Latest Updated on LAAC and Its Clinical Evidence

Saibal Kar, MD, FACC, FAHA, FSCAI

Associate Professor

Heart Institute, Cedars Sinai Medical Center, Los Angeles, CA

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PICS-AICS
Pediatric and Adult Interventional Cardiac Symposium

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Disclosure Information

WATCHMAN: Where do we stand

Saibal Kar MD, FACC, FAHA, FSCAI

As a faculty member for this program, I disclose the following relationships with industry:

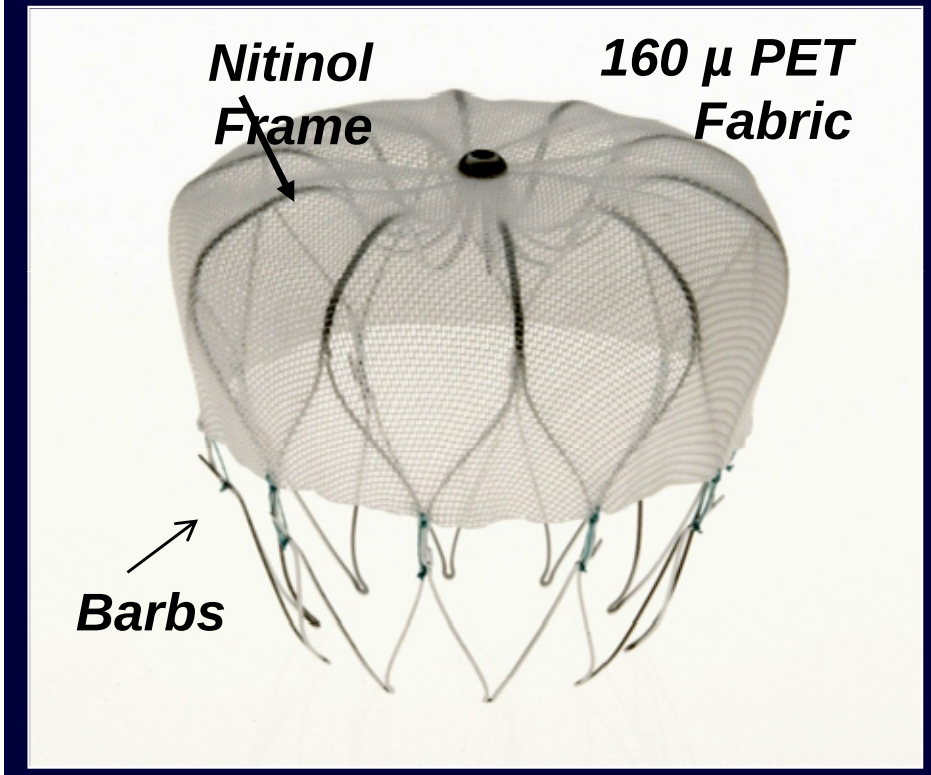
(GRS): Grant/Research Support (C): Consultant (SB): Speaker's Bureau
(MSH): Major Stock Holder (AB): Advisory Board (E): Employment
(O):Other Financial or Material Support

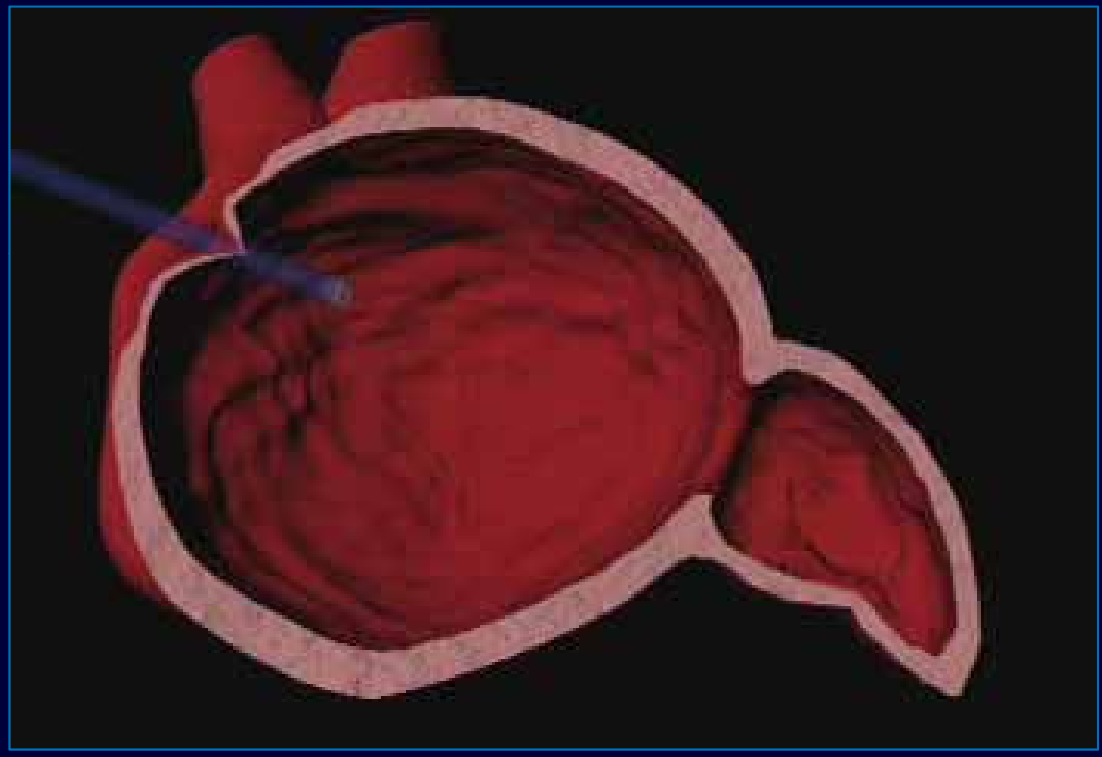
Boston Scientific : GRS, C.
St Jude Medical : GRS,
Coherex : C, E, O
Inceptus : C
SentreHeart : C

Introduction

- Percutaneous closure of the left atrial appendage rather than long term anticoagulant therapy is option to prevent stroke in non rheumatic AF patients
- Watchman device is the only LAA occlusion device to have completed two randomized studies against coumadin
- Watchman device is investigational in US, and approved for clinical usage in Europe, Australia and some countries in Asia

WATCHMAN® Left Atrial Appendage Occluder System(Boston Scientific)

