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

David R. Holmes, Jr., M.D.

Mayo Clinic, Rochester

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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

Presenter Disclosure Information

David R. Holmes, Jr., M.D.

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

The following relationships exist related to this presentation:

Both Mayo Clinic and I have a financial interest in technology related to this research. That technology has been licensed to Atritech.

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PREVAIL
Participating Centers

Swedish Cardiovascular Research

Iowa Heart Center

St. Lukes Hospital, Milwaukee

Minneapolis Heart Institute

Mt. Sinai School of Medicine

Baylor Research Institute

Bryan LGH

Cardiology Associates of N. Mississippi

Emory University Hospital Midtown

Mercy Gilbert Medical Center

The Lindner Center

Lahey Clinic

Massachusetts General

Texas Cardiac Arrhythmia Research Foundation

Carolinas Medical Center

Foundation for Cardiovascular Medicine and Alvarado Hospital

St. Thomas Research Institute

Baptist Hospital of Miami

Cleveland Clinic

Orange County Heart Institute and Research Center

Pinnacle Health Cardiovascular Institute (MHVG)

ZASA Clinical Research

William Beaumont

Columbia University Medical Center

Hospital of the University of Pennsylvania

Mayo Clinic

New York University School of Medicine

NorthShore University Health System

Englewood Hospital and Medical Center

Florida Hospital Orlando

University of Michigan

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Ten additional centers are listed on the next slide

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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Background

- People with AF have 5 times the risk of stroke compared to people without AF[1]
- Stroke is more severe for patients with AF, as they have a 70% chance of death or permanent disability[1]
- AF-associated ischemic strokes generally occlude large intracranial arteries depriving a more extensive region of the brain of blood flow[2]
- Compared with non-AF patients, AF patients have poorer survival and more recurrences of stroke during the first year of follow-up[3]
- Relative or absolute contraindications to long-term anticoagulation are present in up to 40% of AF patients, usually due to a history of bleeding or an elevated risk of falls and trauma. In fact, anticoagulation is not currently utilized in up to 50% of eligible AF patients[3]
- The economic burden of stroke will continue to rise globally as the incidence of stroke increases[4]
- 91% of stroke in AF is caused by thrombus formed in the LAA[5]

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[1]Holmes DR. *Seminars in Neurology.* 2010;30:528–536
[2]Tu HT et al, *Cerebrovascular Disease.* 2010;30(4):389-95
[3]Patel et al, Cardiol Res Pract. 2012; 2012: 610827
[4]Klein A et al, *Datamonitor.* July 2011
[5]Blackshear JL, Odell JA, *Ann of Thor Surgery*, 1996;61:755-759

The WATCHMAN® product is a device for percutaneous closure of the left atrial appendage

- WATCHMAN is a self-expanding nitinol frame with fixation anchors and a permeable fabric cover
- It is designed to be permanently implanted at or slightly distal to the opening of the LAA to trap potential emboli before they exit the LAA

WATCHMAN® LAA Closure Device
Images on file at Boston Scientific Corporation

- Five sizes of device (21, 24, 27, 30 and 33 mm) allow for precise fit within ostium
- It is implanted via a transseptal approach by use of a catheter-based delivery system
- The delivery catheter is capable of recapturing the device if necessary
- Received CE mark in 2005

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WATCHMAN Clinical Program History

- PROTECT AF was a randomized clinical trial which demonstrated WATCHMAN device is non-inferior to warfarin for stroke/thromboembolic protection in patients with non-valvular AF
  - 800 patients enrolled (463 randomized device patients) at 59 centers to be followed through 5 years
  - Reduction in pericardial effusions, procedure related stroke, and procedure time demonstrated from early to late enrolled patients[1]
- Continued Access trial (CAP) demonstrated continued safety improvement with experience
  - Serious pericardial effusion rate was reduced to 2.2%
  - No procedure related strokes occurred
  - Relative risk reduction of 56% (p=0.002) in procedure or device related safety events
  - Relative risk reduction of 58% (p=0.014) in serious pericardial effusions[2]

