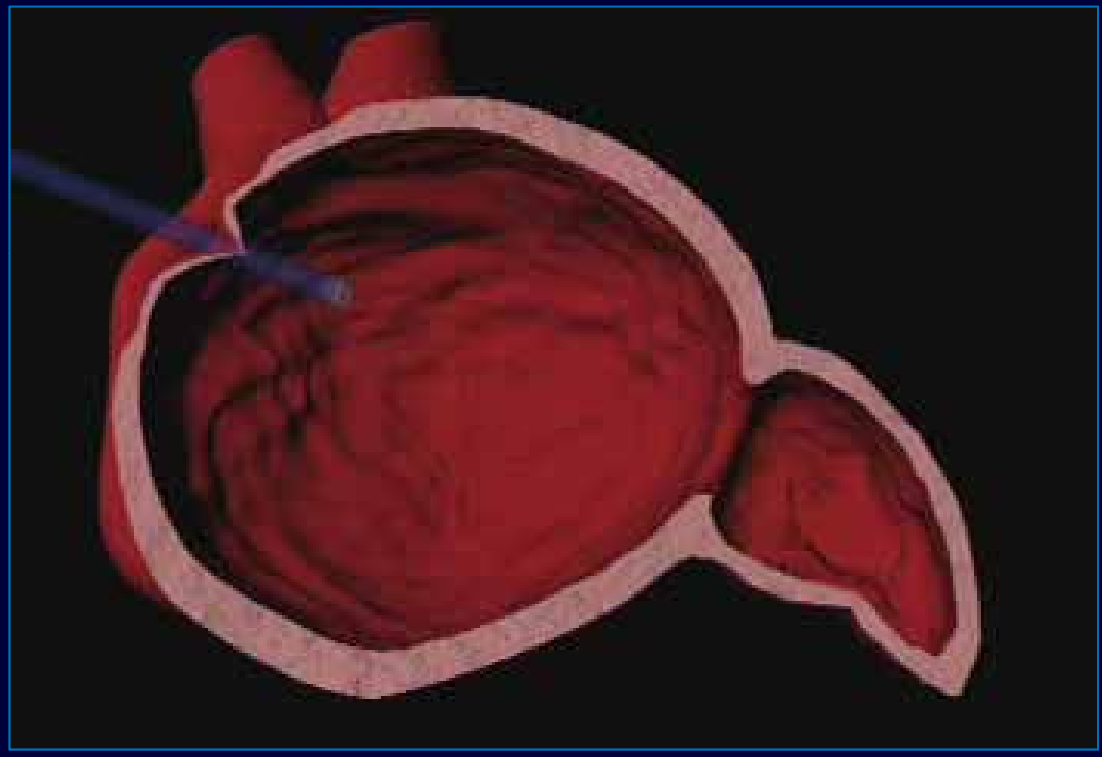


- **Lariat Device (Sentreheart)**


*Suture delivery device*

# WATCHMAN® Left Atrial Appendage Occluder System(Atritech Inc)



# Clinical Studies

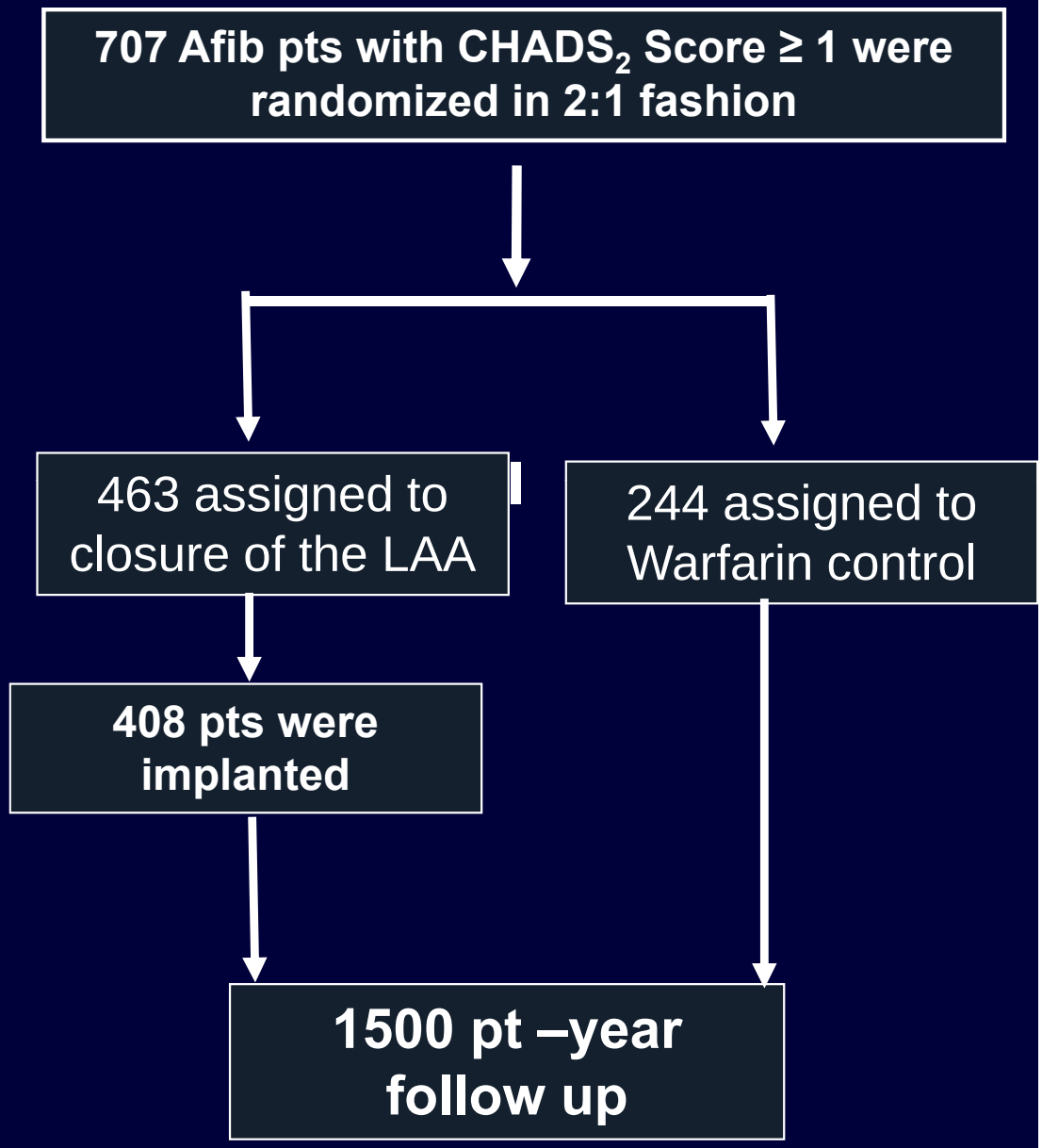
| STUDY | PATIENTS | SITES | COMMENTS |
|---|---|---|---|
| Pilot | 66 | 8 | • 318 patient years of follow-up<br>• 30 patients with 5+ years of follow-up |
| PROTECT AF | 800 | 59 | • 1,500 patient years of follow-up<br>• 27 months average follow-up per patient |
| Continued Access Registry (CAP) | 566 | 26 | • Significantly improved safety results |
| ASAP | 150 | 4 | • Treat patients contra-indicated for warfarin |
| EVOLVE | 69 | 3 | • Evaluate next generation WATCHMAN |
| PREVAIL | 400 | ≤50 | • Same endpoints as PROTECT AF<br>• Revised inclusion/exclusion criteria<br>• Initiate enrollment October 2010<br>• Enrollment completed in June 2012 |

TOTAL 2051

# PROTECT AF Trial

## Design

- **DESIGN**: Prospective randomized, non-inferiority trial of LAA closure versus coumadin in Afib pts for prevention of stroke
- **OBJECTIVE**: Effectiveness and Safety of LAA closure for prevention stroke in comparison to coumadin for afib pts
- **PRIMARY END POINT**: Composite end point of stroke, cardiovascular death or system embolisation
- **PRIMARY SAFETY END POINT:** Device embolization, Bleeding