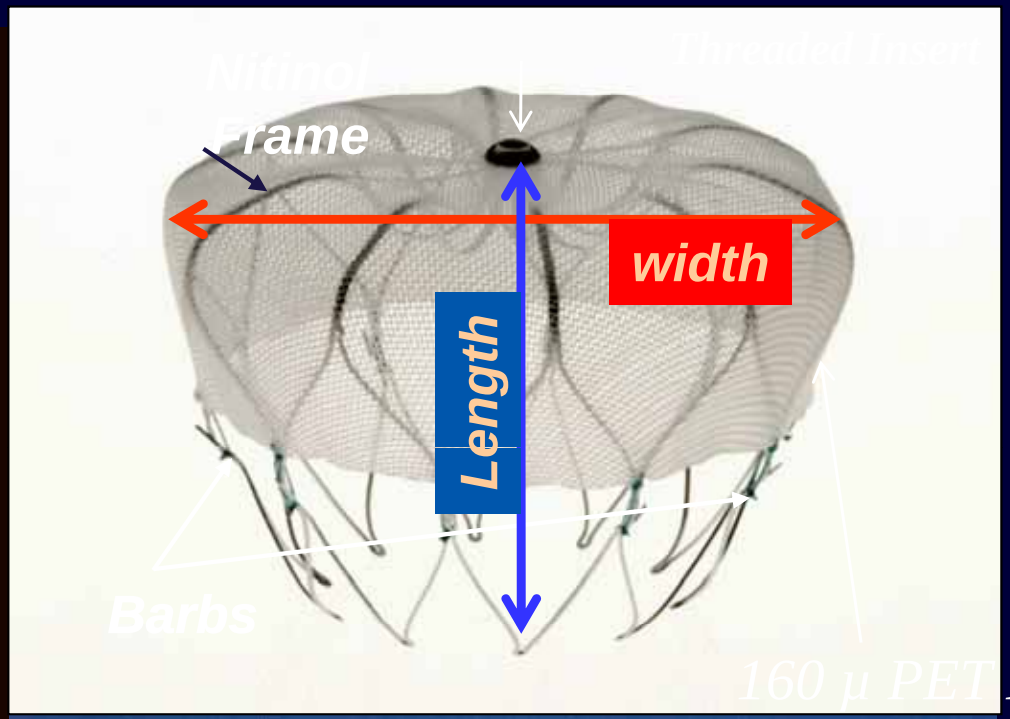


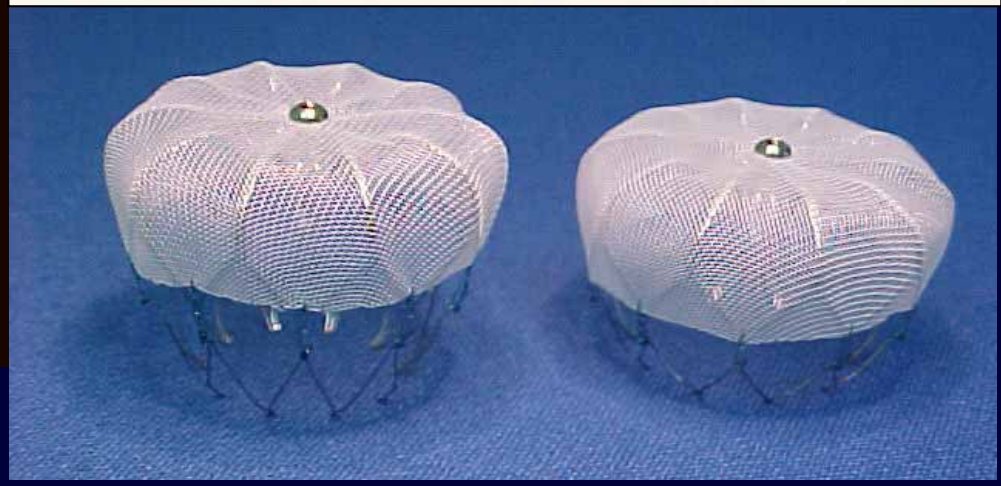


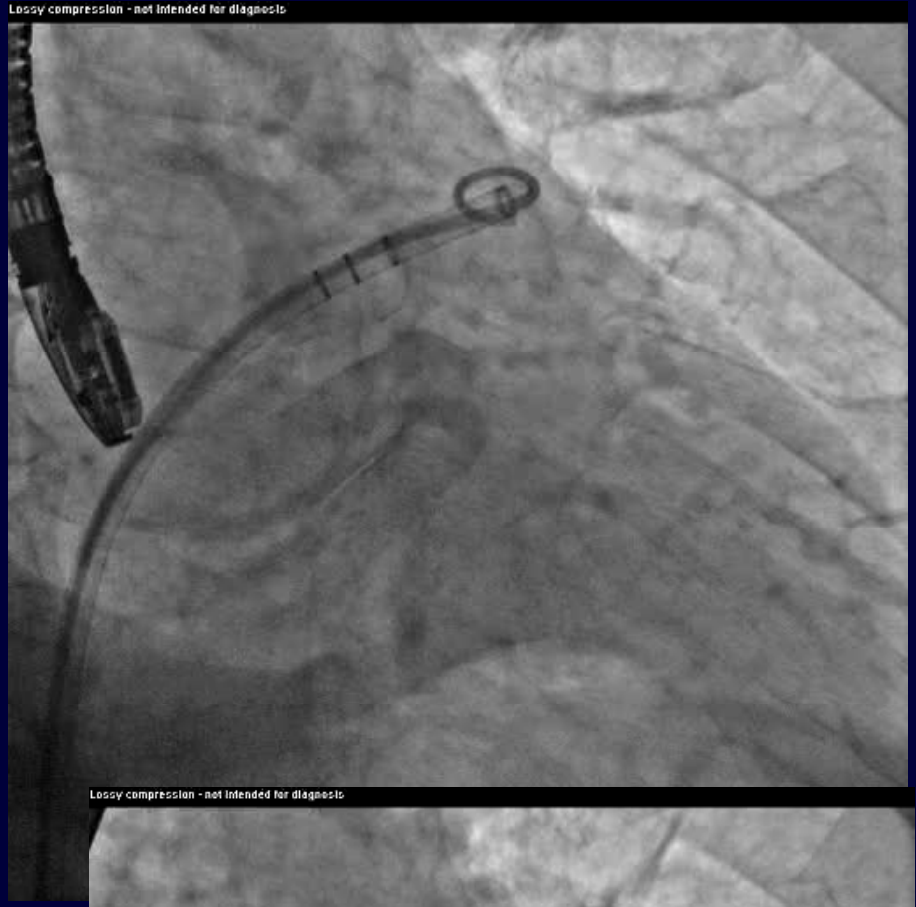
Sizes: 21, 24, 27, 30, 33 mm

Watchman® LAA occlusion system (Boston Scientific)

- Nitinol Frame
- PET Fabric Cap
- Barbs
- Threaded Insert
- Various Sizes (21, 24,27,30,33mm)
- *Length = width of device*



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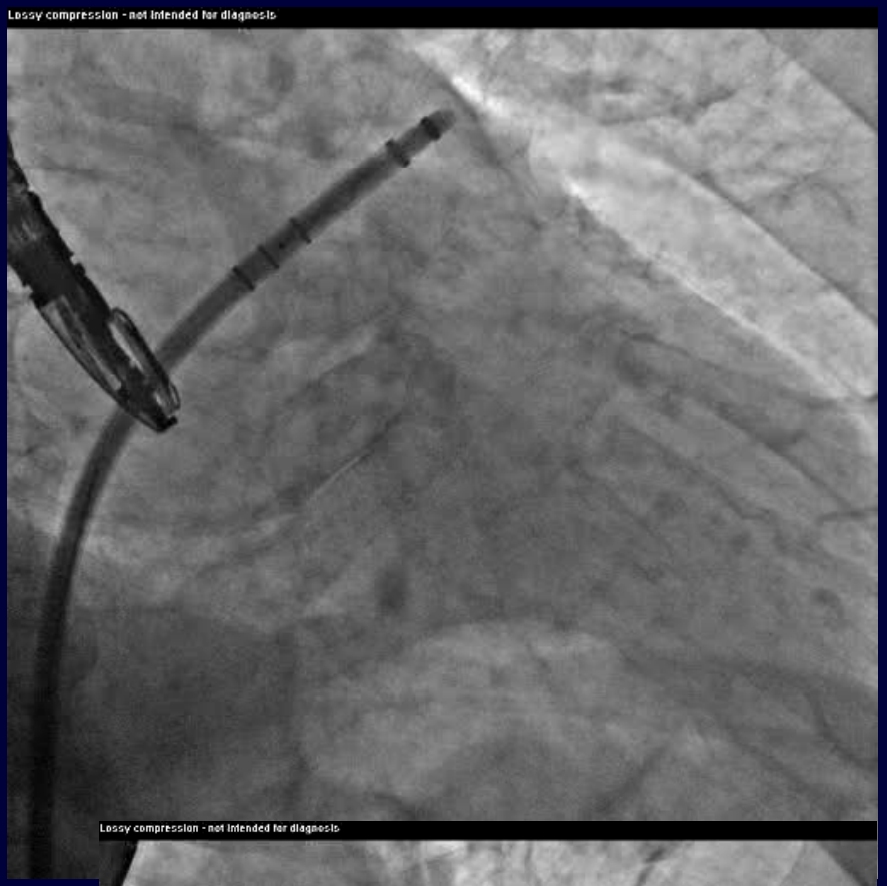
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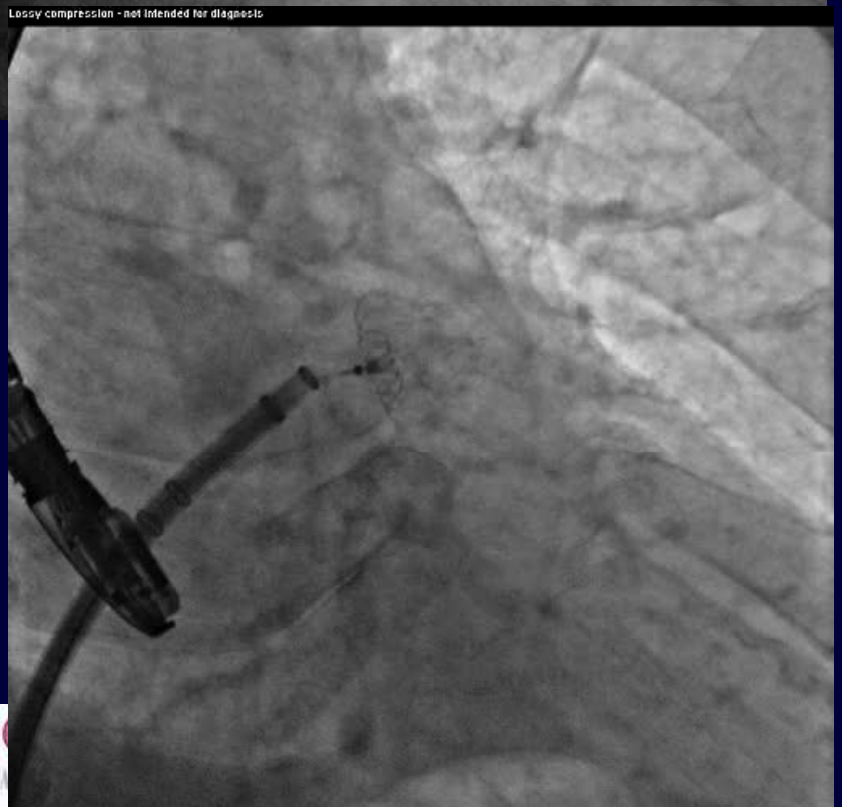
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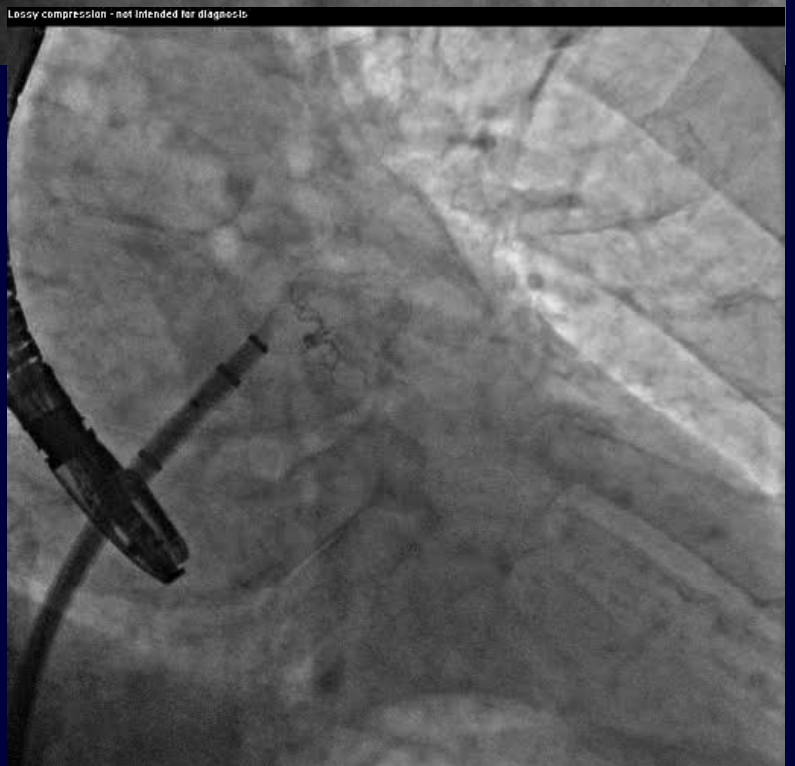
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Clinical Studies