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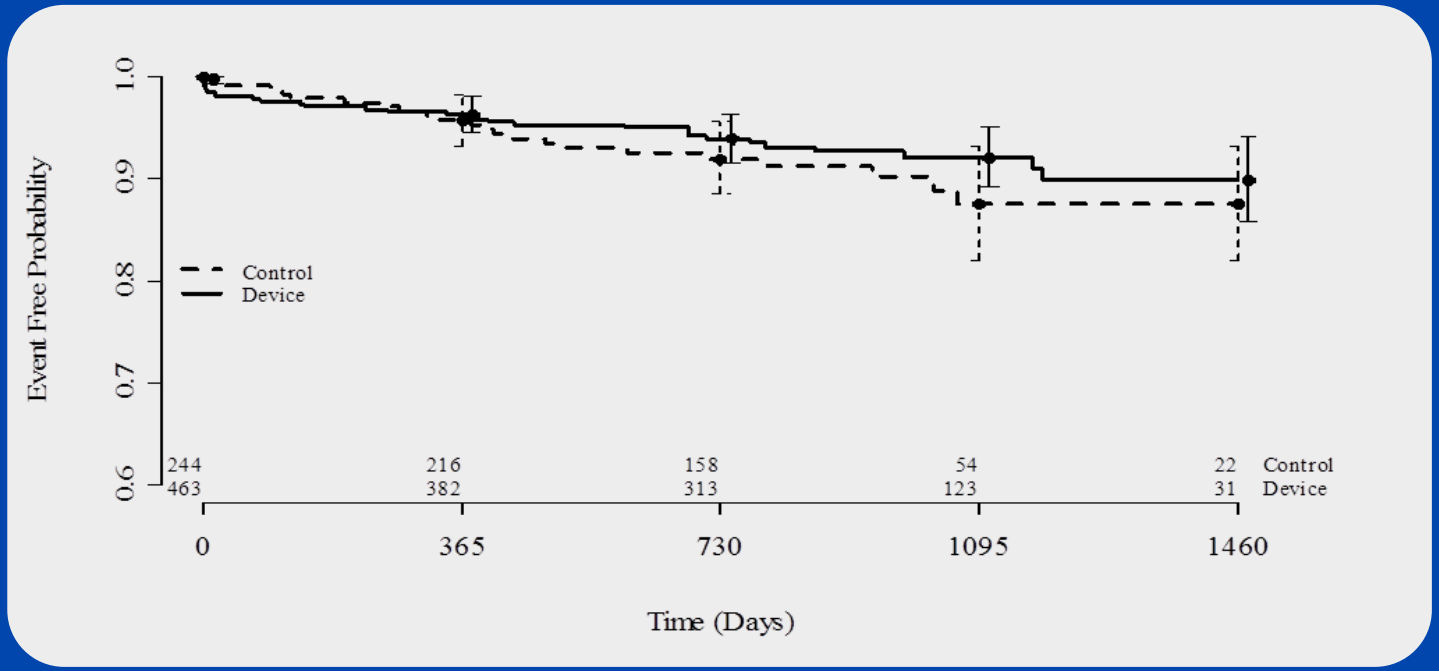
[1] Holmes DR et al. *Lancet.* 2009;374:534–42
[2] Reddy VY et al. *Circulation*. 2011;123:417-424

PROTECT AF
Primary Efficacy Results

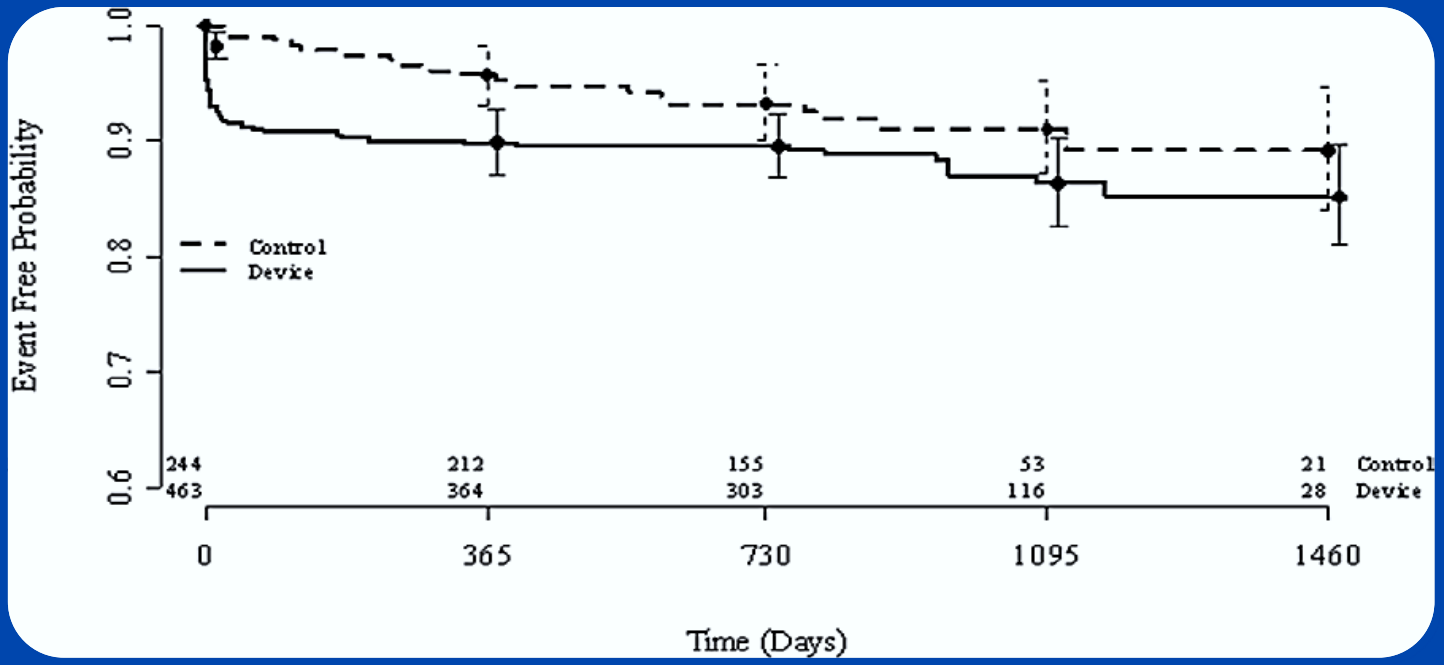
	Device	Control		Posterior Probabilities	
	Observed rate (events per 100 pt-yrs) (95% CrI)	Observed rate (events per 100 pt-yrs) (95% CrI)	Rate Ratio Intervention/Control (95% CrI)	Non-inferiority	Superiority
Primary Efficacy	3.0 (2.1, 4.3)	4.3 (2.6, 5.9)	0.71 (0.44, 1.30)	>0.99	0.88



Reddy, VY et al. Circulation. 2013;127:720-729;.