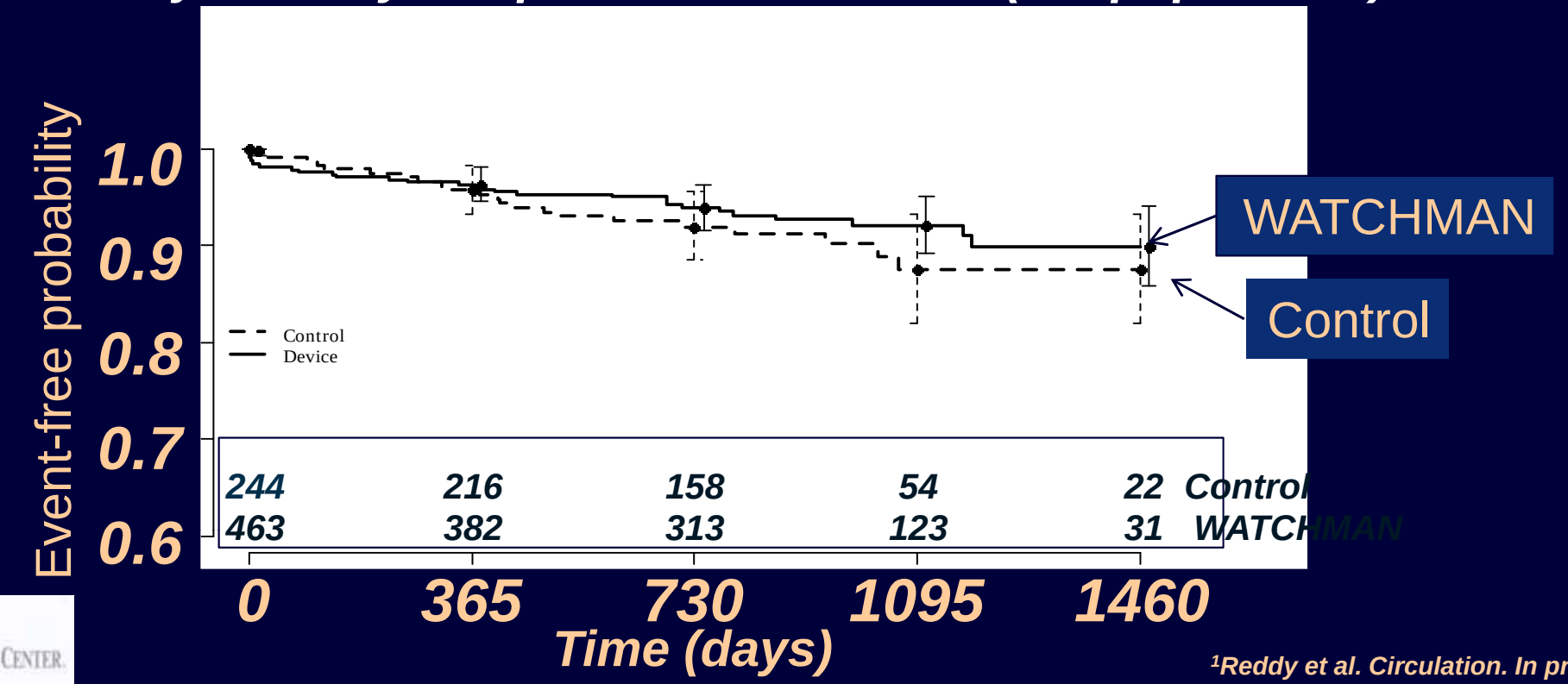


# PROTECT-AF Trial:
# LAA Closure is effective in stroke prevention

WATCHMAN was non-inferior to warfarin therapy for the prevention of stroke, cardiovascular death, or systemic embolism in patients with nonvalvular AF[1]

| Cohort 1500 Pt-Yrs | WATCHMAN Rate (Events/Pt-Yrs) | | CONTROL (warfarin) Rate (Events/Pt-Yrs) | | Relative Risk | 95% CI |
|---|---|---|---|---|---|---|
| Intention-To-Treat | 3.0 | 31/1025.7 | 4.3 | 24/562.7 | 0.71 | 0.44, 1.30* |
| Post-Procedure | 2.5 | 25/1015.7 | 4.3 | 24/562.7 | 0.58 | 0.35, 1.09 |

## Primary Efficacy Endpoint at 1500 Pt-Yrs (ITT population)




[1]Reddy et al. Circulation. In press.

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# PROTECT AF

## *Intent-to-Treat: Primary Safety Results*

| Cohort | WATCHMAN | Control | Relative Risk (95% CI) |
|---|---|---|---|
| | Rate (95% CI) | Rate (95% CI) | |
| 600 pt-yrs | 11.6(8.5, 15.3) | 4.1(1.9, 7.2) | 2.85(1.48, 6.43) |
| 900 pt-yrs | 8.7(6.4, 11.3) | 4.2(2.2, 6.7) | 2.08(1.18, 4.13) |
| 1065 pt-yrs | 7.4(5.5, 9.7) | 4.4(2.5, 6.7) | 1.69(1.01, 3.19) |
| 1350 pt-yrs | 6.2(4.7, 8.1) | 3.9(2.3, 5.8) | 1.60(0.99, 2.93) |
| 1500 pt-yrs | 5.5(4.2, 7.1) | 3.6(2.2, 5.3) | 1.53(0.95, 2.70) |

- Acute WATCHMAN events drove the rate at the first interim analysis; enrollment was ongoing and there was limited long-term follow-up
- Favorable long term WATCHMAN results lead to decrease over time; enrollment was completed, few late WATCHMAN events

# Protect AF
## Summary

- Protect AF trial was the first study that demonstrated that LAA closure was non inferior to long term anticoagulation in prevention of stroke
- There were certain safety issues of the procedure which decreased over time

# Safety of Percutaneous Left Atrial Appendage Closure
## Results from WATCHMAN LAA System for Embolic Protection in Patients with AF (PROTECT AF ) and the Continued Access Registry

*Reddy, Homes, Doshi, Neuzil, Kar*

***Circulaltion. 2011;123:417-424***.

# Performance Metrics

## *PROTECT AF vs CAP*

| | PROTECT AF | PROTECT AF | | CAP | p-value* | p-value± |
|---|---|---|---|---|---|---|
| | | Early | Late | | | |
| Procedure Time (Mean ± SD) | 62 ± 34 | 67 ± 36 | 58 ± 33 | 50 ± 21 | <0.001 | <0.001 |
| Implant Success | 485/542 (89.5%) | 239/271 (88.2%) | 246/271 (90.8%) | 437/460 (95.0%) | 0.001 | 0.001 |
| 45-day Warfarin Discontinuation Among Implanted | 414/478 (86.6%) | 194/235 (82.6%) | 220/243 (90.5%) | 352/371 (94.9%) | <0.001 | <0.001 |

*From tests comparing the PROTECT AF cohort with CAP
±From tests for differences across three groups (early PROTECT AF, late PROTECT AF, and CAP)

- Improvements seen over time in PROTECT AF
  - Shorter implant time, higher implant success rate, higher warfarin discontinuation rate
- Trends confirmed in CAP

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**Reddy, Holmes, Kar et al. Circulation 2011**

# Safety Event Rates

## *PROTECT AF vs CAP*

| | PROTECT AF | PROTECT AF | | CAP | p-value* | p-value± |
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| | | Early | Late | | | |
| Procedure/Device Related Safety Adverse Events within 7 Days | 42/542 (7.7%) | 27/271 (10.0%) | 15/271 (5.5%) | 17/460 (3.7%) | 0.007 | 0.006 |
| Serious Pericardial Effusions within 7 Days | 27/542 ***(5.0%)*** | 17/271 (6.3%) | 10/271 (3.7%) | 10/460 (**2.2%**) | 0.019 | 0.018 |
| Procedure Related Stroke | 5/542 ***(0.9%)*** | 3/271 (1.1%) | 2/271 (0.7%) | 0/460 ***(0.0%)*** | 0.039 | 0.039 |

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- Improvements seen over time for acute safety events
- Fewer total procedure/device related events

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# PROTECT AF

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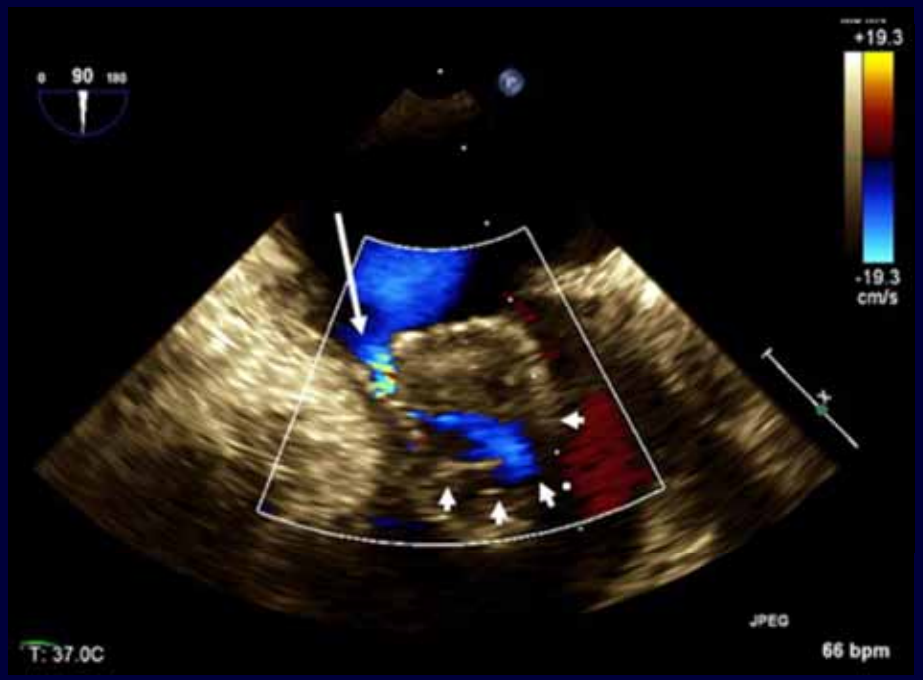
**Reddy, Holmes, Kar et al. Circulation 2011**