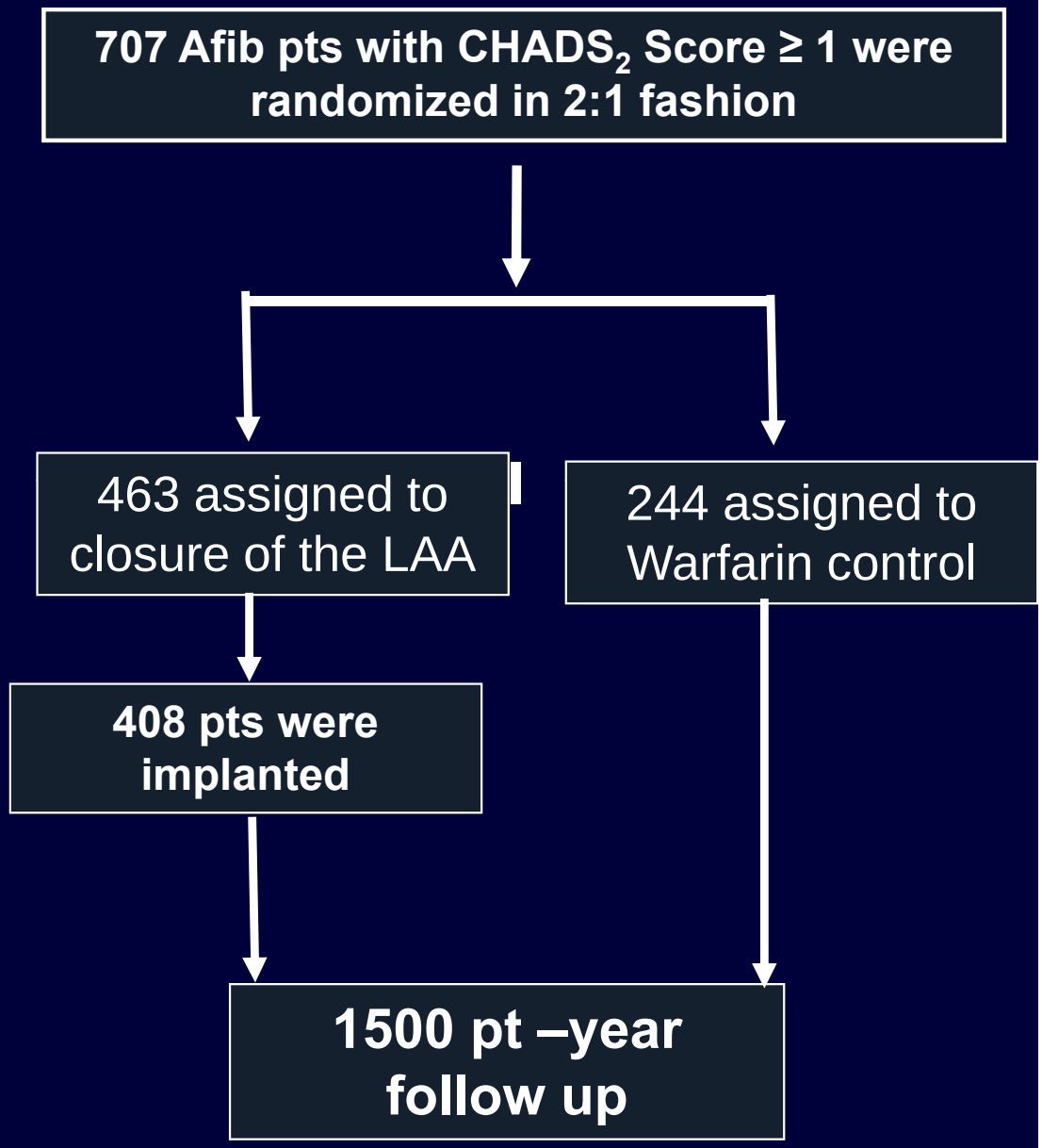
STUDY	PATIENTS	SITES	COMMENTS
Pilot	66	8	• 318 patient years of follow-up • 30 patients with 5+ years of follow-up
PROTECT AF	800	59	• 1,500 patient years of follow-up • 27 months average follow-up per patient
Continued Access Registry (CAP)	566	26	• Significantly improved safety results
ASAP	150	4	•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

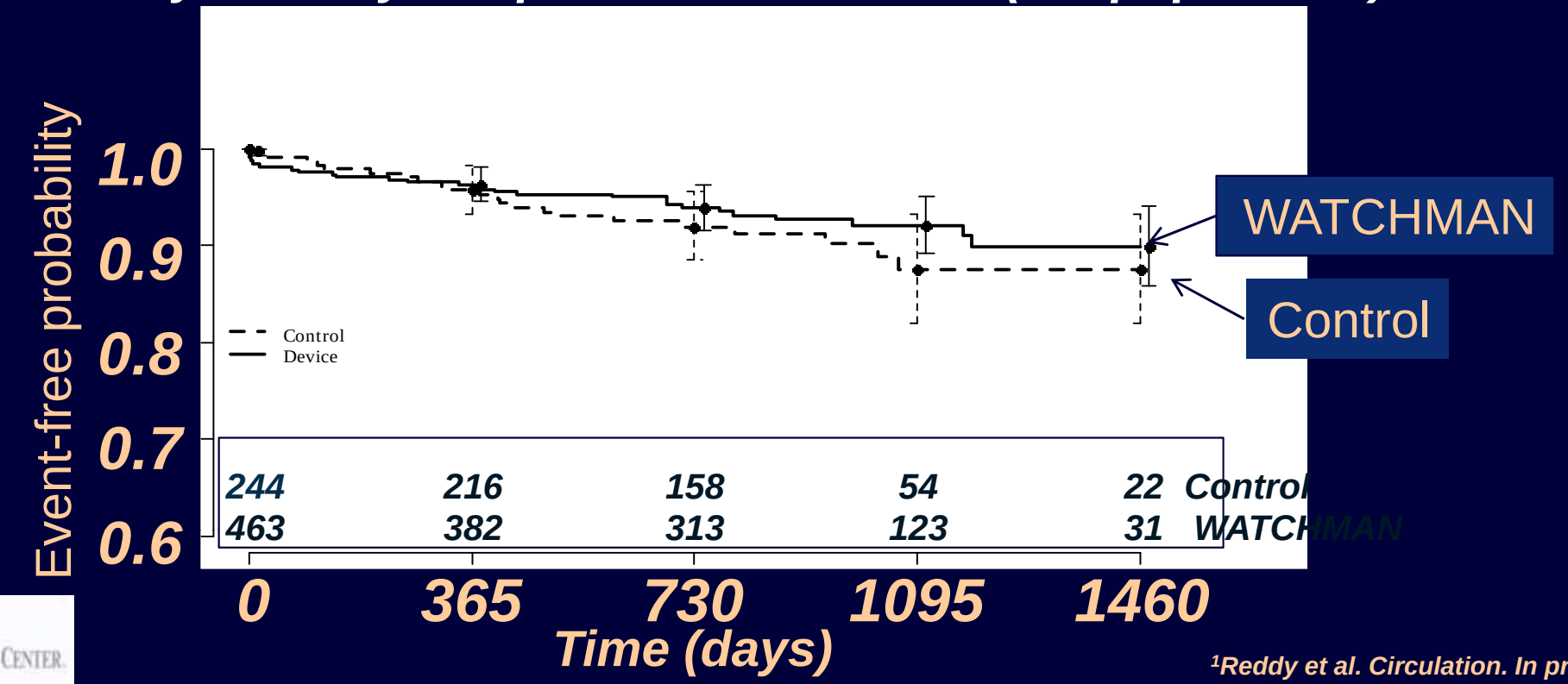


PROTECT-AF Trial:
LAA Closure is effective in stroke prevention

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 Rate (95% CI)	Control Rate (95% CI)	Relative Risk (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

Continued Access Registry (CAP)

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±
		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

*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 for acute safety events
- Fewer total procedure/device related events

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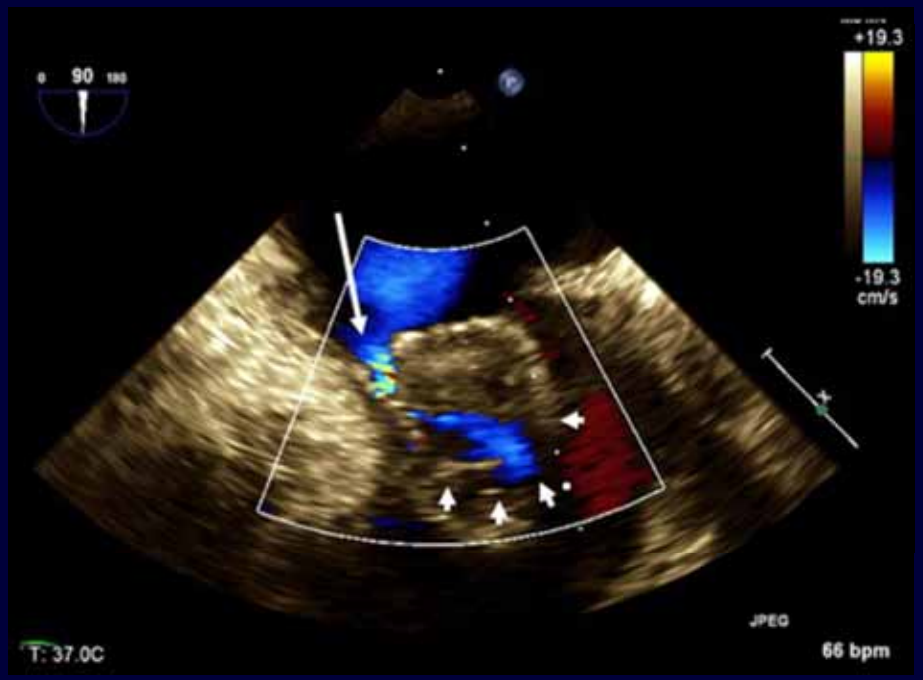
Reddy, Holmes, Kar et al. Circulation 2011

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. et al. J Am Coll Cardiol 2012;59:923-929