PROTECT AF
Primary Safety Results

	Device	Control	
	Observed rate (events per 100 pt-yrs) (95% CrI)	Observed rate (events per 100 pt-yrs (95% CrI)	Rate Ratio Intervention/Control (95% CrI)
Primary Safety	5.5 (4.2, 7.1)	3.6 (2.2, 5.3)	1.53 (0.95, 2.70)



Reddy, VY et al. Circulation. 2013;127:720-729;.

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

Rationale

- Concerns with early PROTECT AF safety results
  - High initial rate of pericardial effusions and procedure related strokes
  - Some WATCHMAN patients did not receive their assigned treatment (i.e., implant failures)
  - Safety outcome of procedures performed by new operators
- Second randomized trial to confirm late PROTECT AF and CAP safety results (PREVAIL)

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Study Purpose

- PREVAIL: Prospective Randomized EVAluation of the WATCHMAN LAA Closure Device In Patients with Atrial Fibrillation Versus Long Term Warfarin Therapy
- Prospective, randomized, multicenter study to provide additional information on the safety and efficacy of the WATCHMAN LAA Closure Technology
- Confirmatory study conducted to provide additional information on the implant procedure and complication rates associated with the device

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Study Goals and Design

- Similar design to PROTECT AF: prospective randomized 2:1 (device: control) trial
- 407 randomized patients from 41 US centers
- Confirm the results of PROTECT AF and demonstrate improved safety profile
- Inclusion of new centers and new operators to document that enhancements to the training program are effective
- Roll-in phase allowed new centers to implant 2 patients prior to randomization phase

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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	$CHADS_2 \geq 1$	$CHADS_2 \geq 2$ and $CHADS_2=1$ patients not eligible for aspirin therapy alone

[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

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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

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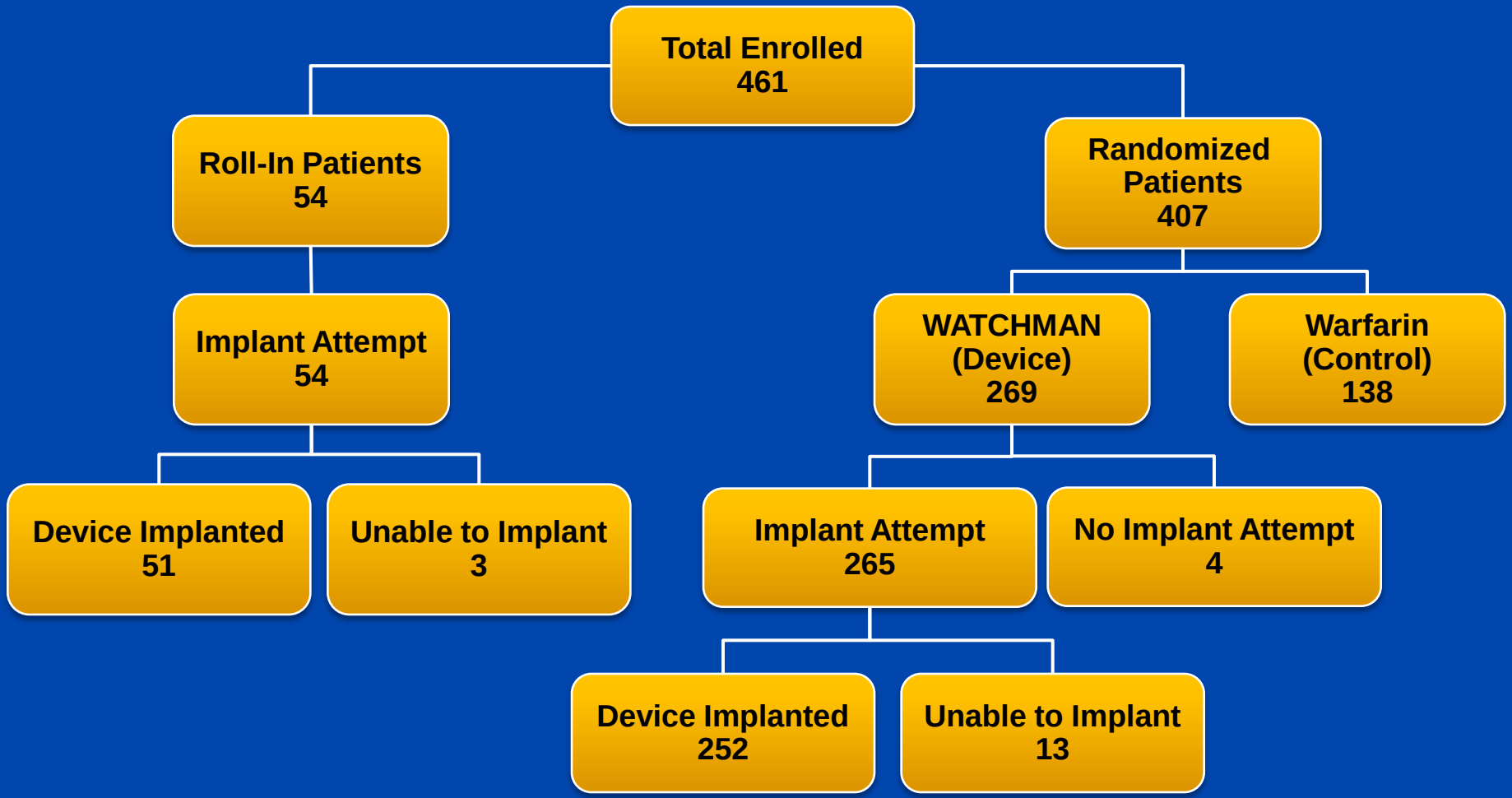
PREVAIL Enrollment