# Impact of incomplete LAA closure following Watchman Device

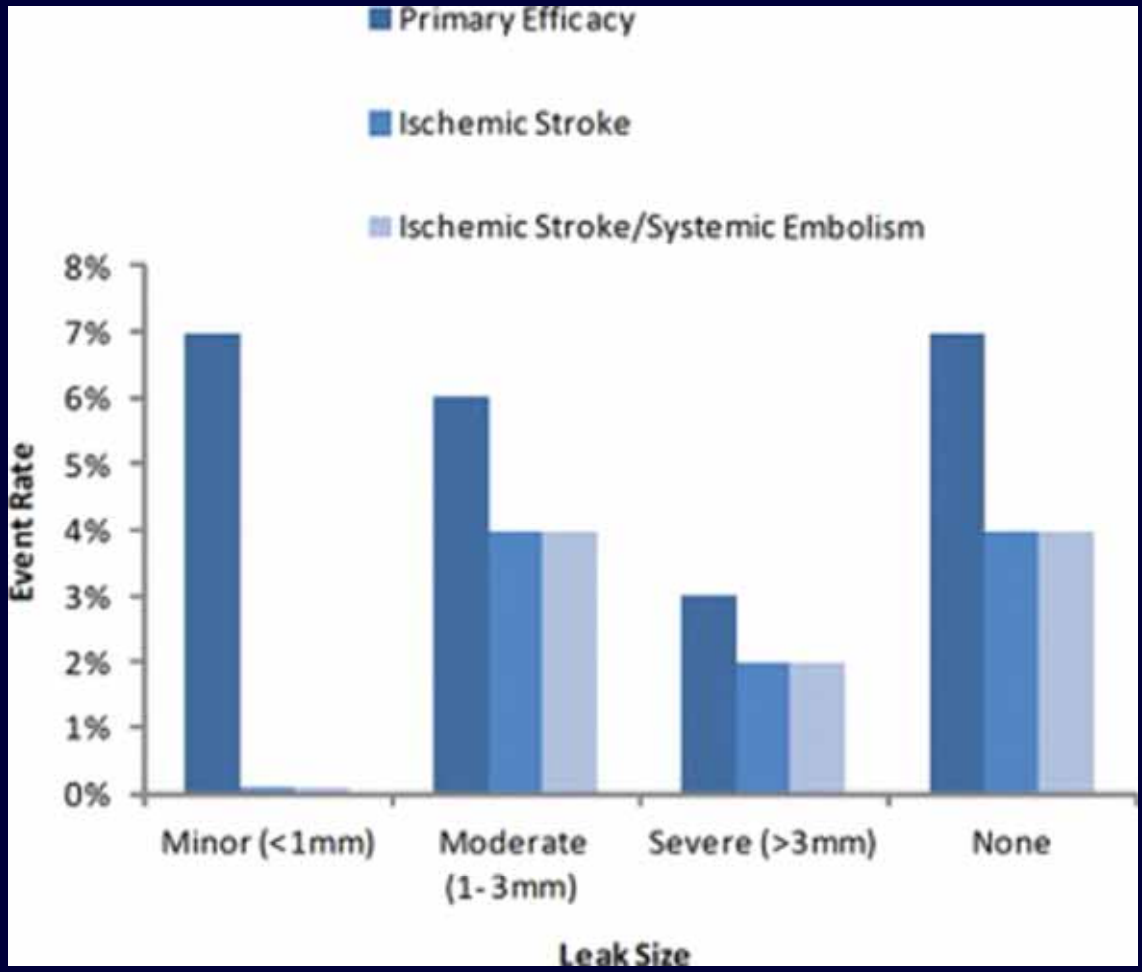
- Frequency and impact of peri-device leak
- 32% pts had small leak <5 mm
- Leaks < 5mm were graded in 3 categories




*Viles-Gonzalez, J. F. Kar S et al. J Am Coll Cardiol 2012;59:923-929*

# Primary Efficacy Endpoint Rates by Leak Severity

- Peri-device flow around the Watchman Device is common and does lead to increase in stroke or thromboembolism




*Viles-Gonzalez, J. F. Kar S, et al. J Am Coll Cardiol 2012;59:923-929*

# Results of Randomized Trial of LAA Closure vs Warfarin for Stroke/ Thromboembolic Prevention in Patients with Non-valvular Atrial Fibrillation (PREVAIL)


***David R. Holmes[1], Shephal Doshi[2], Saibal Kar[3], Jose Sanchez[4], Vijay Swarup[5], Brian Whisenant[6], Miguel Valderrabano[7], Kenneth Huber[8], Daniel Lustgarten[9], Vivek Reddy[10] on behalf of the PREVAIL investigators***

*[1]Mayo Clinic, Rochester, MN, USA, [2]Pacific Heart Institute / St. John's Health Center, Santa Monica, CA, [3]Cedars-Sinai Medical Center, Los Angeles, CA, [4]Mercy Heart and Vascular, St. Louis, MO, [5]Arizona Heart Rhythm Research Center, Phoenix, AZ, [6]Intermountain Medical Center, Murray, UT, [7]The Methodist Hospital Research Institute, Houston, TX, [8]Cardiovascular Consultants, PC, Kansas City, MO, [9]Fletcher Allen Health Care Inc., Burlington, VT, [10]Mount Sinai School of Medicine, Cardiology, New York, NY*