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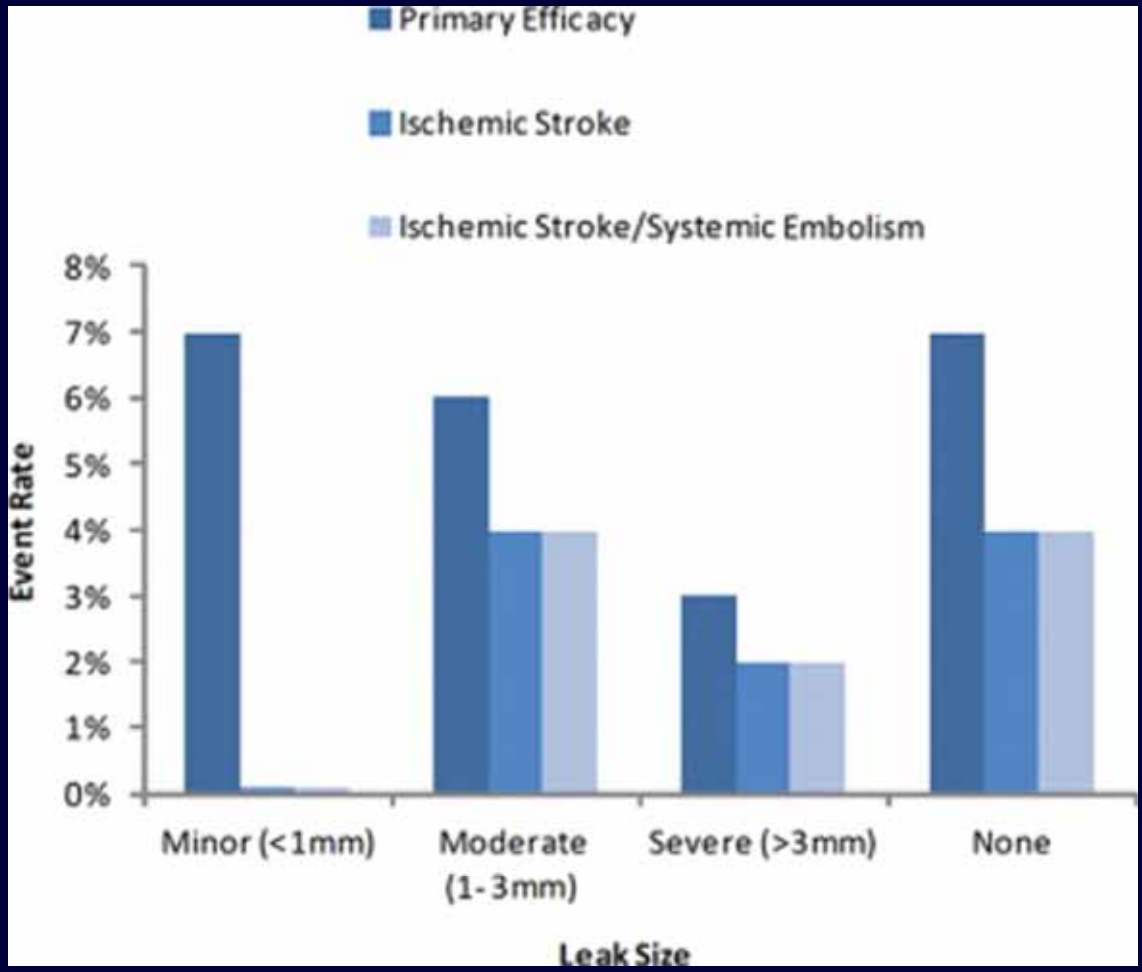
Primary Efficacy Endpoint Rates by Leak Severity

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



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

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Regulatory Update

- April 2009: FDA Panel voted 7 to 5 in favor of approval of Watchman Device
- March 2010: FDA announced non approval and requested further studies
- CAP registry was stopped
- November 2010: Confirmatory PREVAIL Study was initiated in higher risk AF patients

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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PREVAIL
Top 10 Participating Centers

Investigational Center	Location	Principal Investigator	Total Enrollment
Pacific Heart / St. Johns	Santa Monica, CA	*Shephal Doshi, MD*	45
Cedars-Sinai Medical Center	Los Angeles, CA	*Saibal Kar, MD*	32
Mercy Heart and Vascular	St. Louis, MO	*J. Mauricio Sanchez, MD*	32
Arizona Heart Rhythm Research Center	Phoenix, AZ	*Vijay Swarup, MD*	30
Intermountain Medical Center	Murray, UT	*Brian Whisenant, MD*	24
Methodist Hospital	Houston, TX	*Miguel Valderrabano, MD*	22
Scripps Green	La Jolla, CA	*Matthew Price, MD*	22
Central Baptist Hospital, Kentucky	Lexington, KY	*Gery Tomassoni, MD*	17
Fletcher Allen	Burlington, VT	*Daniel Lustgarten, MD*	17
St. Lukes Hospital, Kansas	Kansas City, MO	*Kenneth Huber, MD*	17

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PROTECT AF vs PREVAIL
Trial Design Differences (abbreviated)

	PROTECT AF	PREVAIL
Randomization	2:1	2:1
Time from randomization to implant	7-14[1] days	2 days
Roll-in	New implanter: 1st 3 patients[2]	New implanter: 1st 2 patients Experienced: 1st patient
Exclusion of clopidogrel	No exclusion	Indication for clopidogrel therapy or has taken clopidogrel within 7 days prior to enrollment
Inclusion differences	$CHADS_2 \geq 1$	$CHADS_2 \geq 2$ or $CHADS_2 = 1$ if any of the following apply*: • Female age >75 • Baseline LVEF > 30 and < 35% • Age 65-74 and has diabetes or coronary artery disease • Age 65 or greater and has documented congestive heart failure

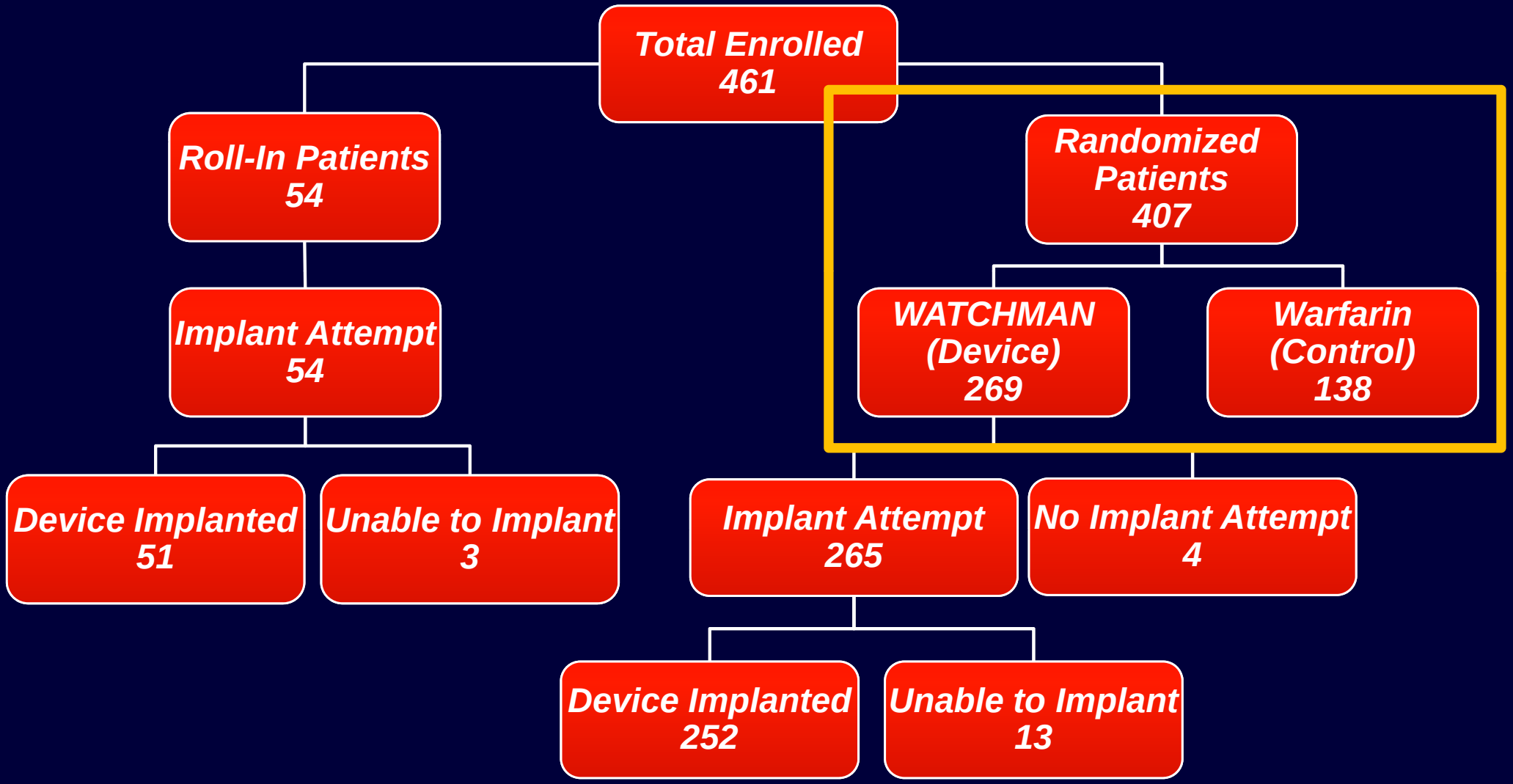
[1] Original protocol allowed 14 days, but was reduced to 7 after a protocol revision
[2] After first 100 study patients, protocol was revised to include roll-in patients for new implanters

**According to the ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation patients requiring warfarin therapy*

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



Demographics
Device Patients

Characteristic	PROTECT AF N=463	CAP N=566	PREVAIL N=269	P value
Age, years	71.7 ± 8.8 (463) (46.0, 95.0)	74.0 ± 8.3 (566) (44.0, 94.0)	74.0 ± 7.4 (269) (50.0, 94.0)	<0.001
Gender (Male)	326/463 (70.4%)	371/566 (65.5%)	182/269 (67.7%)	0.252
$CHADS_2$ Score (Continuous)	2.2 ± 1.2 (1.0, 6.0)	2.5 ± 1.2 (1.0, 6.0)	2.6 ± 1.0 (1.0, 6.0)	<0.001
$CHADS_2$ Risk Factors				
CHF	124/463 (26.8%)	108/566 (19.1%)	63/269 (23.4%)	
Hypertension	415/463 (89.6%)	503/566 (88.9%)	238/269 (88.5%)	
Age ≥ 75	190/463 (41.0%)	293/566 (51.8%)	140/269 (52.0%)	
Diabetes	113/463 (24.4%)	141/566 (24.9%)	91/269 (33.8%)	
Stroke/TIA	82/463 (17.7%)	172/566 (30.4%)	74/269 (27.5%)	

