Left Atrial Appendage Occlusion: A Valid Option to Anticoagulation for Long-term Prevention of Stroke

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Boston Scientific, St Jude Medical
• Consulting Fees/Honoraria	• Boston Scientiific
• Major Stock Shareholder/Equity	• Coherex
• Royalty Income	
• Ownership/Founder	
• Intellectual Property Rights	
• Other Financial Benefit	

Introduction

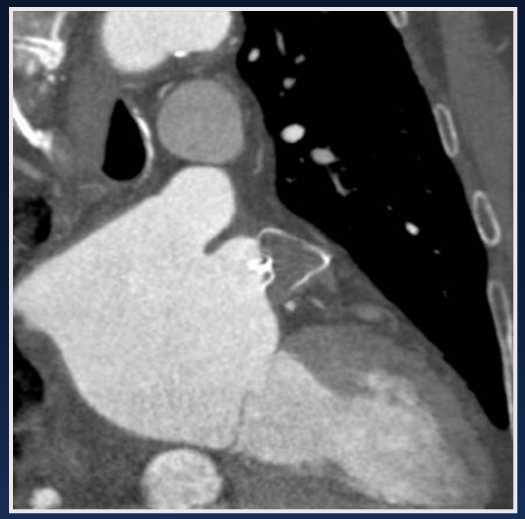
- Ischemic stroke is the major complication associated with atrial fibrillation (AF)
- Warfarin and the newer antithrombotic agents (Dabigatran, Rivaroxaban, Ep) is effective in reduction of the ischemic stroke risk in AF patients
- However long term antithrombotic therapy have limitations
  - Compliance
  - Bleeding risk
  - Drug failure

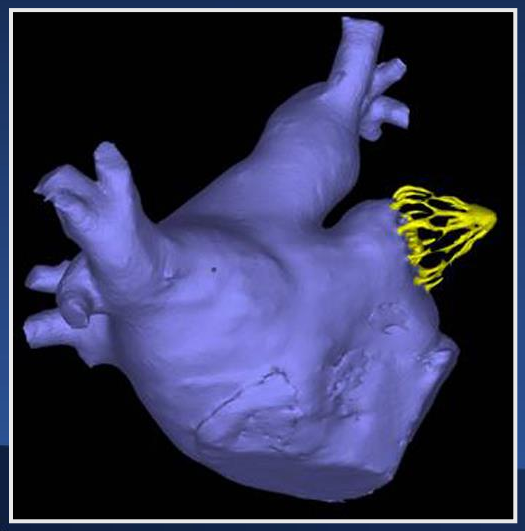
Hypothesis of Left atrial appendage closure

- Thrombus arrising in the Left atrial appendage(LAA) is the major cause of stroke in patients with atrial fibrillation (AF)
- Percutaneous closure of the LAA rather than long term anticoagulant therapy is option to prevent stroke in AF patients
- Recently studies are completed or are ongoing using different devices have supported this hypothesis