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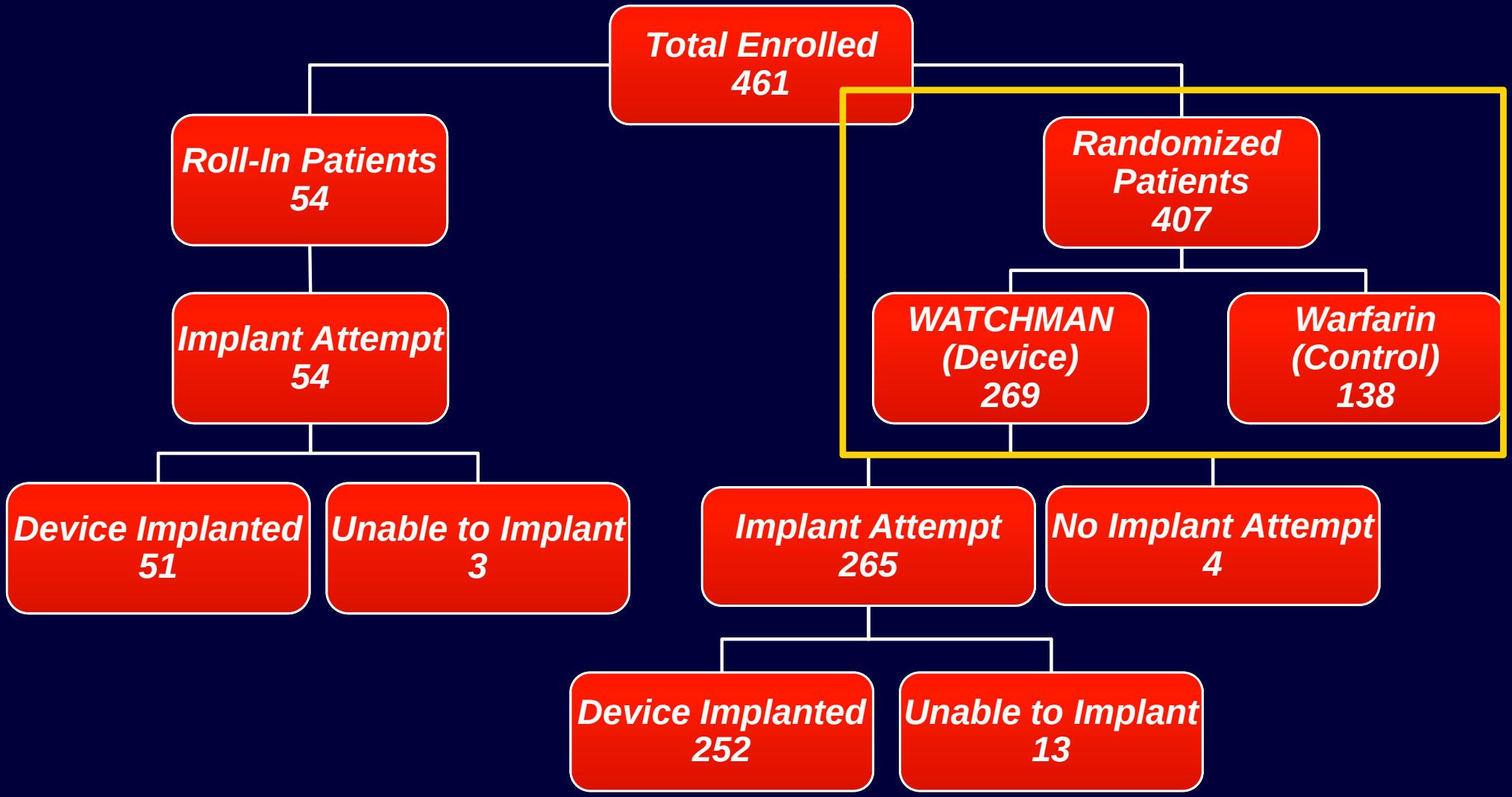
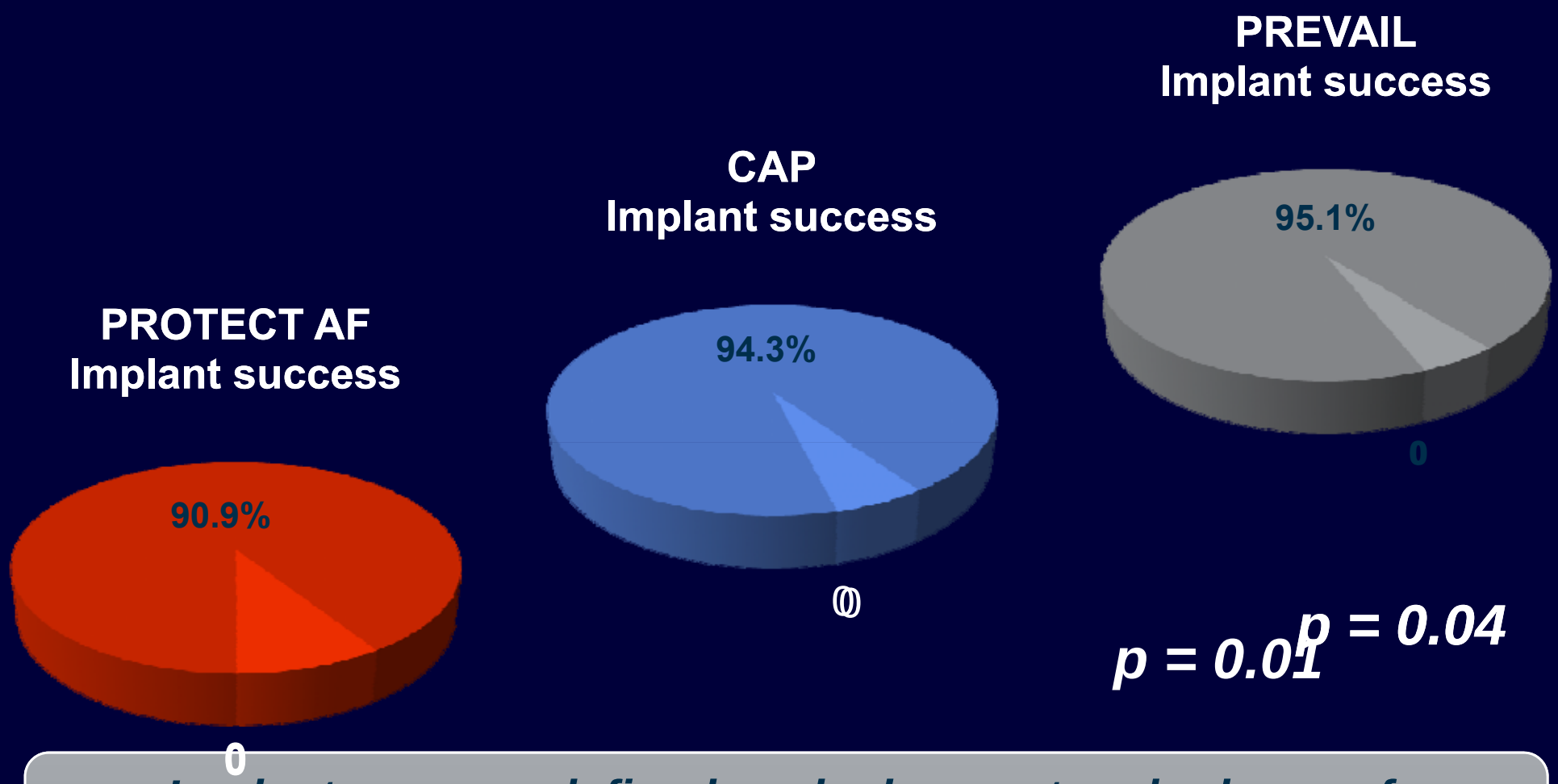
# Primary Endpoints

- Acute (7-day) occurrence of death, ischemic stroke, systemic embolism and procedure or device related complications requiring major cardiovascular or endovascular intervention
  - Timepoint = 7 days post randomization
- Comparison of composite of stroke, systemic embolism, and cardiovascular/unexplained death
  - Timepoint = 18 months
- Comparison of ischemic stroke or systemic embolism occurring >7 days post randomization
  - Timepoint = 18 months

# PREVAIL Enrollment



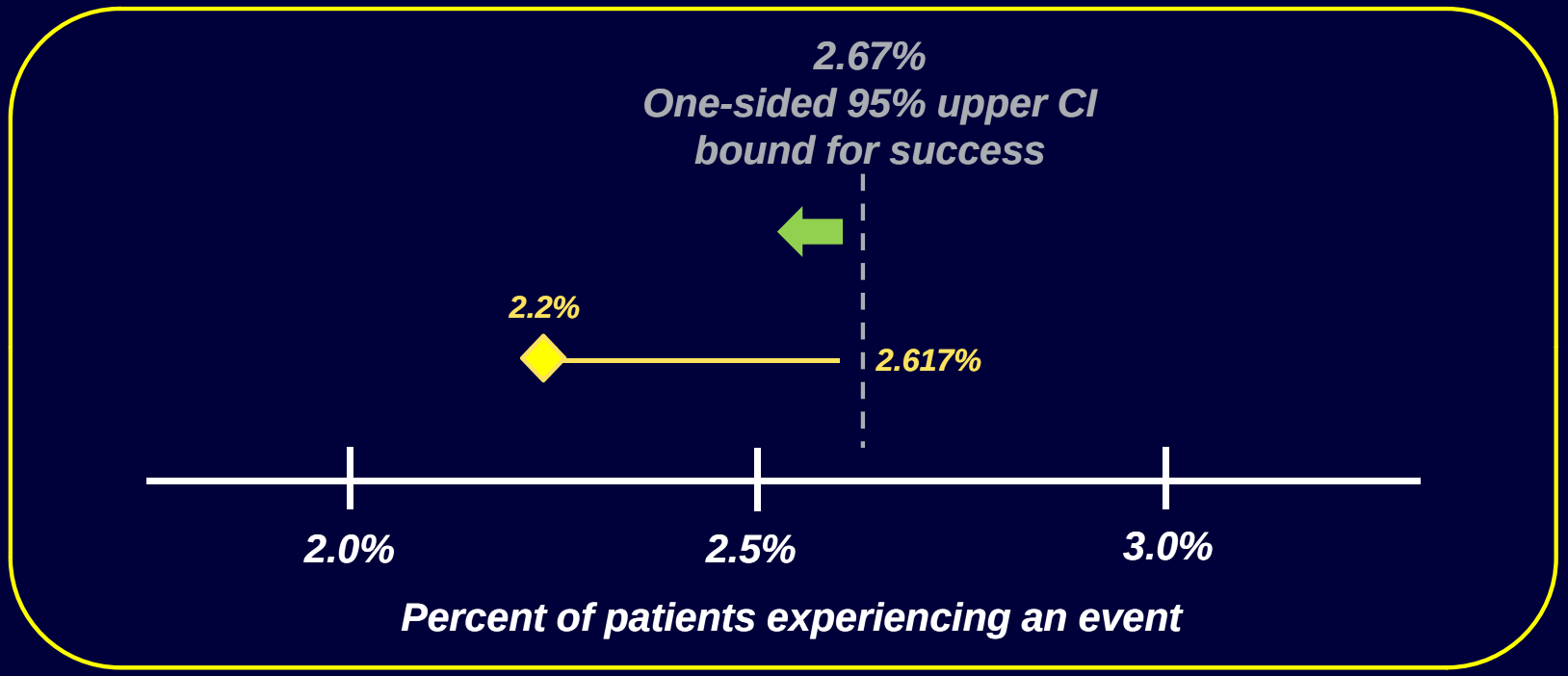
# Procedure Implant Success




*Implant success defined as deployment and release of the device into the left atrial appendage*

*PROTECT AF and CAP data from Reddy, VY et al. Circulation. 2011;123:417-424.*

# First Primary Endpoint
# Acute (7-day) Procedural Safety




- 6 events in device group = 2.2% (6/269)
- Pre-specified criterion met for first primary endpoint (95% Upper confidence bound < 2.67%)
  - 95% CI = 2.618%