Most notable differences:
Age, Diabetes, and Prior Stroke/TIA

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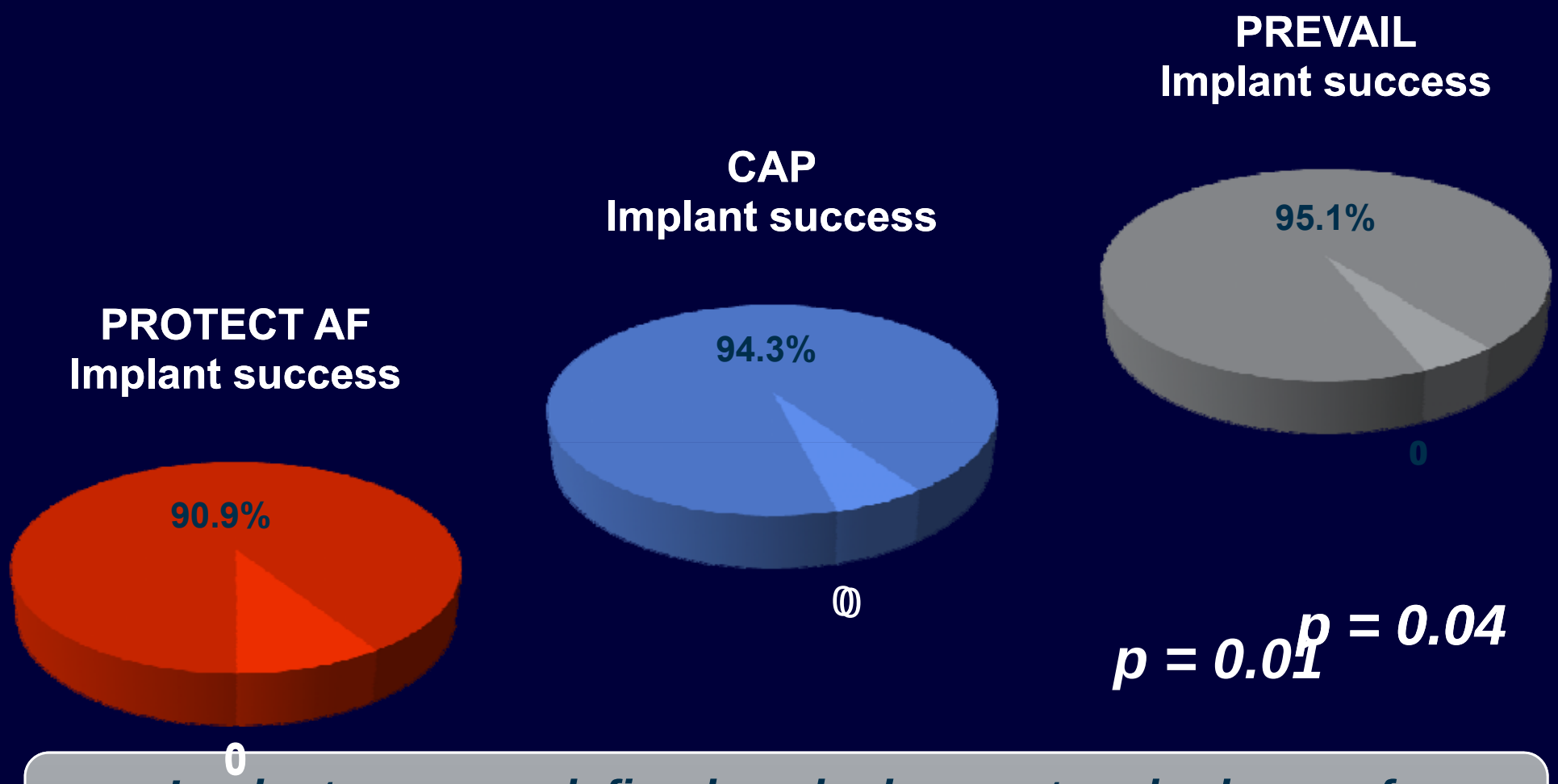
PROTECT AF and CAP data from Reddy, VY et al. Circulation. 2011;123:417-424.

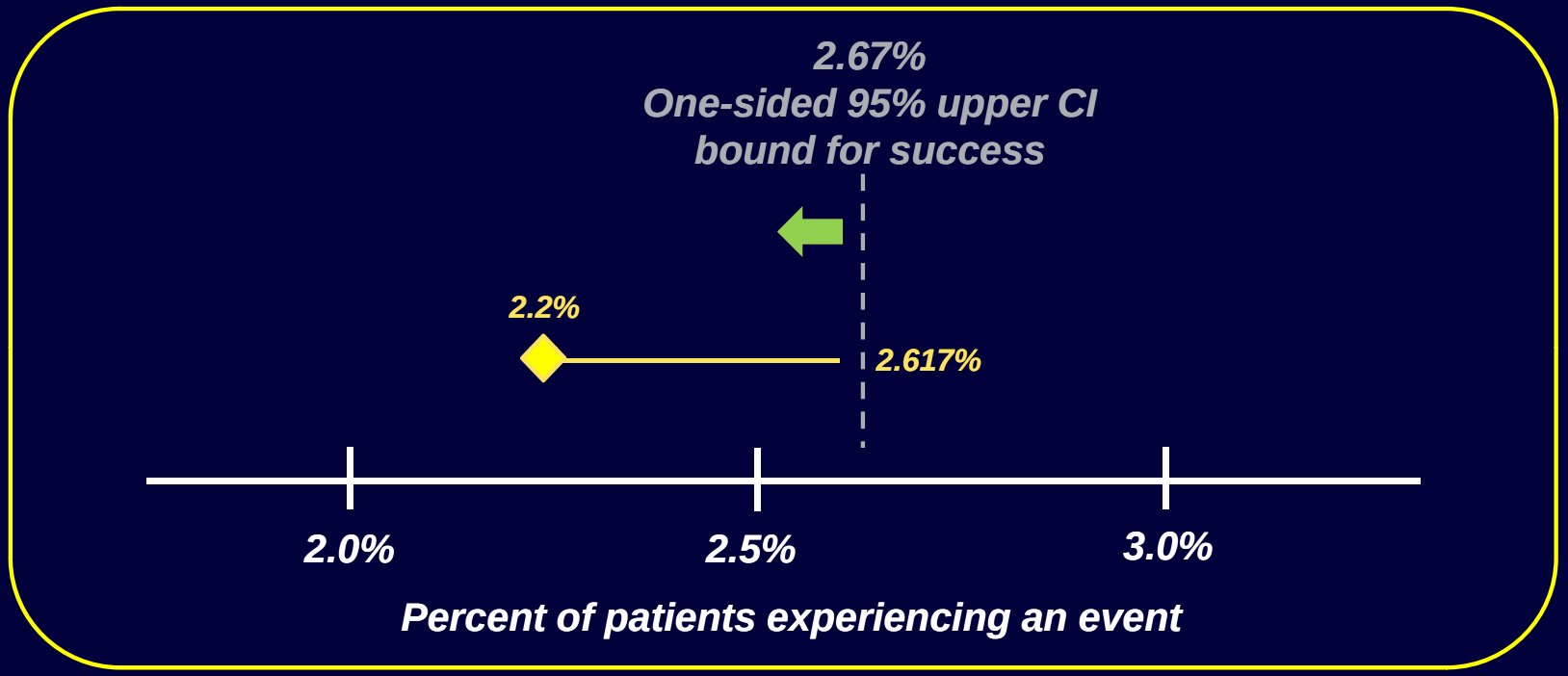
Procedure Implant Success



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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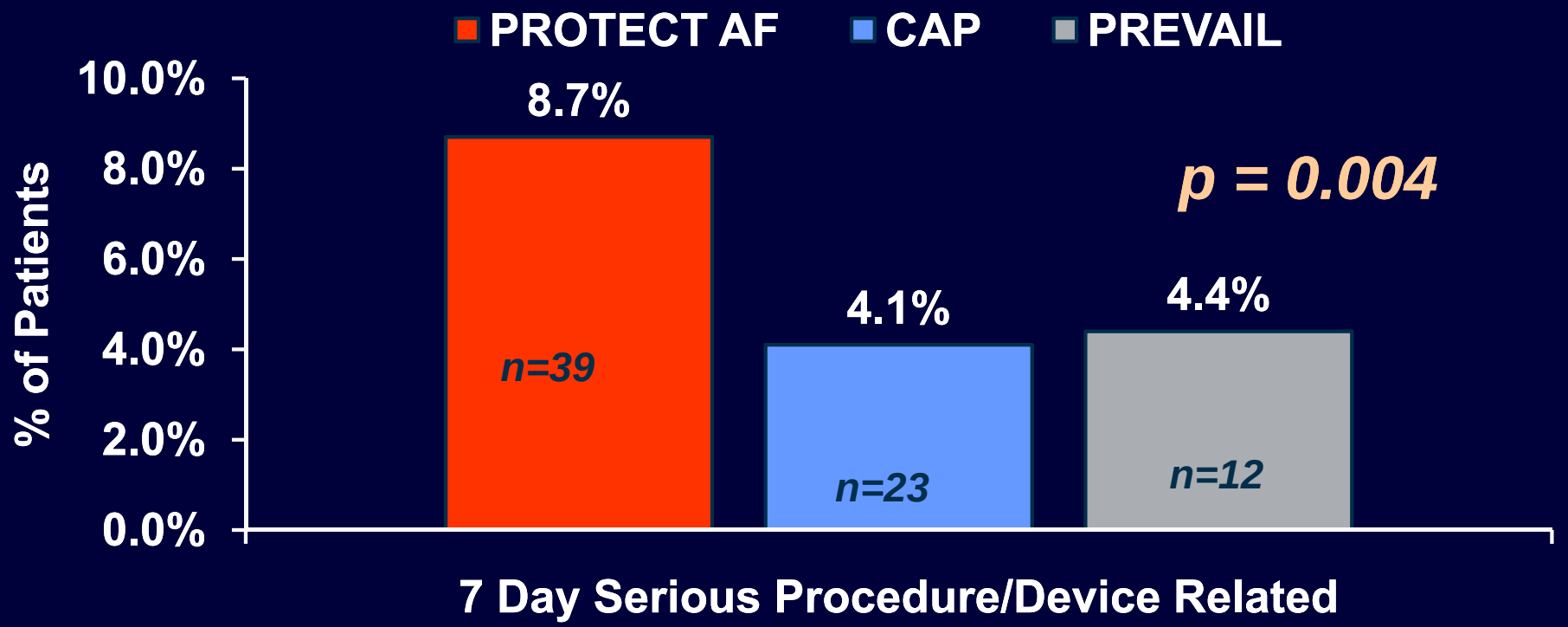
CI is one-sided