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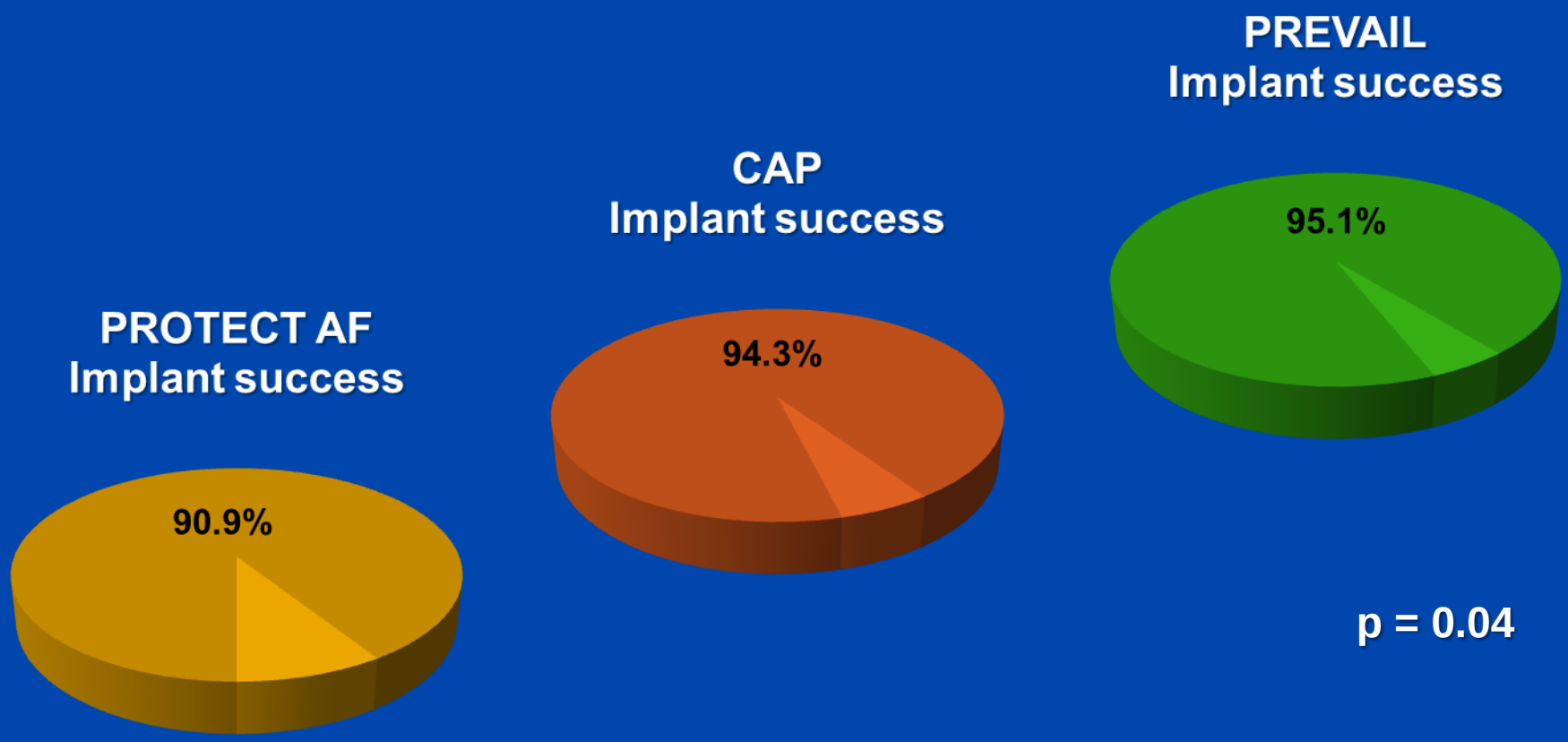
PROTECT AF and CAP data
from Reddy, VY et al. *Circulation*. 2011;123:417-424.