*Results are preliminary; final validation not yet complete*

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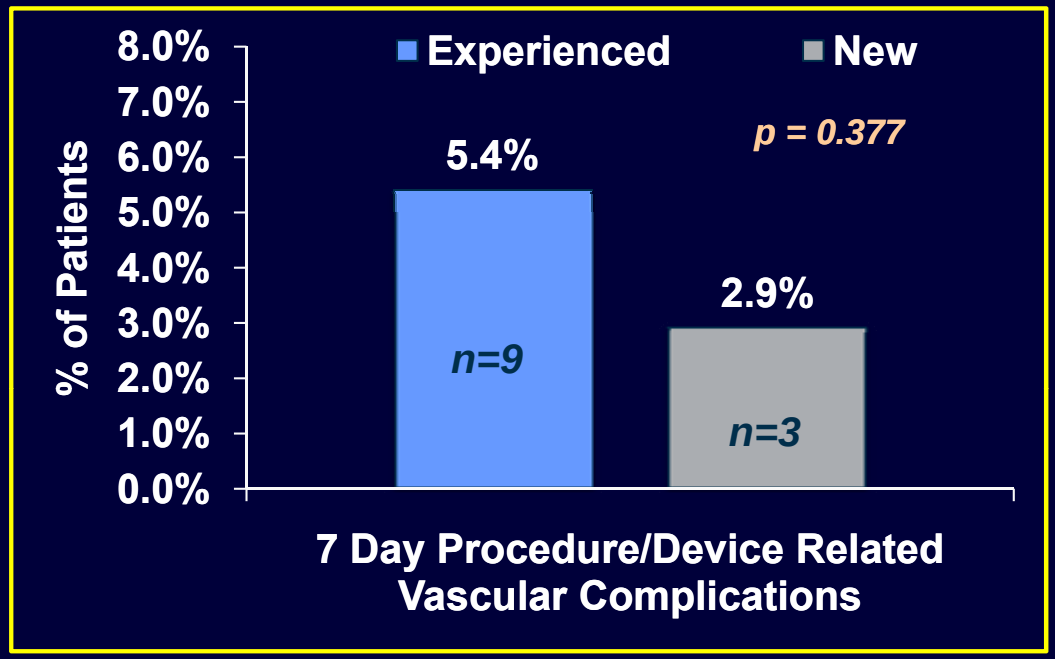
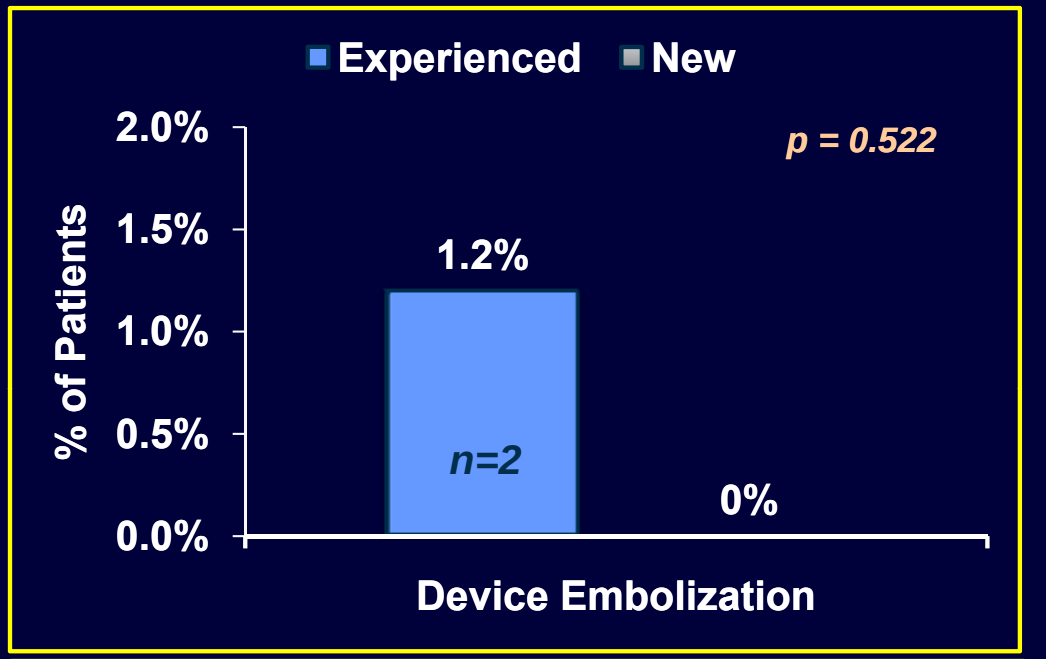
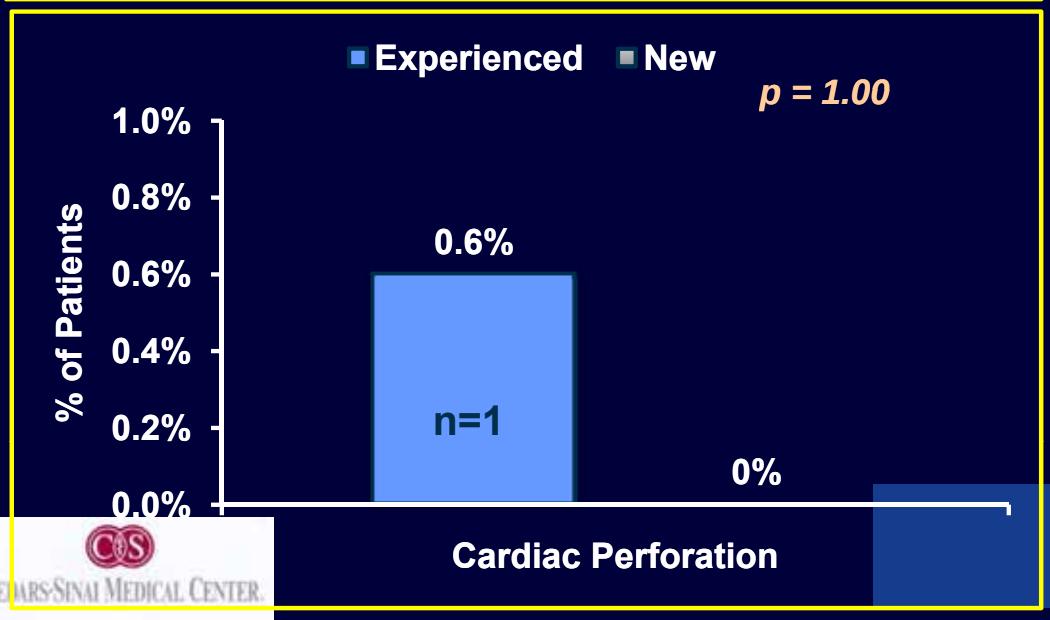
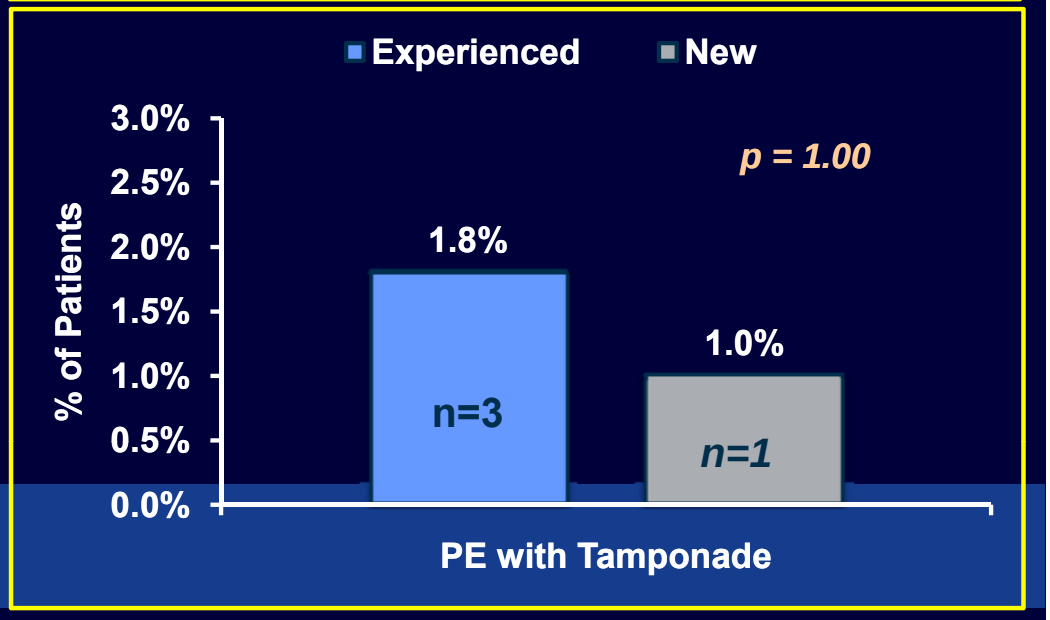
*CI is one-sided*