Vascular Complications

- *Composite of vascular complications includes cardiac perforation, pericardial effusion with tamponade, ischemic stroke, device embolization, and other vascular complications[1]*

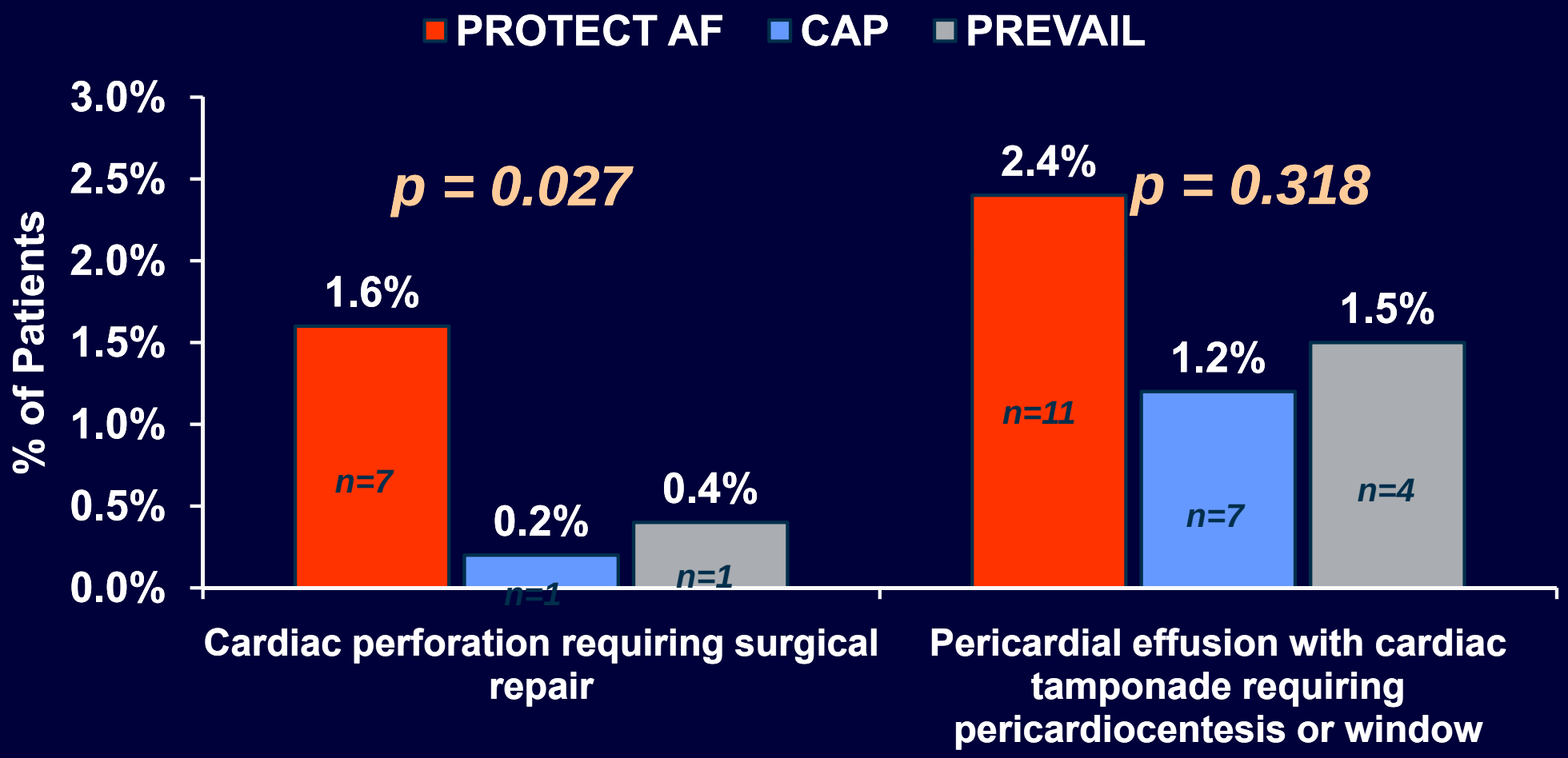


No procedure-related deaths reported in any of the trials

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

[11]Includes observed PE not necessitating intervention, AV fistula, major bleeding requiring transfusion, pseudoaneurysm, hematoma

Pericardial Effusions Requiring Intervention



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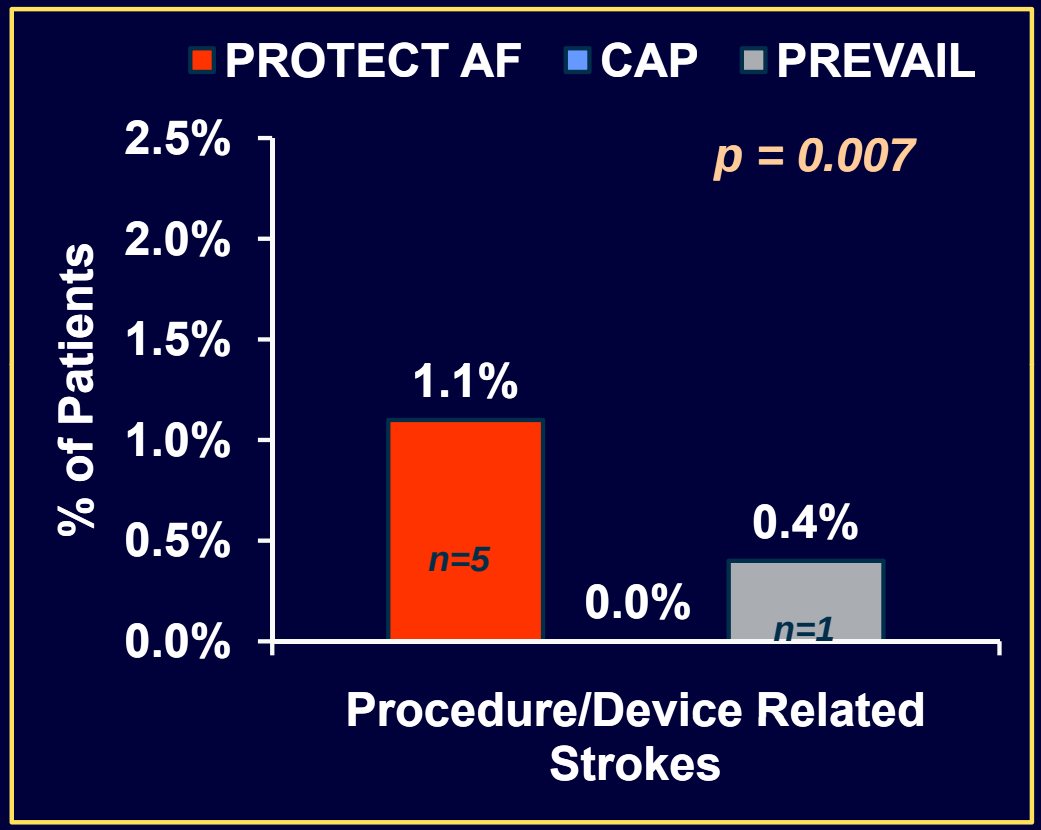
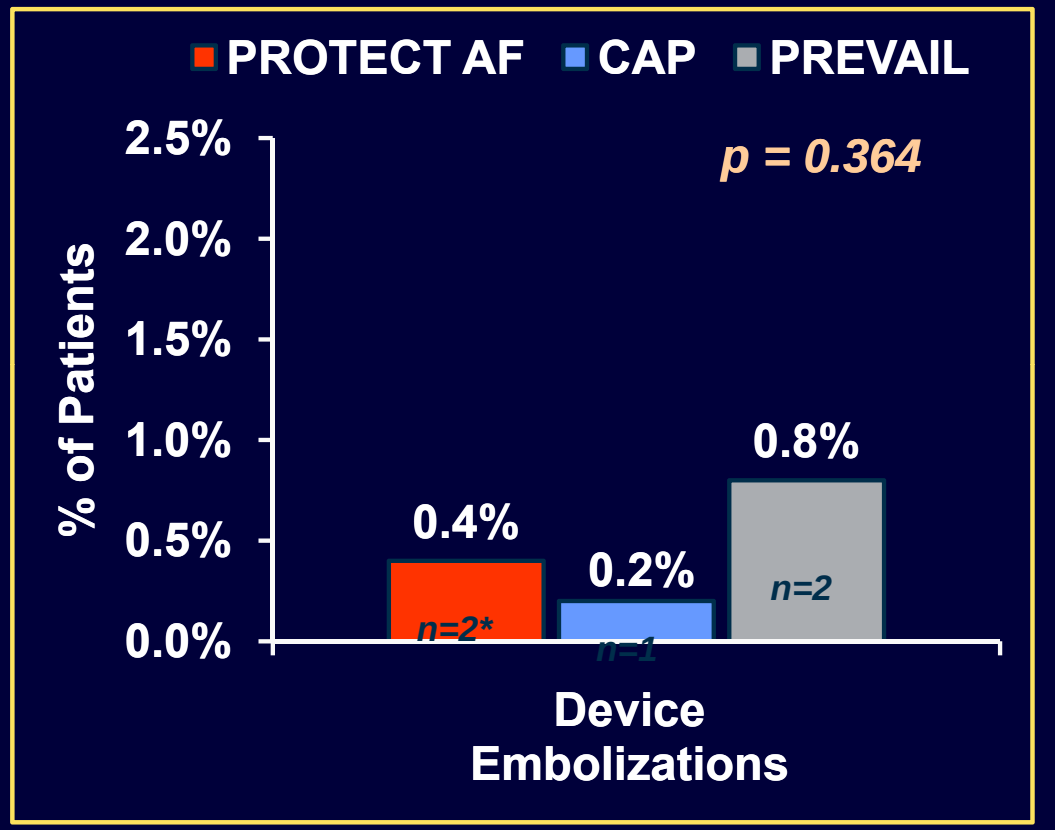
PROTECT AF and
from Reddy, VY et al. Circulation. 2011;12