Stroke and Atrial Fibrillation

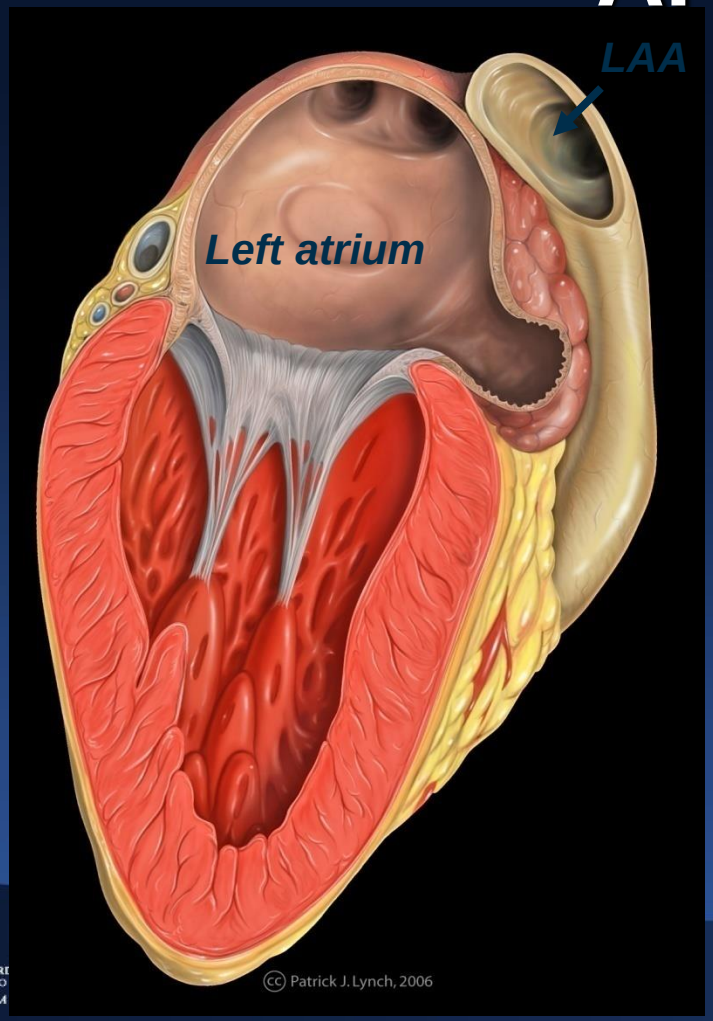
Alternative to Warfarin or NOACS

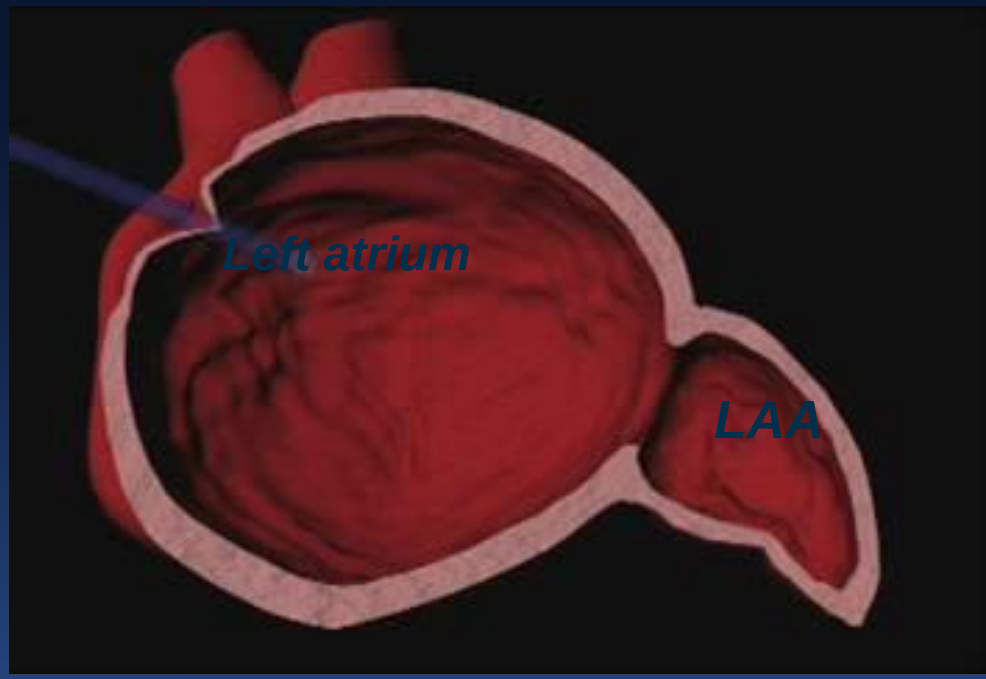




- **Patients who could be treated with warfarin/NOACS**
- **Patients who chose not to be treated with warfarin/NOACS**
- **Contraindications to warfarin/NOACS**

Left atrial appendage(LAA) is the source of thrombus in over 90% of AF patients





Prevention of stroke in AF: Treatment Options

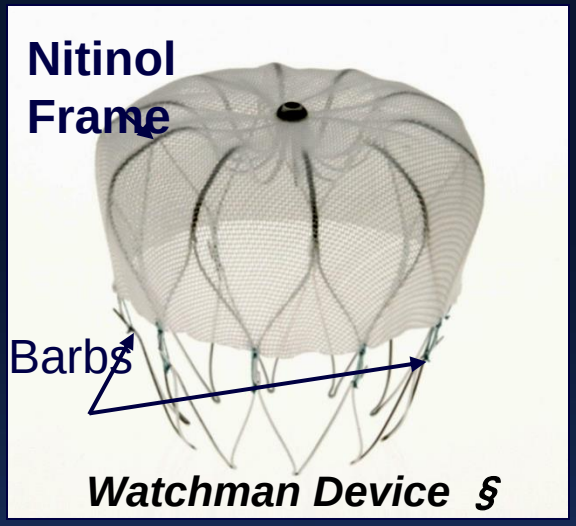
- Long Term antithrombotic therapy
  - Coumadin therapy
  - New oral anticoagulants: Dabigatran, Rivaroxaban, Apixaban
  - Antiplatelet agents
- Surgical Amputation or Ligation of LAA
- Percutaneous Occlusion of the LAA
  - The Watchman® System
  - Amplatzer Cardiac Plug
  - Coherex WaveCrest LAA Occlusion System

New Oral Agents versus Coumadin

- Equivalent or slightly better in reduction of stroke
- 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

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

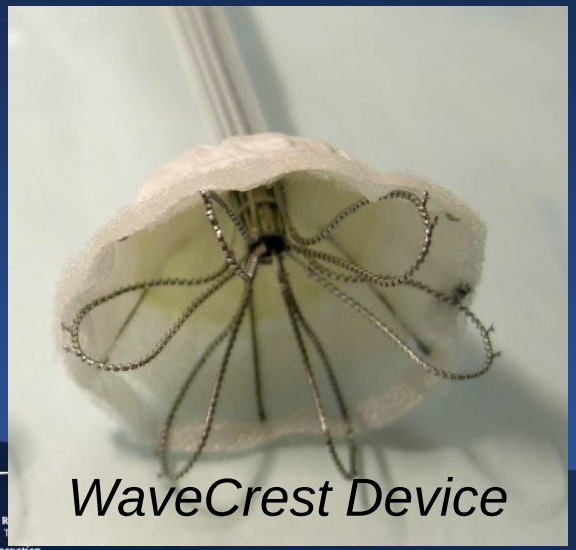
LAA occlusion Devices (Endovascular approach)