Procedure Implant Success



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

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

First Primary Endpoint

- Acute occurrence of death, ischemic stroke, systemic embolism and procedure or device related complications requiring major cardiovascular or endovascular intervention
  - Timepoint = through 7 days post randomization or hospital discharge, whichever is later
  - Performance goal comparison
  - No comparison with prior studies required
- Additional safety analysis to compare event rates in PREVAIL to prior WATCHMAN studies and determine safety profile

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Events adjudicated by an independent Clinical Events Committee

First Primary Endpoint

N Subjects	% (n/N)	95% CI[1]
269	2.2% (6/269)	2.618%

[1]CI is one-sided

- 6 events in device group
- Success based on upper 95% CI bound for percentage of subjects with event
- Pre-specified criterion met for first primary endpoint (95% Upper confidence bound < 2.67%)

Results are preliminary; final validation not yet complete

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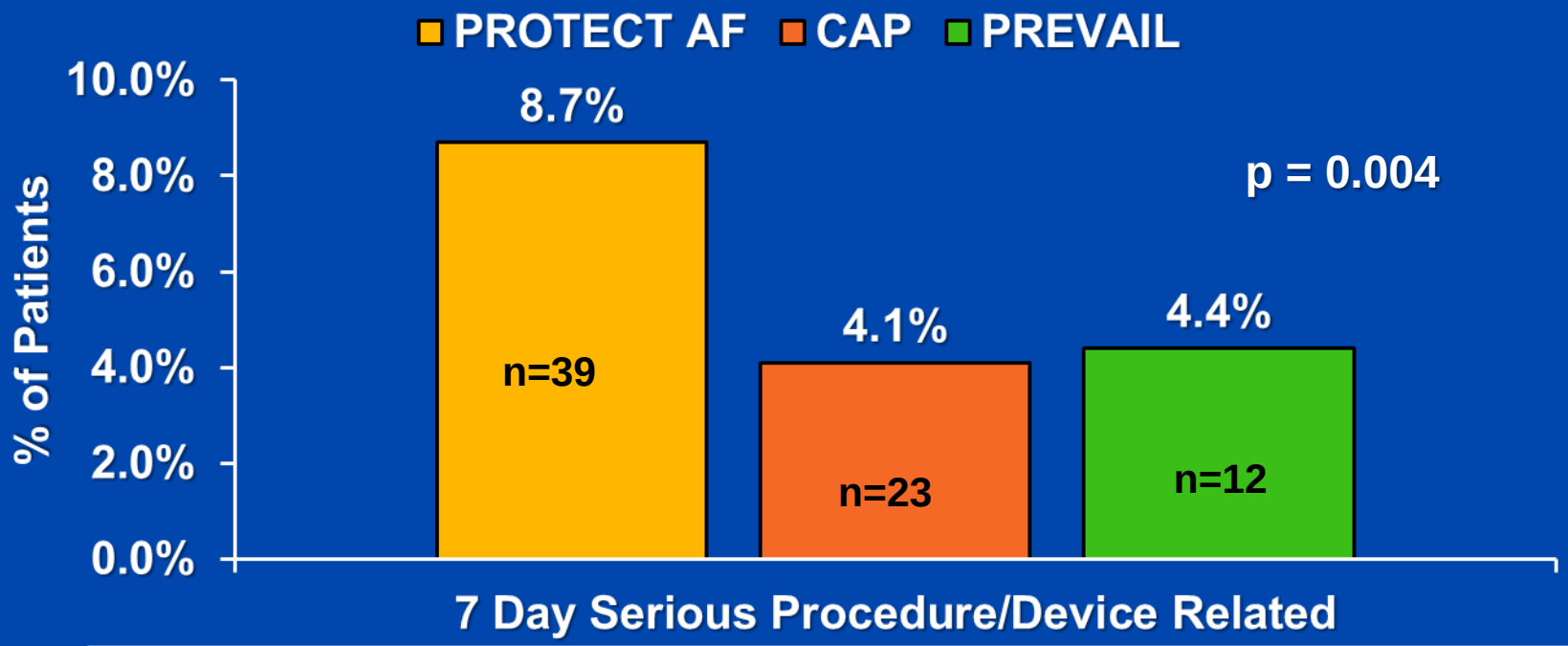
Vascular Complications