# PREVAIL Complications
## New vs Experienced Operator

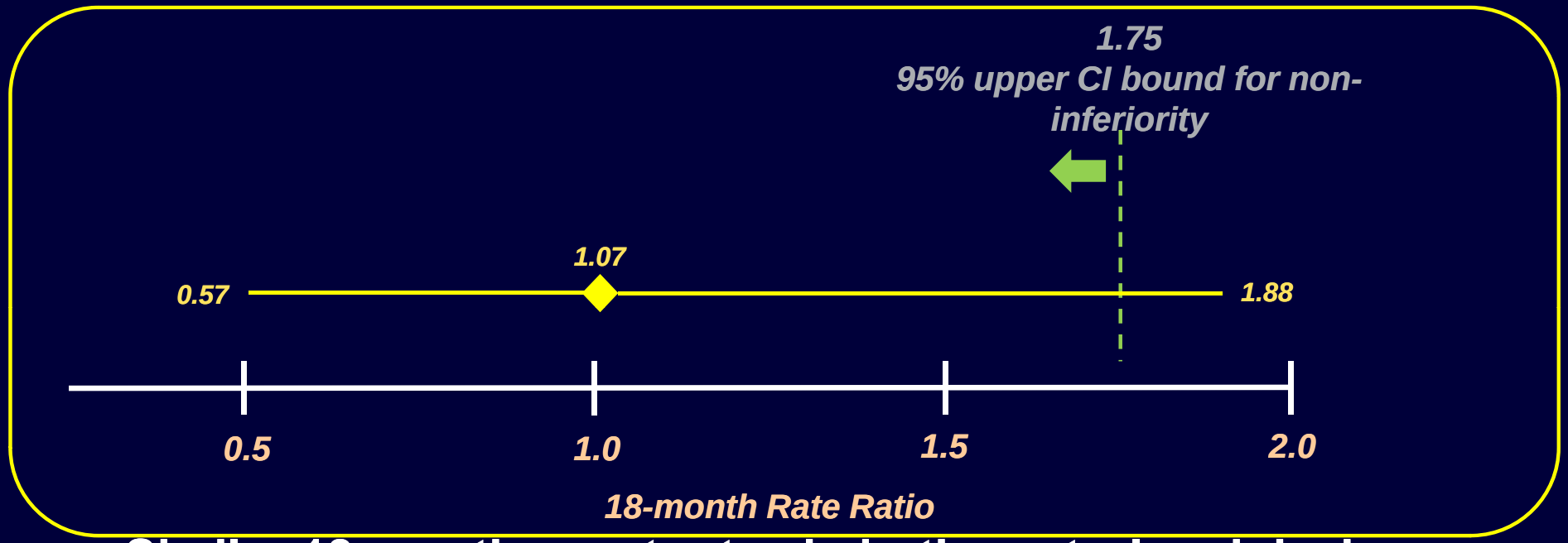


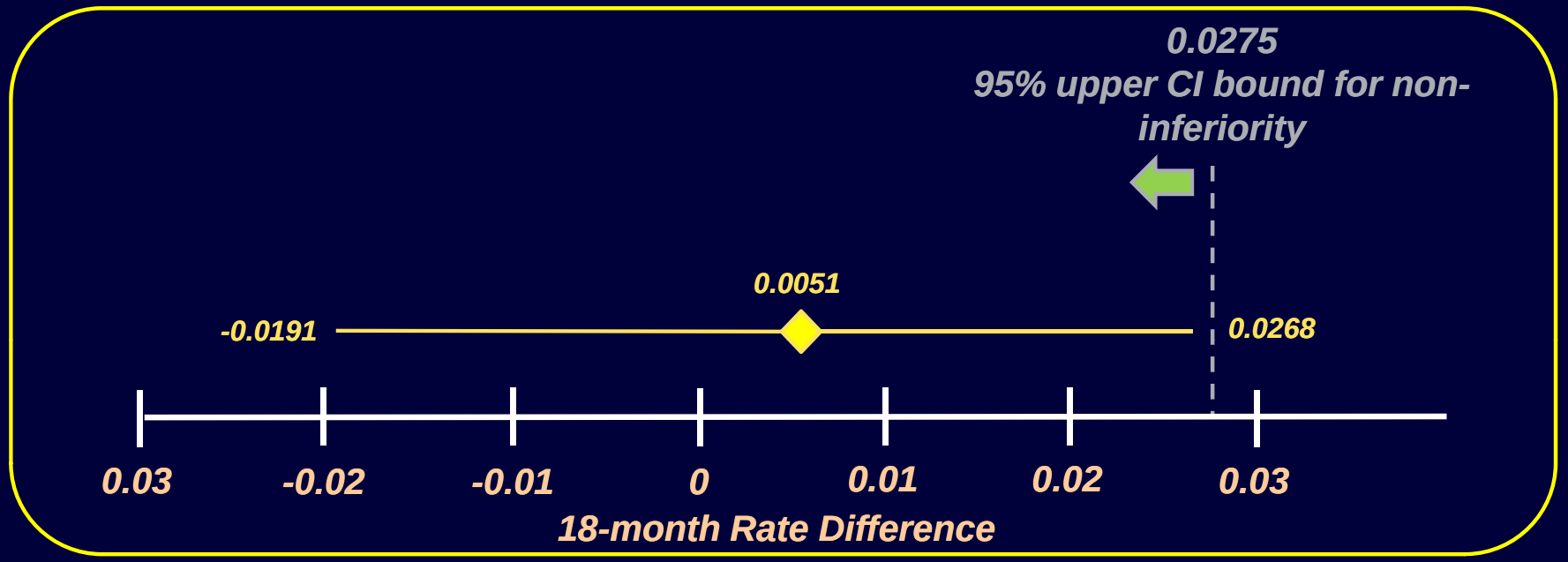
# Second Primary Endpoint
# Composite 18-month Efficacy




- Similar 18-month event rates in both control and device groups = 0.064
- Upper 95% CI bound slightly higher than allowed to meet success criterion (<1.75)
  - Limited number of patients with follow-up through 18 months thus far (Control = 30 pts, Device = 58 pts)

*Results are preliminary; final validation not yet complete*

# Third Primary Endpoint
# 18-month Thrombolic Events




- Endpoint success in the presence of an over performing control group

| Device 18-Month Rate | Control 18-Month Rate |
|---|---|
| 0.0253 | 0.0201 |

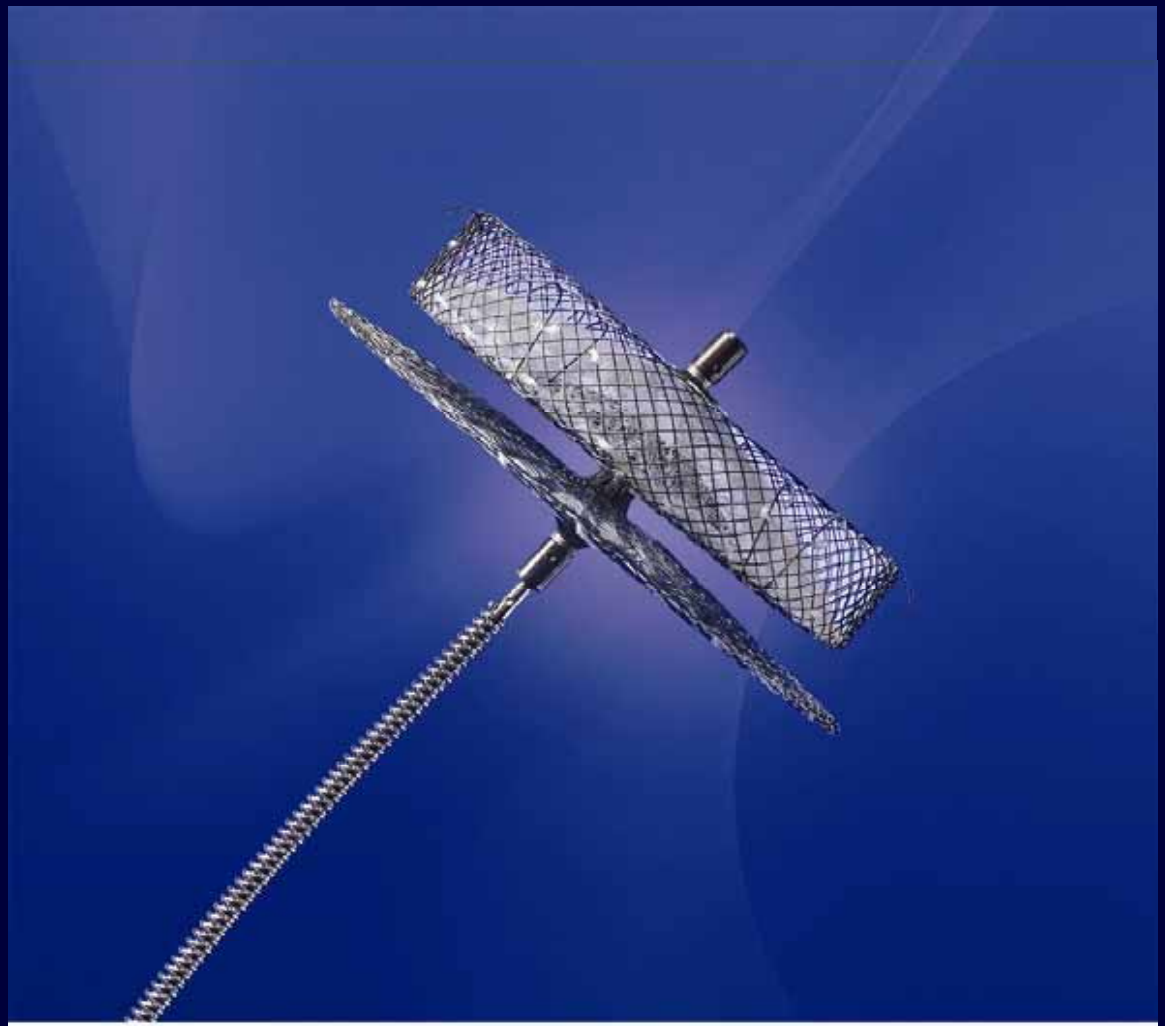
- Pre-specified non-inferiority criterion met for third primary endpoint (95% CI Upper Bound < 0.0275%)