Watchman Device §

Amplatzer Cardiac Plug §

Investigational in US

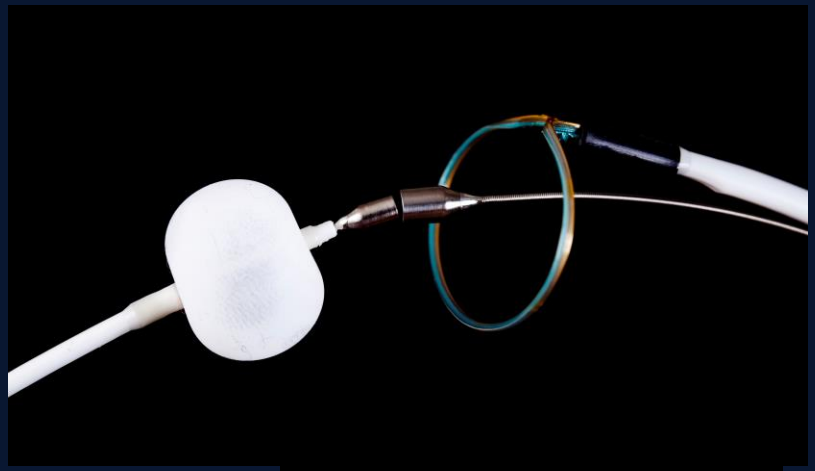


WaveCrest Device

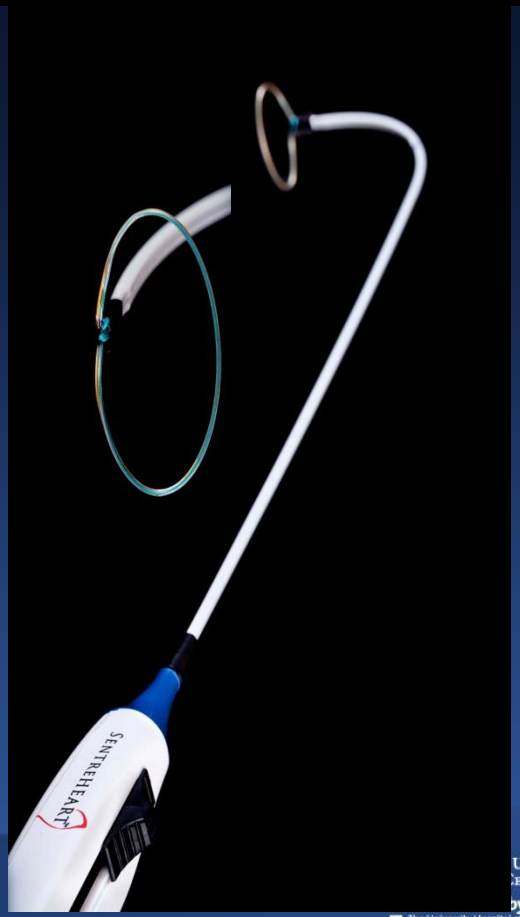
Investigational in Europe

LAA occlusion Devices

Transpericardial approach



- **Lariat Device (Sentreheart)**



Clinical Studies

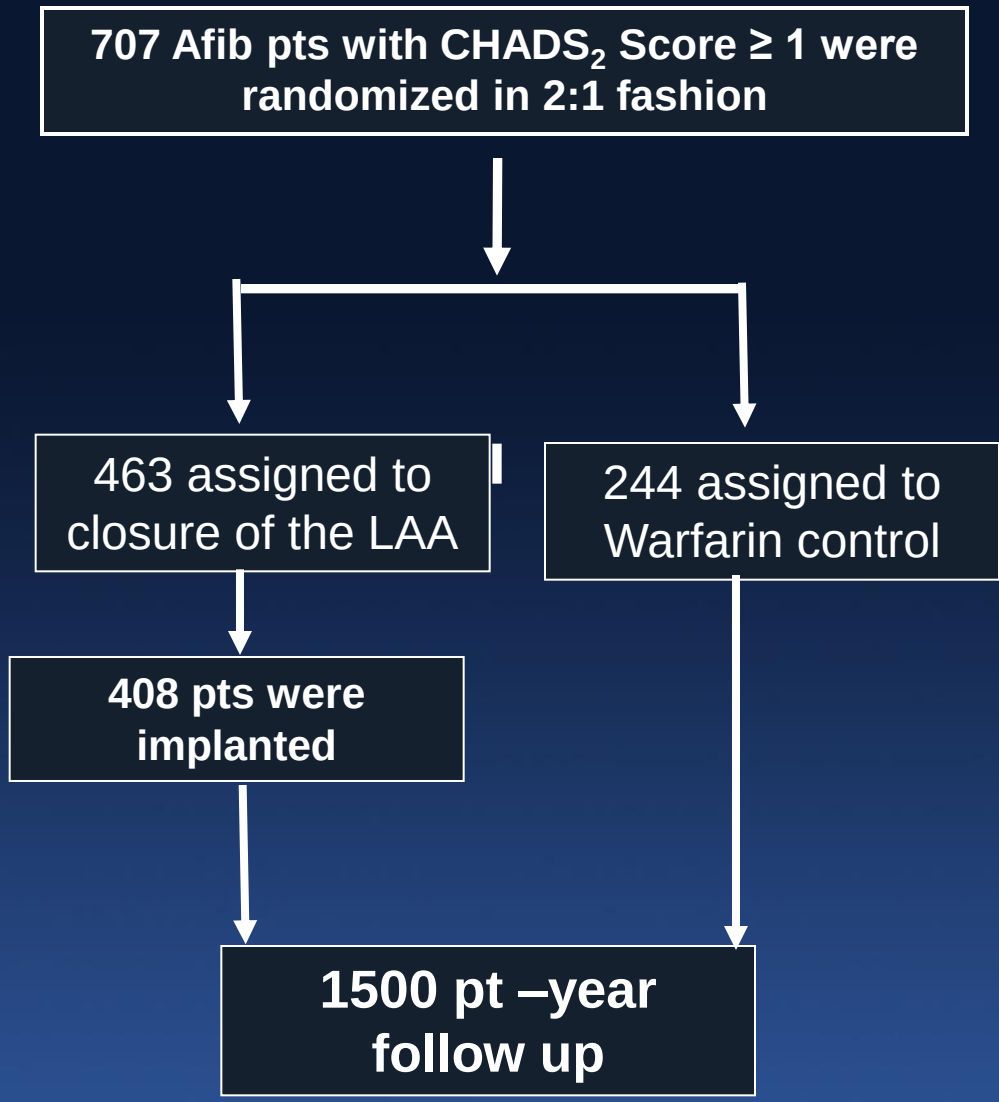
STUDY	PATIENTS	SITES	COMMENTS
Pilot	66	8	• 318 patient years of follow-up • 30 patients with 5+ years of follow-up
PROTECT AF	800	59	• 1,500 patient years of follow-up • 27 months average follow-up per patient
Continued Access Registry (CAP)	566	26	• Significantly improved safety results
ASAP	150	4	• 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