- **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 and groin bleeding

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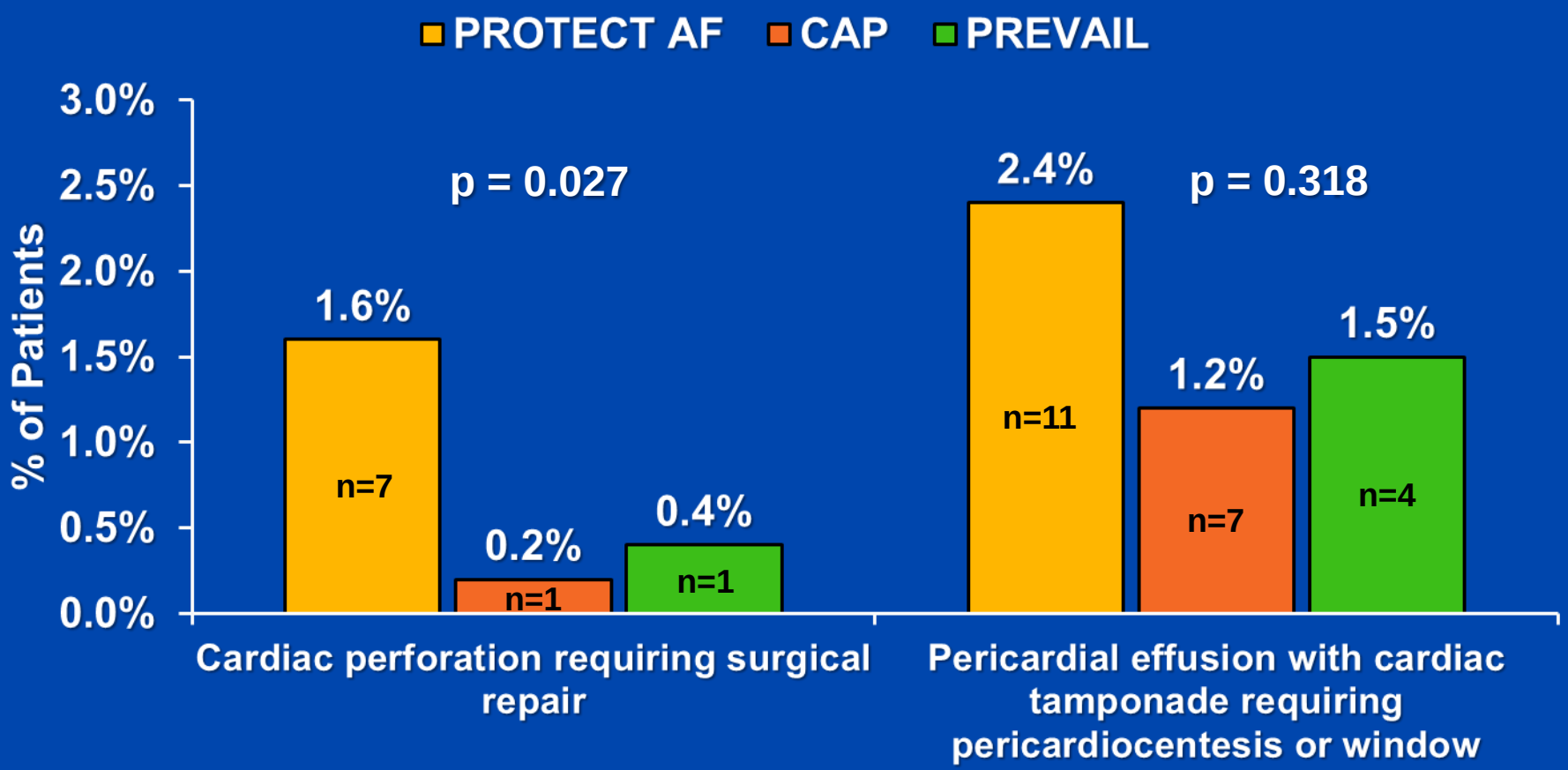
Pericardial Effusions Requiring Intervention



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PROTECT AF and CAP data
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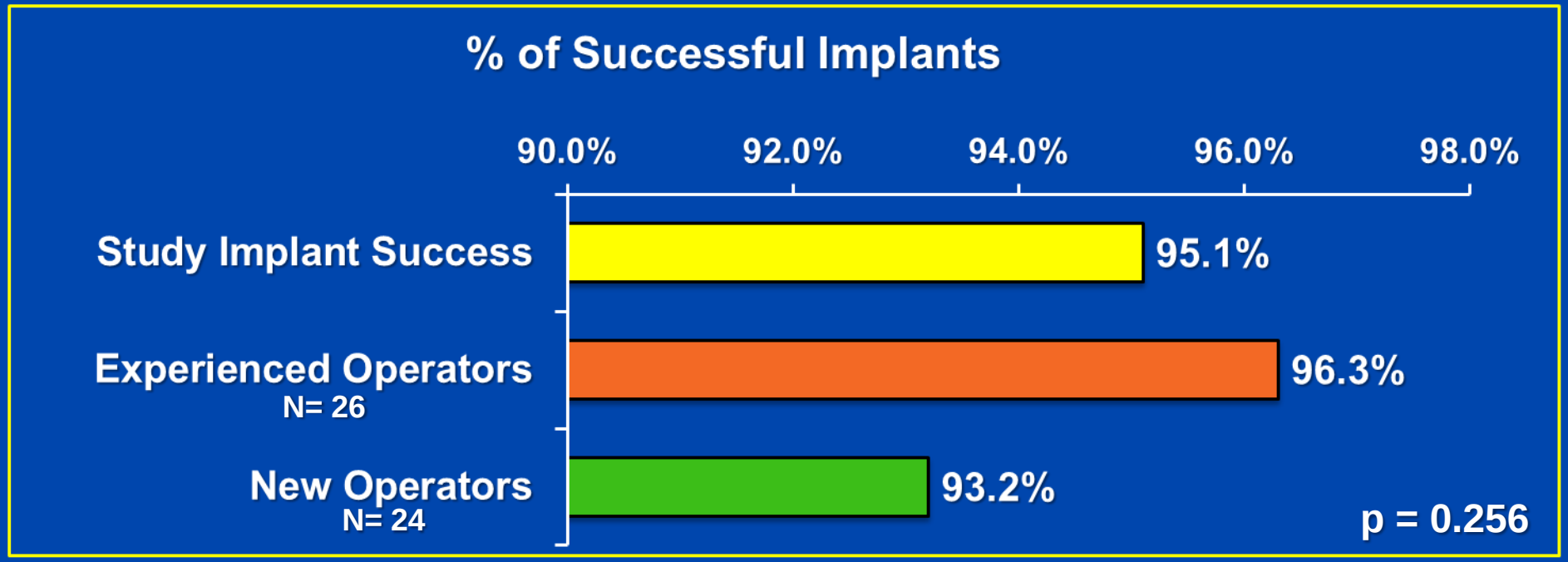
PREVAIL Implant Success
New vs Experienced Operators