*Results are preliminary; final validation not yet complete*

# PREVAIL: Summary

- Despite implantation in higher risk patients the Watchman device can be safely implanted by new operators
- 2 of 3 primary endpoints were met even in the presence of an over performing control group
- The Watchman device is an alternative to oral anticoagulation therapy for thromboembolic prevention in patients with non valvular atrial fibrillation

# AMPLATZER® Cardiac Plug




- **CE Mark – 2008**
  > 400 implants WW
- **U.S. – 2010**
  Limited to investigational use under approved clinical protocol

# Clinical Studies using ACP Plug

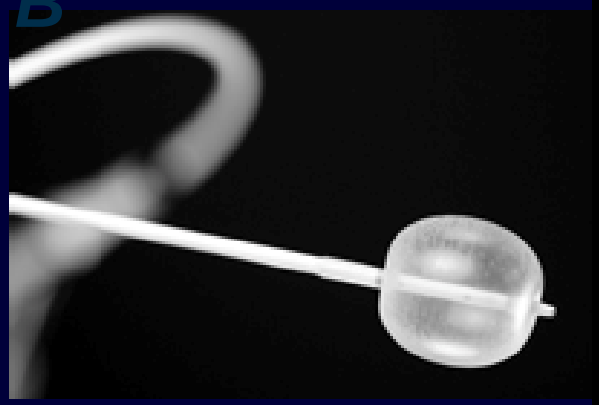
- CE Mark since 2008
- European Post Market registry
  - 204pts enrolled in 20 countries
- US Clinical Trial
  - Pilot study; Just completed enrollment of 45 pts ( 31 device 14 medical Rx)
  - Prospective randomized study expected to start later in 2011

# Summary

- **Higher risk patient population not tolerable to anticoagulation with $CHADS_2$ score of 2.6 and prior history of stroke 37.9%**
- **Excellent implant success rate 96.6% and occlusion rate 99.5% at 6 months**
- **Rate of safety events (5.4%) compares favorably with other devices and previous ACP publications**
- **Only 2 (1.98%) strokes at 101 patient years compared with the $CHADS_2$ prediction of 5.6%**
- **Training, implant technique and experience mitigate risk of safety events**