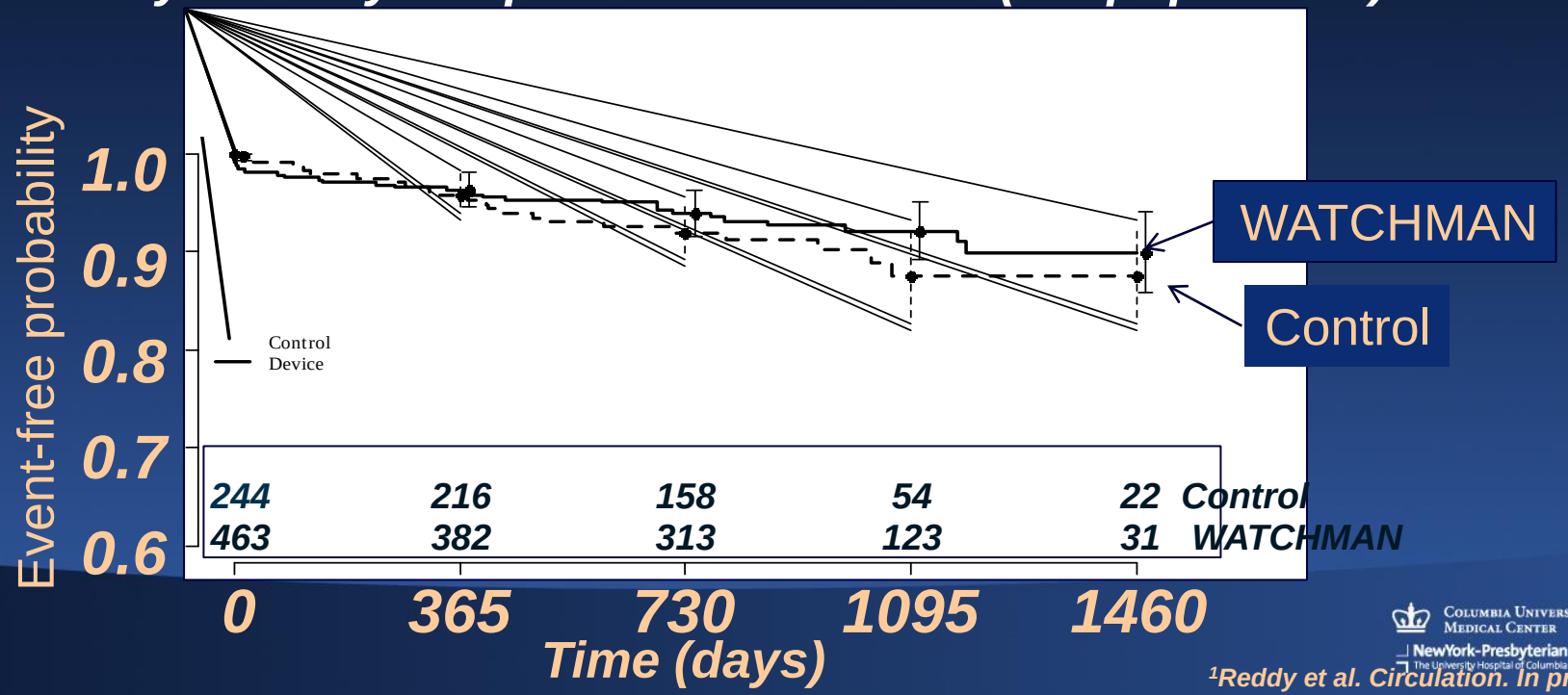


PROTECT-AF Trial: LAA Closure is effective in stroke prevention

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.

Long Term Results of PROTECT AF:
The Mortality Effects of Left Atrial Appendage Closure *versus* Warfarin for Stroke Prophylaxis in AF

Vivek Y. Reddy[1,2,3], Shephal K Doshi[2], Horst Sievert[4], Maurice Buchbinder[5], Petr Neuzil[3], Kenneth Huber[6], Saibal Kar[7], Jonathan L. Halperin[1], Brian Whisenant[8], Vijay Swarup[9] and David Holmes[10]

[1]Mount Sinai School of Medicine, NY; [2]Pacific Heart Institute, CA; [3]Homolka Hospital, Prague; [4]Sankt Katharinen, Frankfurt; [5]Foundation for Cardiovascular Medicine, CA; [6]St Luke's Hospital, MO; [7]Intermountain Medical Center, UT; [8]Cedars Sinai Medical Center, CA; [9]Arizona Heart Rhythm Center, AZ; [10]Mayo Clinic, MN