- 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



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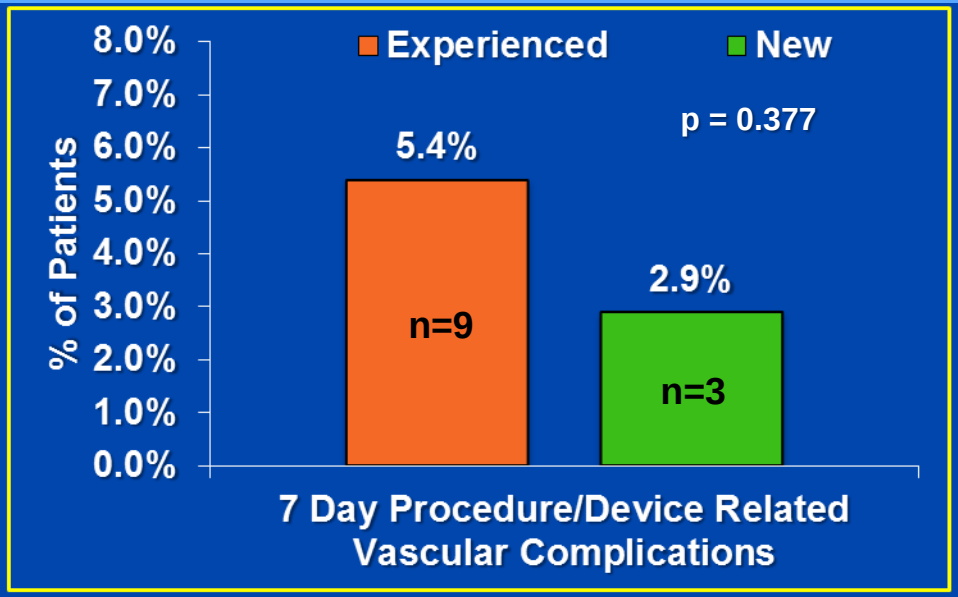
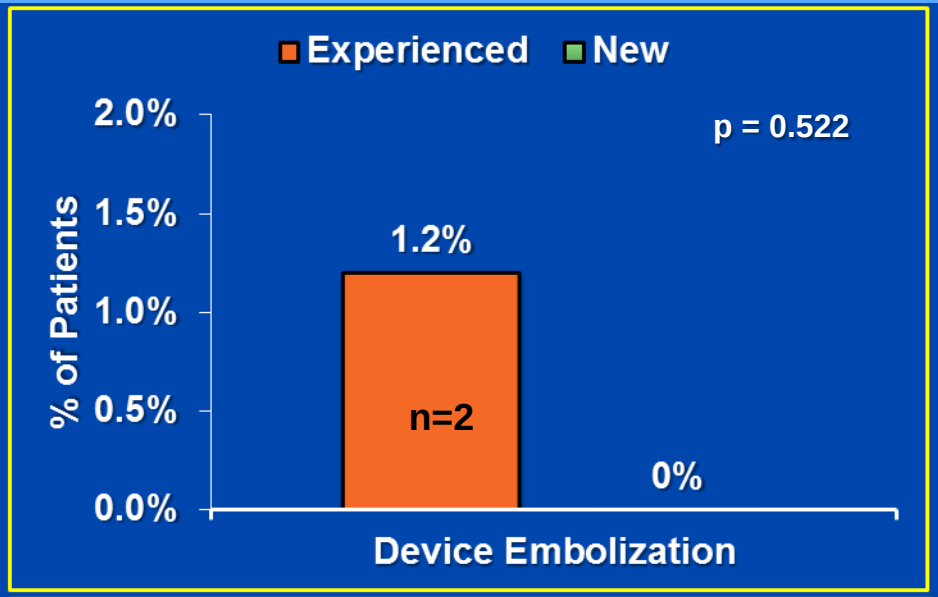
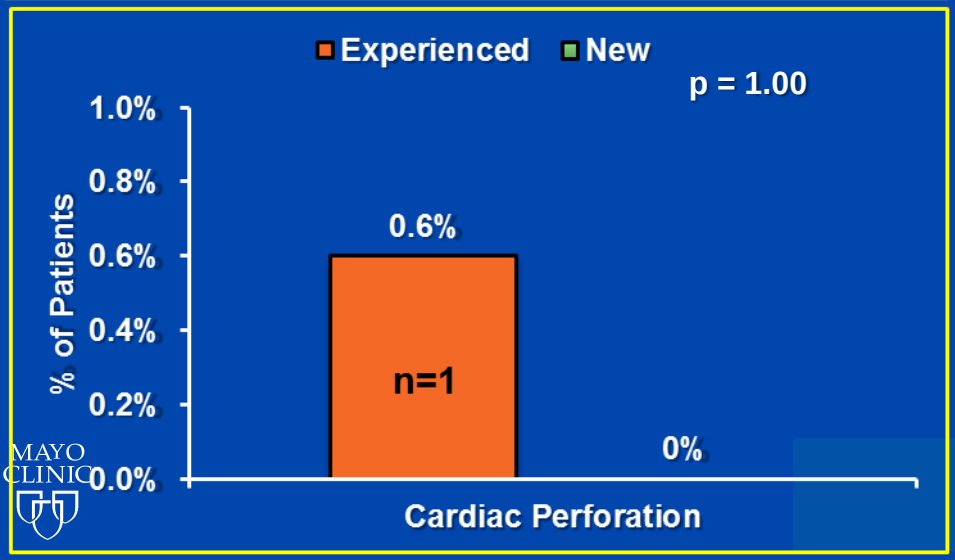
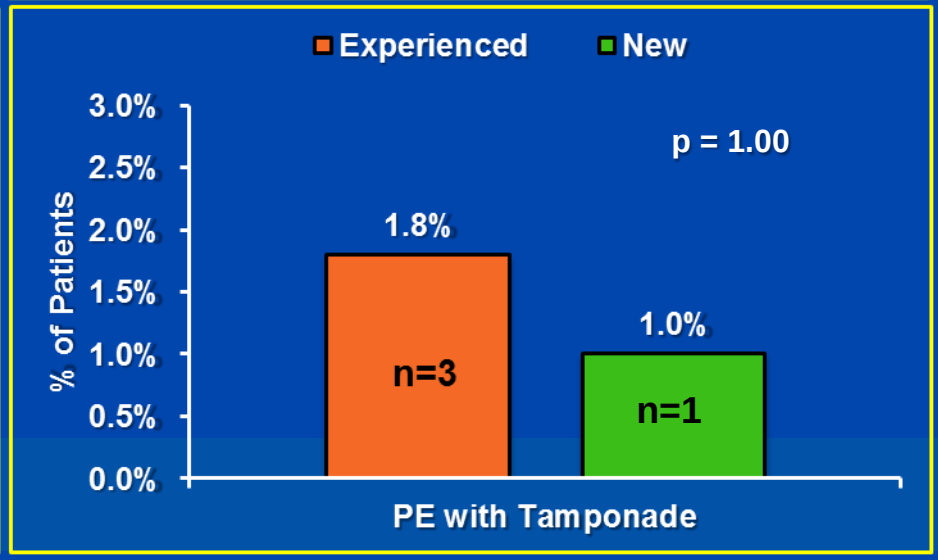
PREVAIL Complications
New vs Experienced Operator