Stroke and Device Embolization





Procedure related strokes were reduced
Device embolizations remained low

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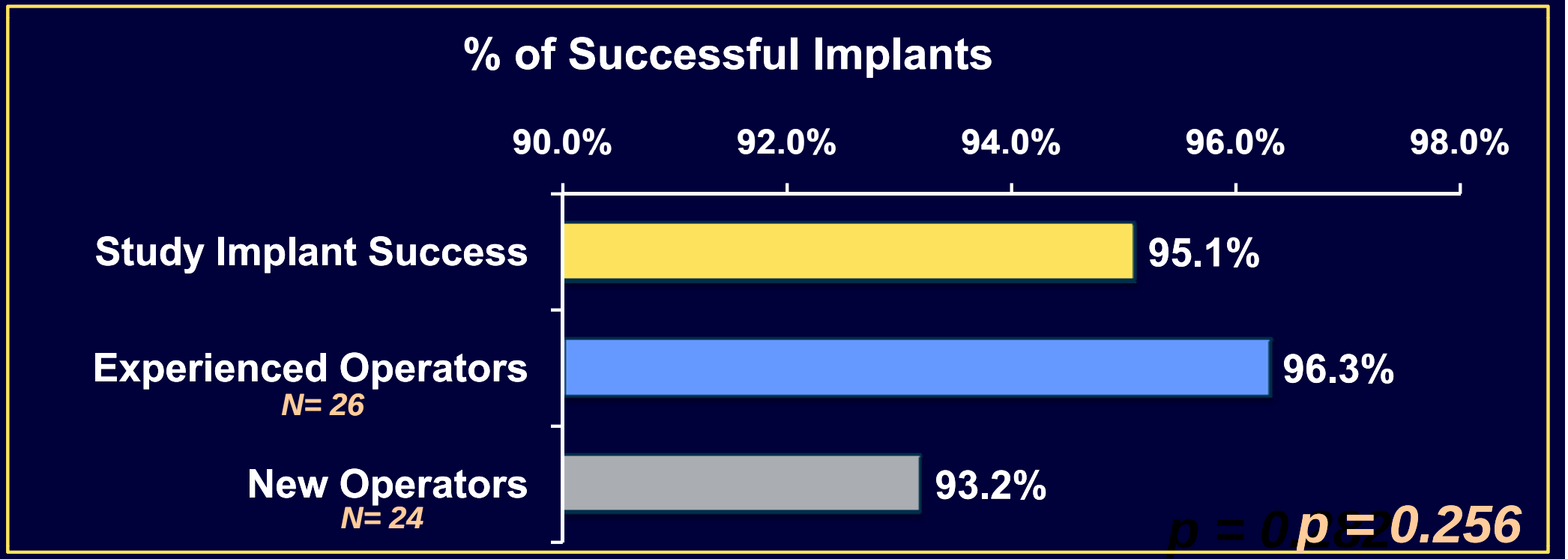
Caution: In the United States, WATCHMAN is an investigational device limited by Federal law to investigational use only. Not for sale in the US. Prior to use please review device instructions, contraindications, warnings, precautions, adverse events, and operating instructions. Only available according to applicable local law.

Intentional device embolization has been reported a
PROTECT AF and
Holmes, D.R. et al. Circulation. 2014;123

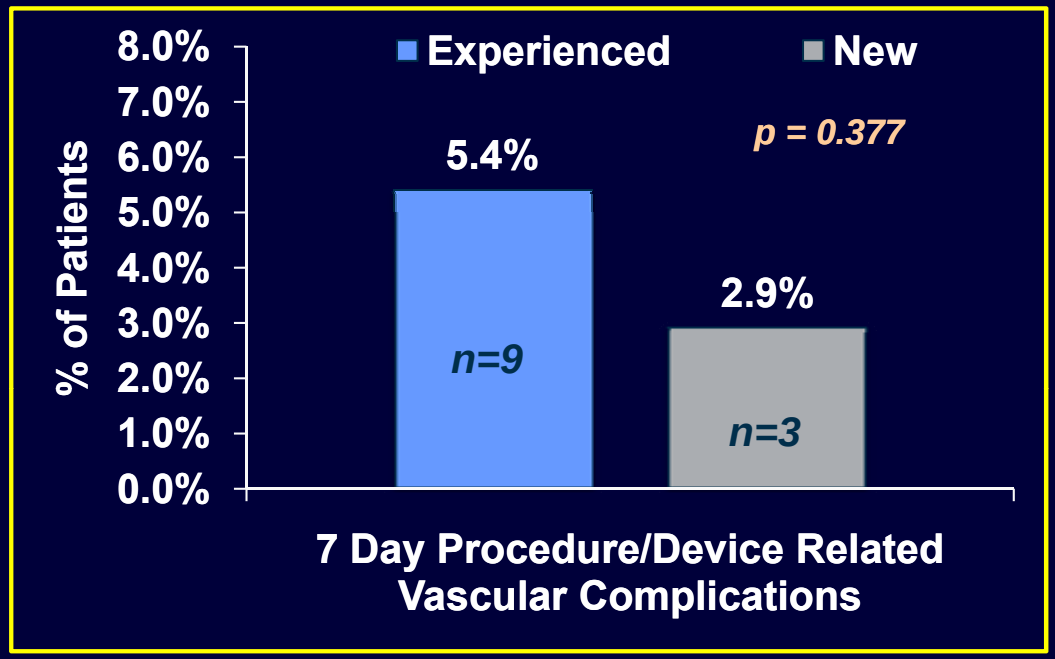
PREVAIL Implant Success

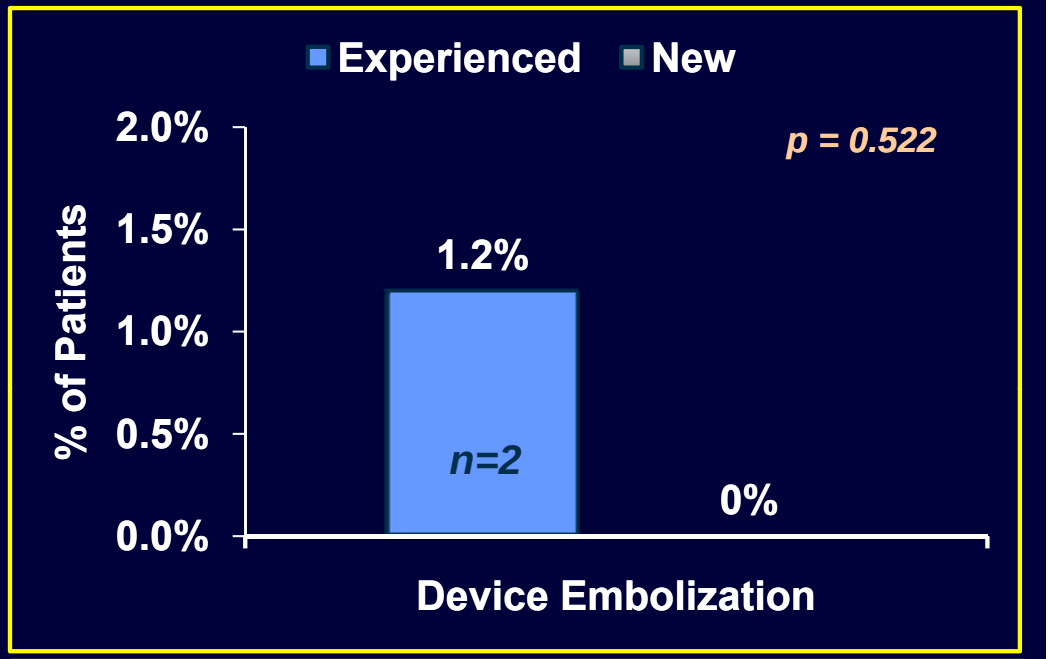
New vs Experienced Operators

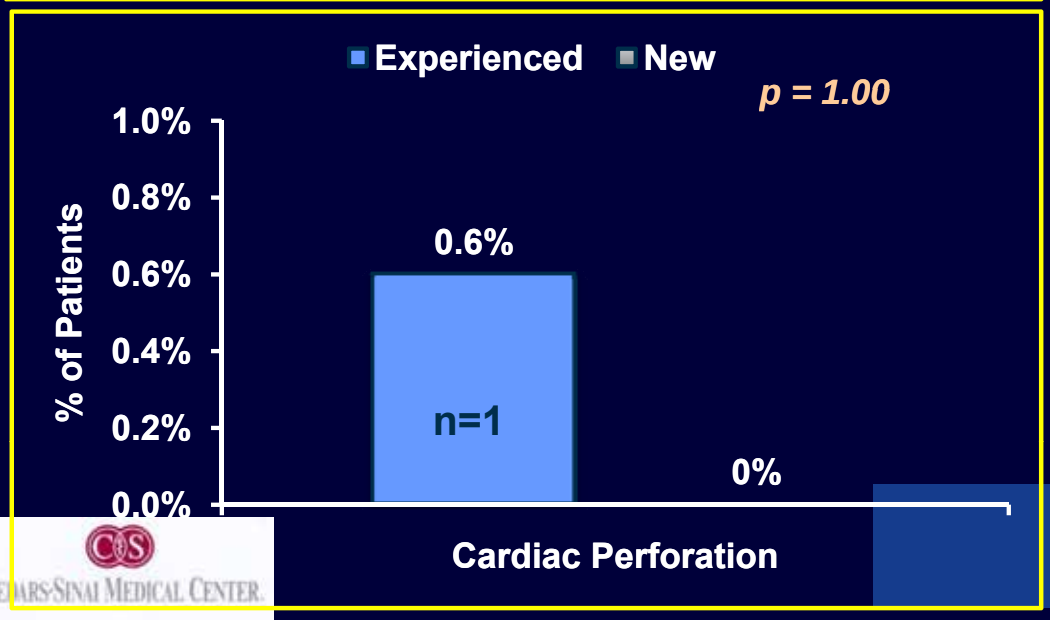
- Protocol required a minimum of 20% of subjects enrolled at new centers and 25% of subjects enrolled by new operators
- 18 out of 41 centers did not have prior WATCHMAN experience
- 40% of patients enrolled at new sites and by new operators