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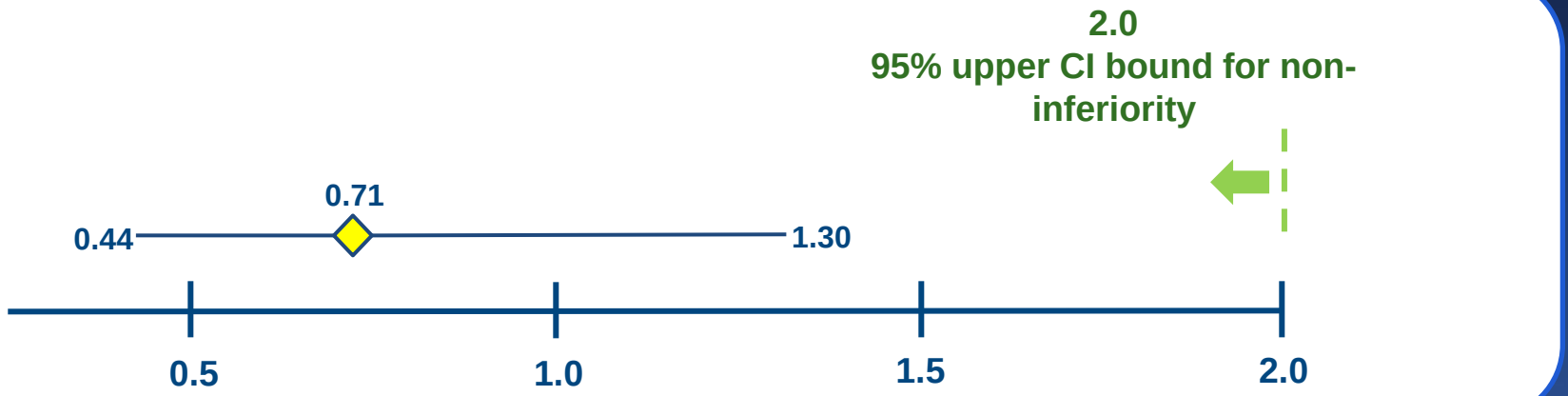
PROTECT-AF:
Efficacy at 1500 pt-yrs / 2.3 yr Follow-up

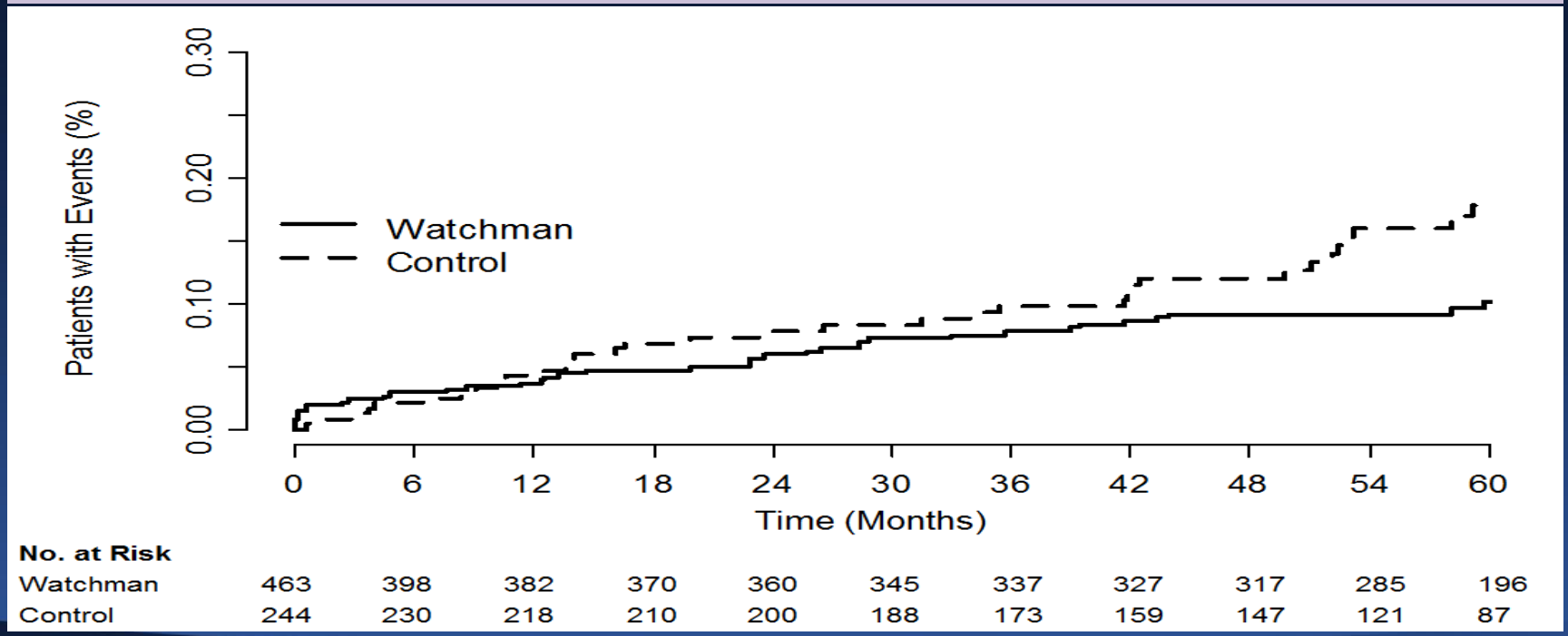
Cohort	WATCHMAN		Control		Rel. Risk (95% CI)		Posterior Probabilities	
	Rate (95% CI)		Rate (95% CI)				Non-inferiority	Superiority
1065 pt-yrs	3.0	1.9, 4.5	4.9	2.8, 7.1	0.62	0.35, 1.25	>0.999	0.900
1500 pt-yrs	3.0	2.1,4.3	4.3	2.6, 5.9	0.71	0.44, 1.30	>0.999	0.846