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Second Primary Endpoint

- Comparison of composite of stroke, systemic embolism, and cardiovascular/unexplained death
  - Bayesian piecewise exponential technique used to model 18-month rates, with the historical priors based on data from the previous pivotal trial, PROTECT AF
  - Non-inferiority design with comparison of rate ratio of 18-month event rates

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Second Primary Endpoint

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Ratio (95% CI)
0.064	0.064	1.07 (0.57, 1.88)

- Similar 18-month event rates in both groups
- 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

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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

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[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

- Comparison of ischemic stroke or systemic embolism occurring >7 days post randomization
  - Bayesian piecewise exponential technique used to model 18-month rates, with the historical priors based on data from the previous pivotal trial, PROTECT AF
  - Non-inferiority based rate difference

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Third Primary Endpoint

Device 18-Month Rate	Control 18-Month Rate	18-Month Rate Difference (95% CI)
0.0253	0.0201	0.0051 (-0.0191, 0.0268)

- Pre-specified non-inferiority criterion met for third primary endpoint (95% CI Upper Bound < 0.0275%)
- Endpoint success in the presence of an over performing control group

Results are preliminary; final validation not yet complete

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First Primary Endpoint
Summary

- Acute (7-day) occurrence of death, ischemic stroke, systemic embolism and procedure or device related complications requiring major cardiovascular or endovascular intervention
  - Pre-specified criterion met for first primary endpoint (95% Upper confidence limit < 2.67%)
- The PREVAIL trial showed:
  - Improved procedural implant success p=0.04
  - Decreased composite vascular complications p=0.004
  - Decreased procedural stroke rates p=0.019
  - Decreased perforations requiring surgical repair p=0.027
  - Little difference in outcome of new versus experienced operators

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Second Primary Endpoint
Summary

- Comparison of composite of stroke, systemic embolism, and cardiovascular/unexplained death
  - Control group had lower than expected event rates (over performing)
  - Similar low event rates in both groups
  - Limited number of patients with follow-up through 18 months thus far (Control = 30 pts, Device = 58 pts)
  - Although event rates were similar, pre-specified non-inferiority criterion was not met (exceeded the upper 95% CI bound)

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Third Primary Endpoint
Summary

- Comparison ischemic stroke or systemic embolism occurring >7 days post randomization
  - Bayesian technique used to model 18-month rates, with the historical priors based on data from the previous pivotal trial, PROTECT AF
  - Pre-specified non-inferiority criterion met (95% CI Upper Bound < 0.0275%)

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Conclusions

- 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

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