A

B

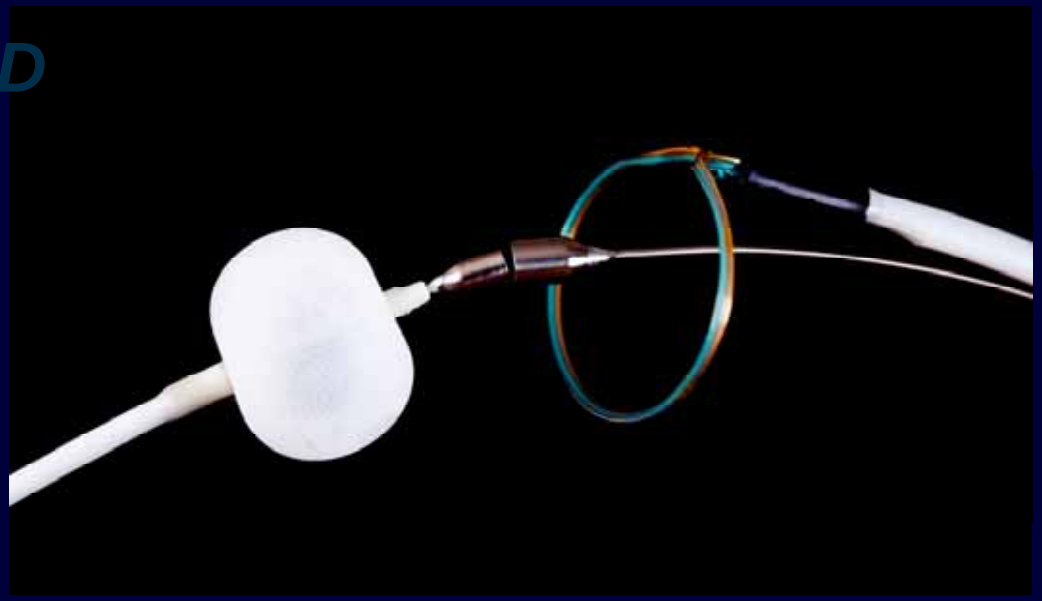


C


gnet guide wire

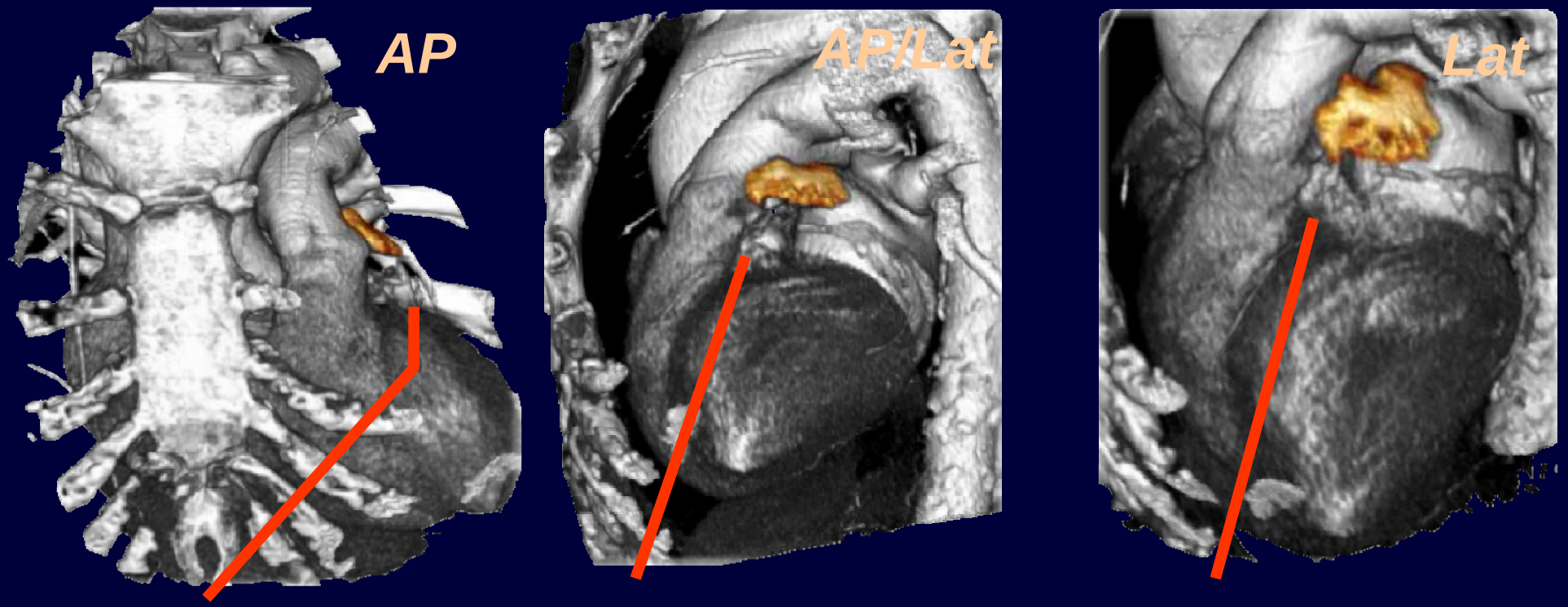
Endocath occlusion balloon

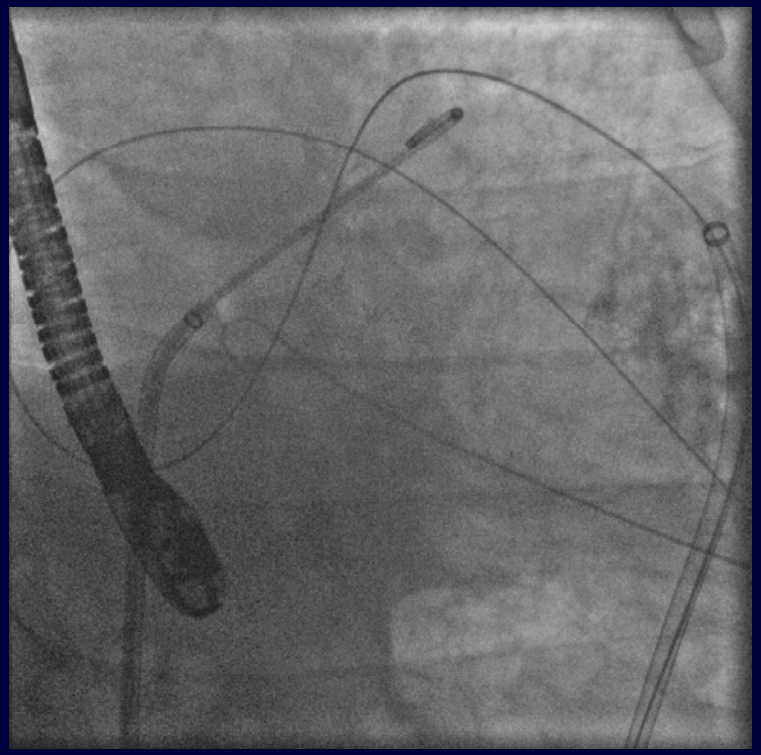
D

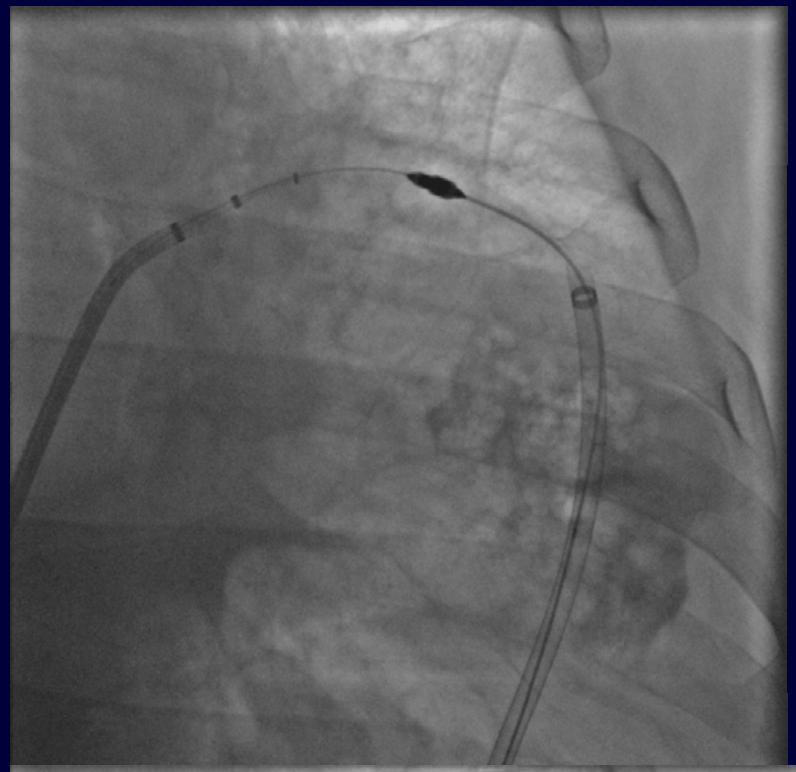


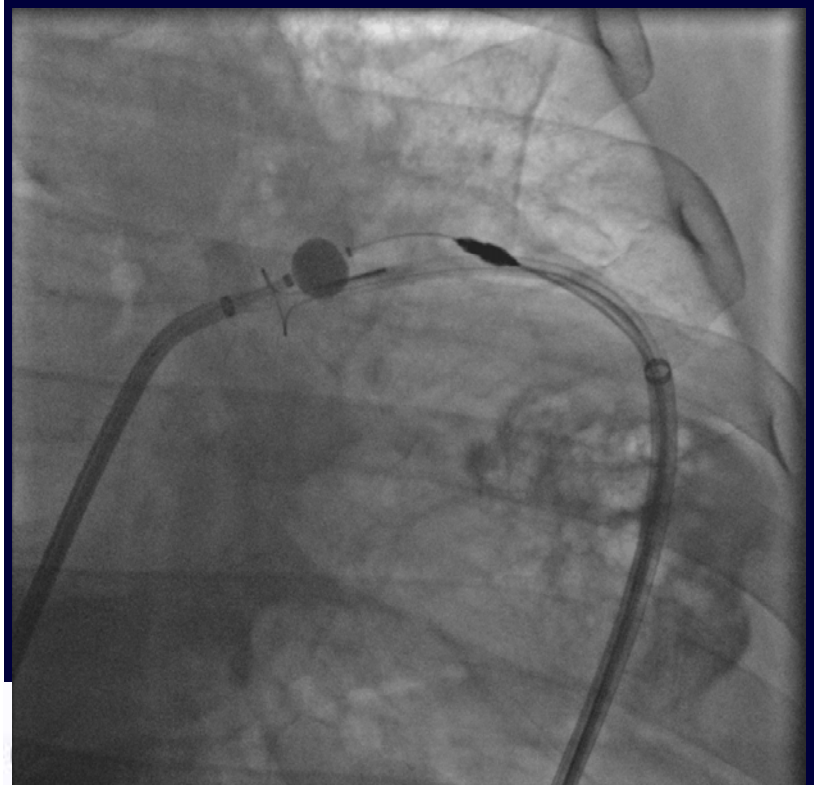
Suture delivery device

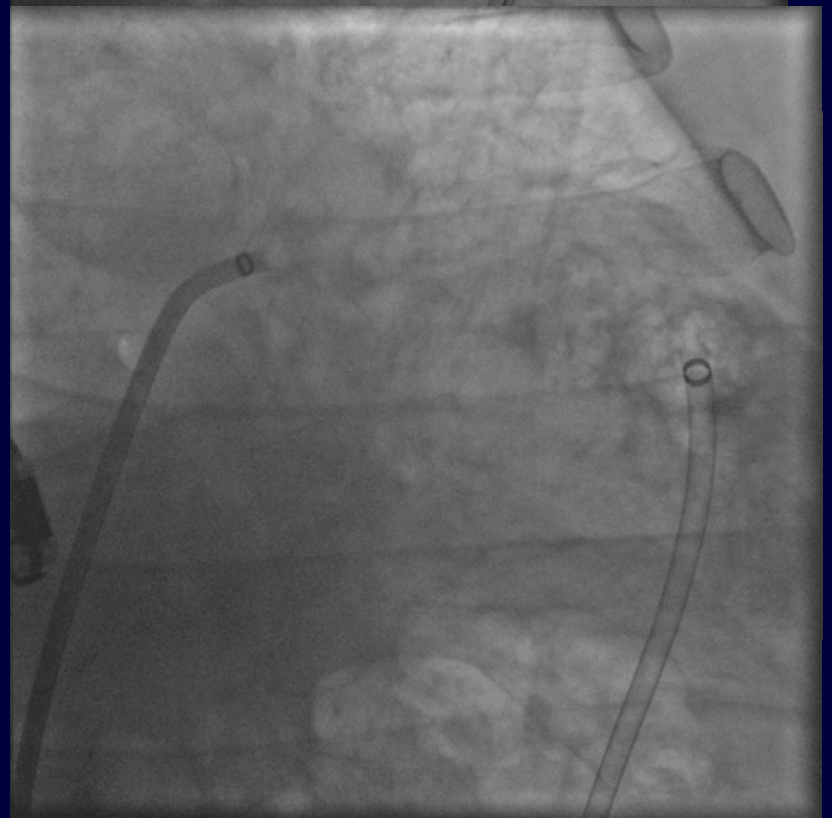
# Figure 1











# *Summary*
# *Oral Anticoagulation vs. LAA occlusion*

| | Stroke risk vs. warfarin HR | Major Bleeding /100 pt-yr | Discontinuation of Drug In study | Contraindication or intolerant |
|---|---|---|---|---|
| **Warfarin** | 1 | 4.7 | 25% | ~15% |
| **Watchman (PROTECT AF)** | 0.71 | 3.5 | N/A | Transient anticoagulation |
| **Dabigatran 150 (RE-LY)** | 0.66* | 3.11 | 21% | ~15% |
| **Apixaban (ARISTOTLE)** | 0.79* | 2.13* | 25.3% | ~15% |
| **Rivaroxaban (ROCKET AF)** | 0.79 | 3.6 | 23.7% | ~15% |

***New OATS reduce stroke risk but have continued bleeding and discontinuation over time***

** Superior to warfarin*

# Summary
# Oral Anticoagulation vs LAA occlusion

| | NEW Oral Anti-Thrombotics | WATCHMAN LAAC |
|---|---|---|
| Complications | • Continued /ongoing bleeding due to drug use (Class effect- Dabigatran, Apixaban, Rivaroxaban and Warfarin) – no mitigation other than stopping the drug.<br>• Gastrointestinal Bleeding, Dyspepsia, Myocardial Infarction (higher with Dabigatran)<br>• Drug effect not reversible (Dabigatran as an example) | Primarily Procedural- pericardial effusions – can be mitigated with detailed implant training |
| Compliance | 20-30% patients discontinue drugs (dabigatran), | A majority of patients can be taken off warfarin (85-95%) |

# Conclusion

- Percutaneous Closure of LAA is an effective alternative to long term anticoagulation
  - Early safety but no long term issues
- Long term antithrombotic agents are effective but have bleeding issues and intolerance
- Ongoing studies are enrolling more paitents to confirm this hypothesis

# Is LAA closure superior to medical treatment

- Left atrial appendage occlusion is most likely superior to antithrombotic therapy in following
  - Patients at bleeding risk
  - Patients who are already on multiple antiplatelet agents
  - Patients intolerant / non compliant for long term antithrombotic therapy

***WE shall PREVAIL***