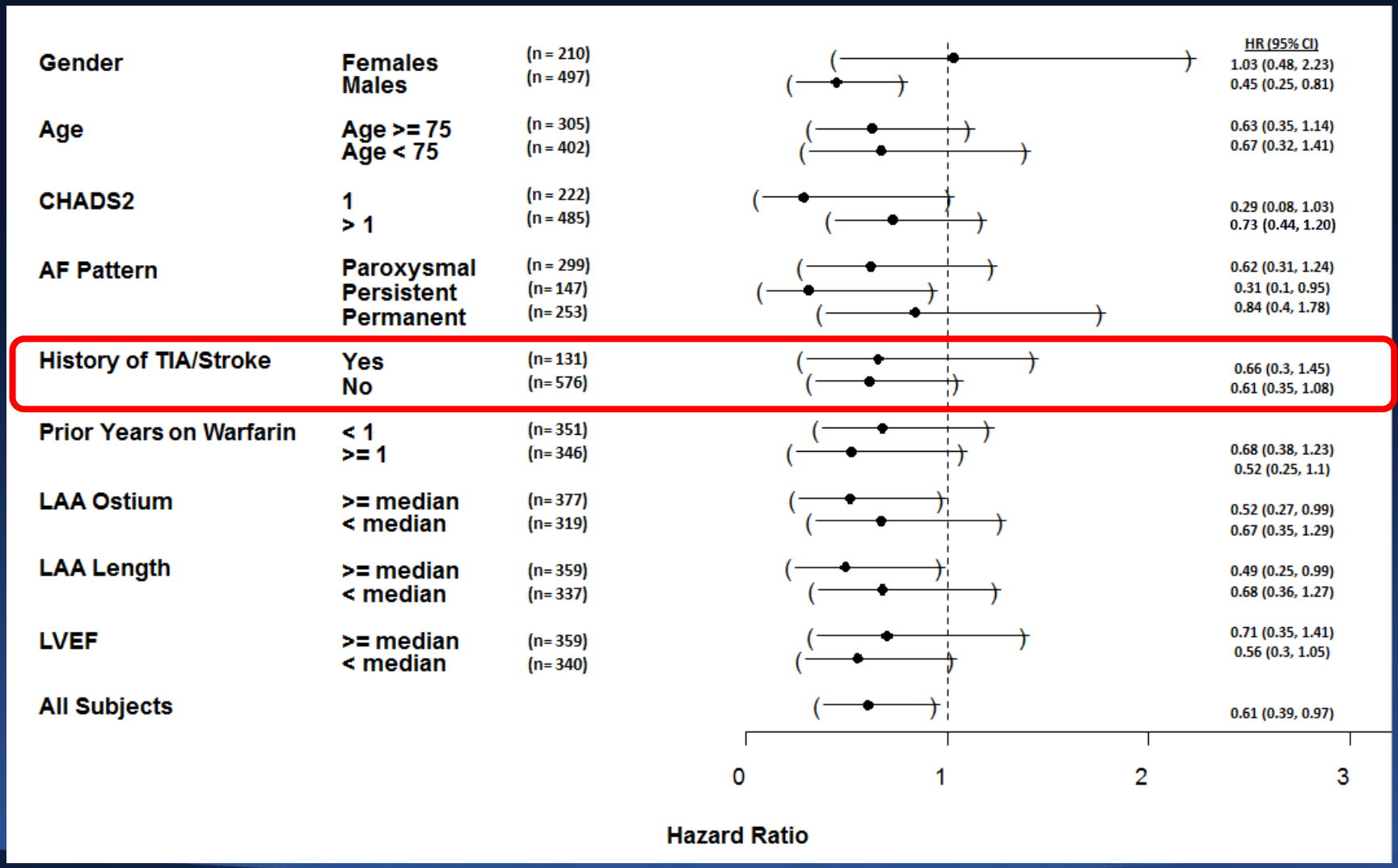
DR.Holmes, VR.Reddy, ZG.Turi, et al, Lancet. 2009;374:534.
V.Reddy, S.Doshi, H.Sievert et al, Circulation 2013;127:720-

PROTECT-AF:
Primary Efficacy Endpoint

Event	Watchman Group (n = 463) Events/ Patient-Years	Watchman Group (n = 463) Observed Rate (Events per 100 Patient-Years) (95% CrI)	Warfarin Group (n = 244) Events/ Patient-Years	Warfarin Group (n = 244) Observed Rate (Events per 100 Patient-Years) (95% CrI)	Rate Ratio (Watchman/Warfarin) (95% CrI)	Posterior Probabilities Non-inferiority	Posterior Probabilities Superiority
Primary Efficacy Endpoint	39/1720.2	2.3 (1.7, 3.2)	34/900.8	3.8 (2.5, 4.9)	0.60 (0.41, 1.05)	>0.999	0.960