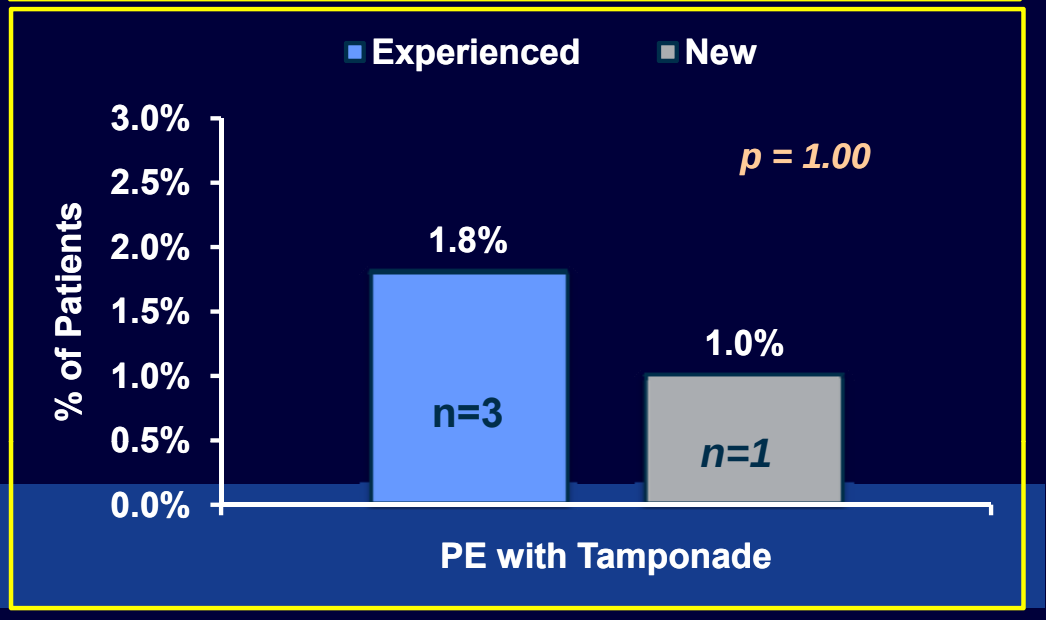


PREVAIL Complications
New vs Experienced Operator

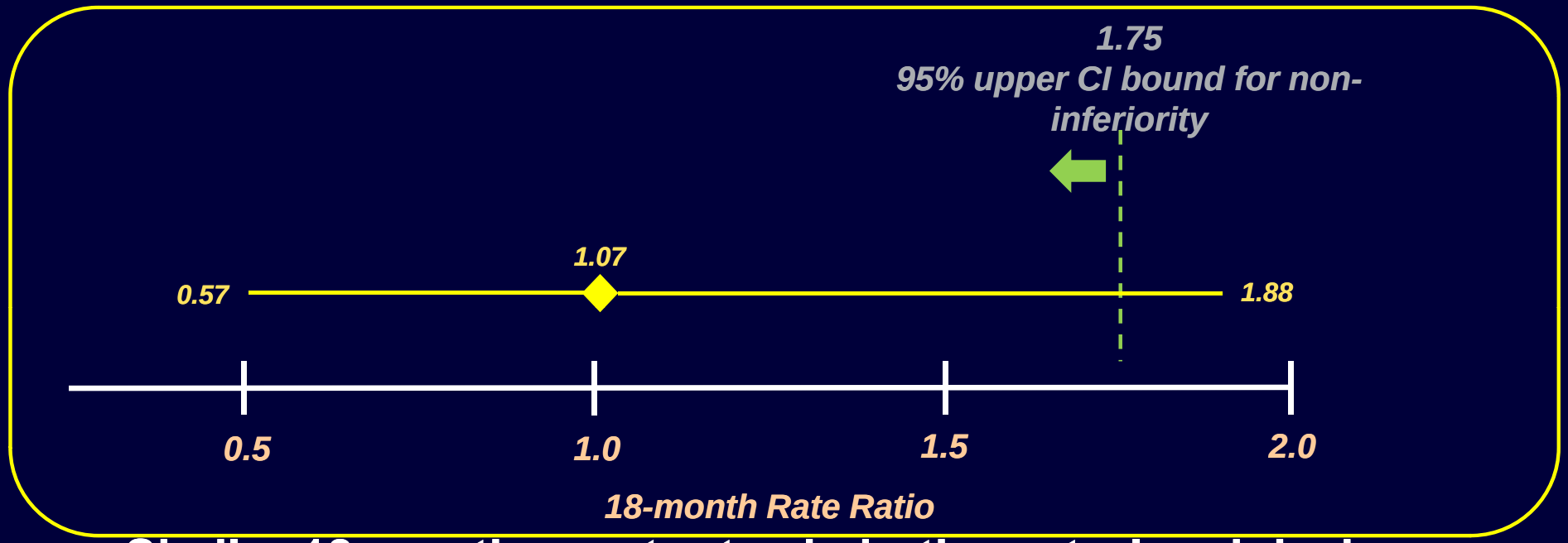








Second Primary Endpoint
Composite 18-month Efficacy



- 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

PREVAIL

Control (Warfarin) Group Performance

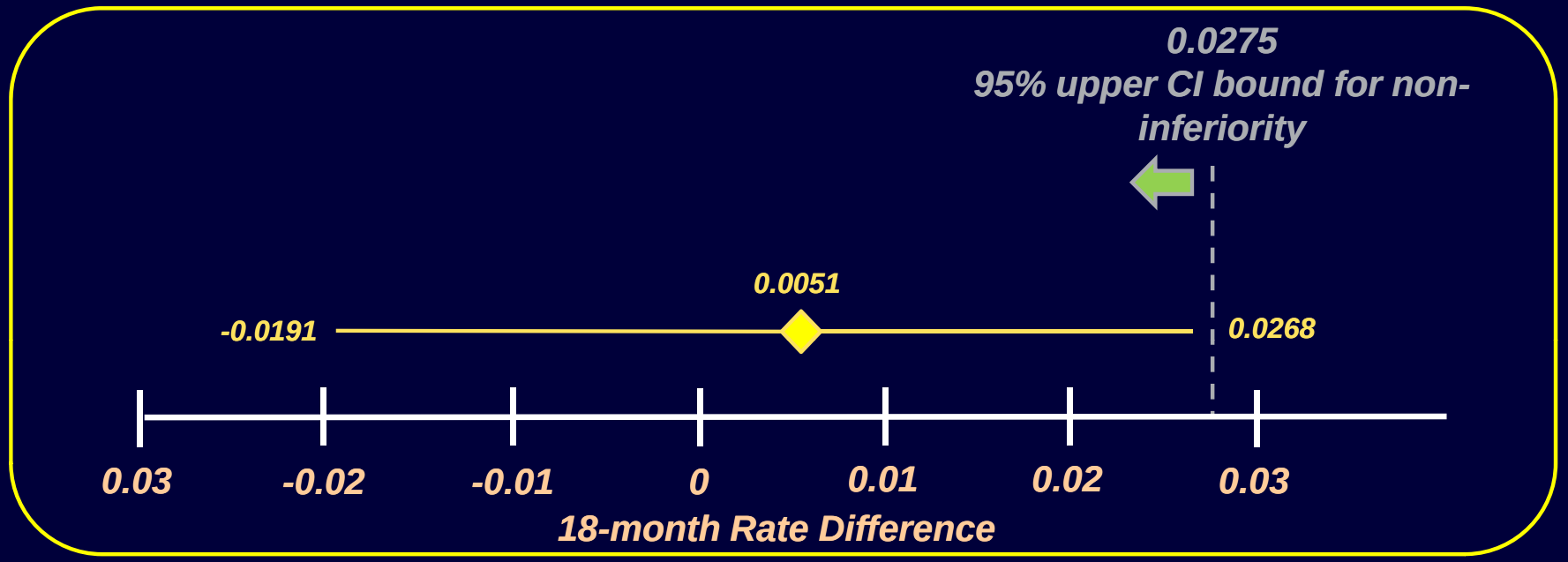
- In spite of the high average $CHADS_2$ score of 2.6 in the control group, the observed rate of stroke in the PREVAIL Control group was lower than in other published warfarin studies
- PREVAIL control group rate = 0.7 (95% CI 0.1, 5.1)
  - Wide confidence bounds due to small number of patients with 18-months of follow-up

Trial	Control (Warfarin) Group Stroke, Systemic Embolism Rate (Per 100 PY)
PROTECT AF[1]	1.6
RE-LY (Dabigatran)[2]	1.7
ARISTOTLE (Apixaban)[3]	1.6
ROCKET AF (Rivaroxaban)[4]	2.2
PREVAIL	**0.7**

Results are preliminary; final validation not yet complete

[1]Ischemic stroke rate from Holmes et al. Lancet 2009; 374:534-42
[2]Connolly et al. N Engl J Med 2009; 361:1139-51
[3]Granger et al. N Engl J Med 2011; 365:981-92
[4]Patel et al. N Engl J Med 2011; 365:883-91

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

Conclusions

- LAA occlusion using the Watchman Device is an alternative to long term antithrombotic therapy in patients with chronic non rheumatic AF
  - Safe and effective
  - Evidence of long term benefits
  - Evidence supported by two randomized studies
  - Procedure is successful even with new operators

Question 1

- The totality of data provides reasonable evidence of safety of the procedure.
  - Yes
  - No

Question 2

- The data provides valid scientific evidence of that provides reasonable assurance of the ***effectiveness*** of the Watchman Device
  - Yes
  - No

Question 3

- The totality of the data provides valid scientific evidence that establishes a reasonable assurance that the benefits associated LAA appendage occlusion outweigh the risks in AF patients who are at high risk of stroke/bleeding
  - Yes
  - No

If in Korea, we believe in evidence based medicine

WATCHMAN Will PREVAIL

CEDARS-SINAI MEDICAL CENTER

LAA Closure/Occlusion/Excision

Recommendations for LAA closure/occlusion/excision		
Recommendations	**Class**	**Level**
Interventional, percutaneous LAA closure may be considered in patients with a high stroke risk and contraindications for long-term oral anticoagulation.	**IIb**	**B**
Surgical excision of the LAA may be considered in patients undergoing open heart surgery.	**IIb**	**C**

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Summary Conclusions

WE HOPE TO PREVAIL

tested in two FDA sponsored randomized which has compared the prevention of LAA clot by occlusion of LAA is non inferior to long term anticoauglation.

- LAA occlusion with the Watchman device is non inferior to coumadin in prevention strokke
- The Watchman device is CE Mark approved in Europe, investigational in US

- It is hoped that the latest long term data and including data from the PREVAIL study will support full approval of the device in US by this year