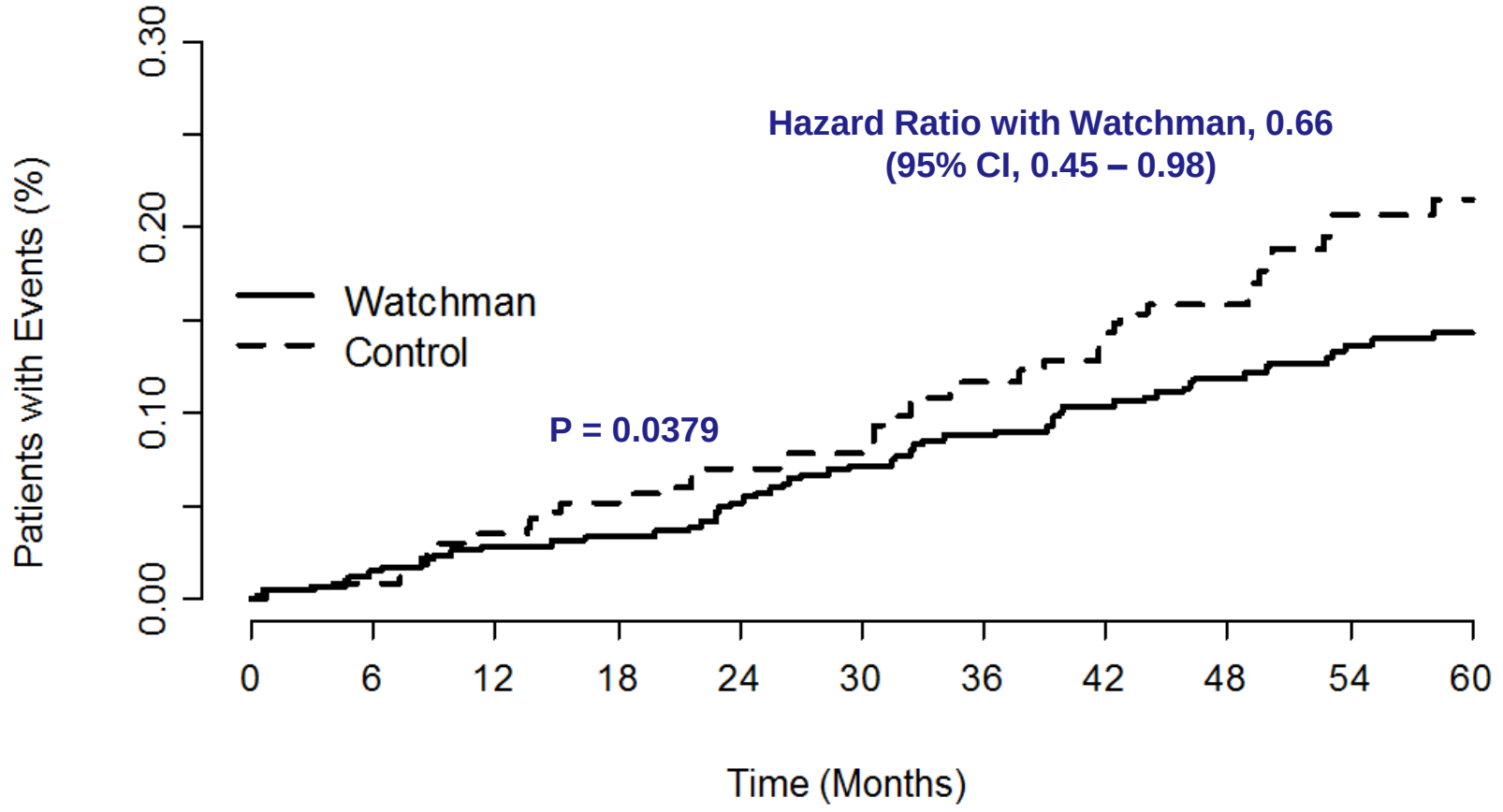
Primary Efficacy Endpoint:
Relative Risks According to Subgroups



PROTECT-AF:
Primary Efficacy Endpoint

Event	Watchman Group (n = 463)		Warfarin Group (n = 244)			Posterior Probabilities	
	Events/ Patient-Years	Observed Rate (Events per 100 Patient-Years) (95% CrI)	Events/ Patient-Years	Observed Rate (Events per 100 Patient-Years) (95% CrI)	Rate Ratio (Watchman/Warfarin) (95% CrI)	Non-inferiority	Superiority
Primary Efficacy Endpoint	39/1720.2	2.3 (1.7, 3.2)	34/900.8	3.8 (2.5, 4.9)	0.60 (0.41, 1.05)	>0.999	0.960
Stroke	26/1720.7	1.5 (1.0, 2.2)	20/900.9	2.2 (1.3, 3.1)	0.68 (0.42, 1.37)	0.999	0.825
Ischemic Stroke	24/1720.8	1.4 (0.9, 2.1)	10/904.2	1.1 (0.5, 1.7)	1.26 (0.72, 3.28)	0.780	0.147
Hemorrhagic Stroke	3/1774.2	0.2 (0.0,0.4)	10/916.2	1.1 (0.5, 1.8)	0.15 (0.03, 0.49)	>0.999	0.999
Systemic Embolization	3/1773.6	0.2 (0.0, 0.4)	0/919.5	0.0	NA	-	-
Cardiovascular Death	17/1774.3	1.0 (0.6, 1.5)	22/919.4	2.4 (1.4, 3.4)	0.40 (0.23, 0.82)	>0.999	0.995

Intention-to-Treat:
All-Cause Mortality



No. at Risk

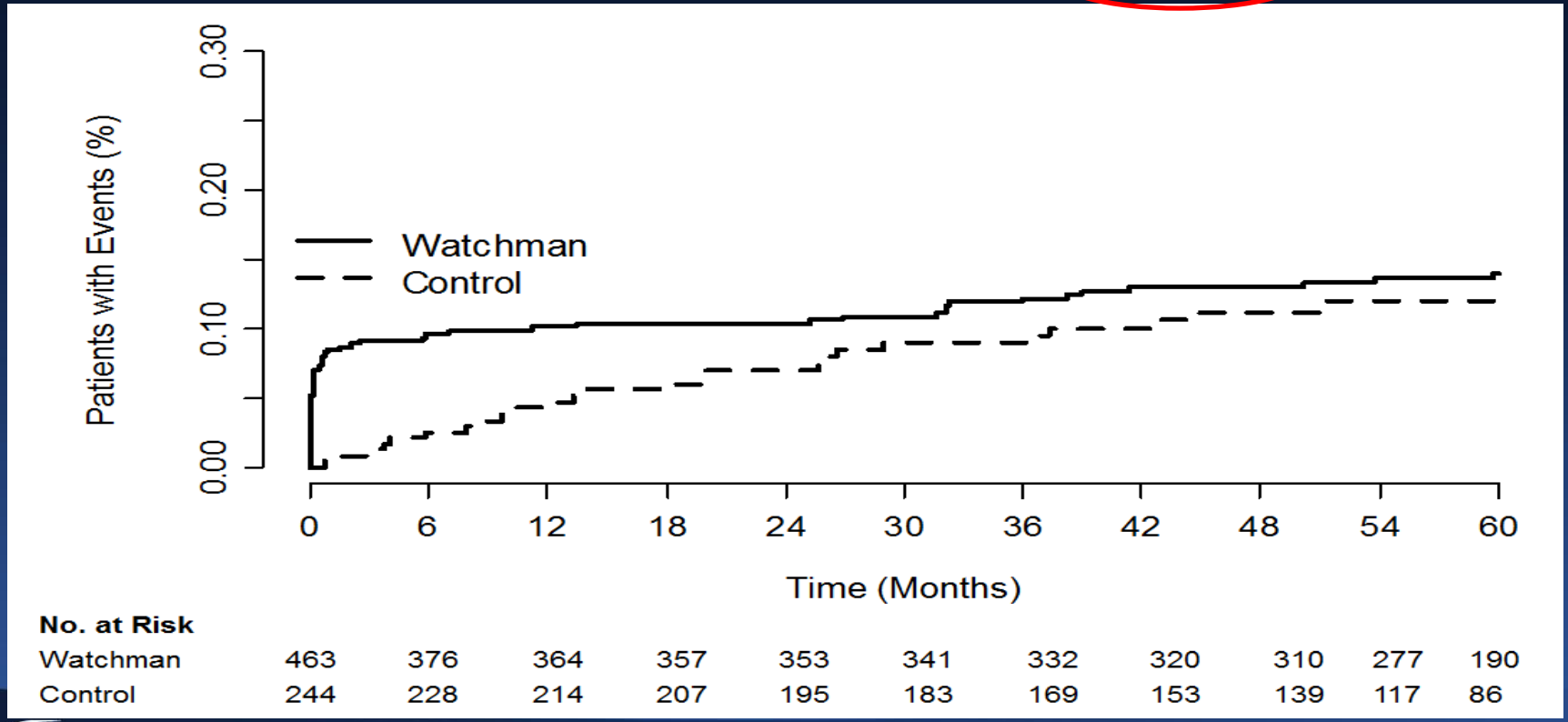
Watchman	463	404	389	381	373	360	352	341	330	294	202
Control	244	233	222	216	204	193	177	163	150	125	92

PROTECT AF:
Causes of Death

Cause	Watchman Group (n=463)	Warfarin Group (n=244)	p value
Cardiovascular	13 / 2.8%	12 / 4.9%	0.1973
Cancer	10 / 2.2%	3 / 1.2%	0.5584
Pulmonary	9 / 1.9%	9 / 3.7%	0.2082
Neurologic	5 / 1.1%	3 / 1.2%	1.0000
Multisystem organ failure	5 / 1.1%	1 / 0.4%	0.6700
Hemorrhagic Stroke	2 / 0.4%	7 / 2.9%	0.0098
Other	9 / 1.9%	6 / 2.5%	0.7844

PROTECT AF:
Primary Safety Endpoint

Event	Watchman Group (n = 463) Events/ Patient-Years	Watchman Group (n = 463) Observed Rate (Events per 100 Patient-Years) (95% CrI)	Warfarin Group (n = 244) Events/ Patient-Years	Warfarin Group (n = 244) Observed Rate (Events per 100 Patient-Years) (95% CrI)	Rate Ratio (Watchman/Warfarin) (95% CrI)	Posterior Probabilities Non-inferiority	Posterior Probabilities Superiority
Primary Safety Endpoint	60/1666.2	3.6 (2.8, 4.6)	27/878.2	3.1 (2.0, 4.3)	1.17 (0.78, 1.95)	0.980	0.196



Primary Safety Endpoint:
Components of the Safety Endpoint

Event	Watchman Group (n = 463) Total Events No. (%)	Early Events No. (%)	Late Events No. (%)	Warfarin Group (n = 244) Events No. (%)
Serious pericardial effusion	22 (4.8%)	22 (4.8%)	0 (0.0%)	---
Major bleeding	22 (4.8%)	3 (0.6%)	19 (4.1%)	18 (7.4%)
Procedure-related stroke	6 (1.3%)	5 (1.1%)	1 (0.2%)	---
Device embolization	3 (0.6%)	3 (0.6%)	0 (0.0%)	---
Hemorrhagic stroke	3 (0.6%)	0 (0.0%)	3 (0.6%)	9 (3.7%)
Other	4 (0.9%)	4 (0.9%)	0 (0.0%)	---

Early = First 7 days
Late = After 7 days

PROTECT AF:
Summary

- The LAA is critical to the pathogenesis of stroke
- "Local" therapy with WATCHMAN was superior to Warfarin
  - 40% reduction of stroke / systemic embolism / CV death
  - 60% reduction in Cardiovascular Mortality
  - 34% reduction in All-Cause Mortality
- Efficacy preserved in patients at highest risk (secondary prevention patients = prior stroke/TIA)
- Safety event rate similar, but bimodal distribution
  - Event rate diminishes with operator experience
    - 2.2% (CAP Registry)
    - 1.9% (PREVAIL: 40% New Operators)

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

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

Reddy, Holmes, Kar et al. Circulation 2011

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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

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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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

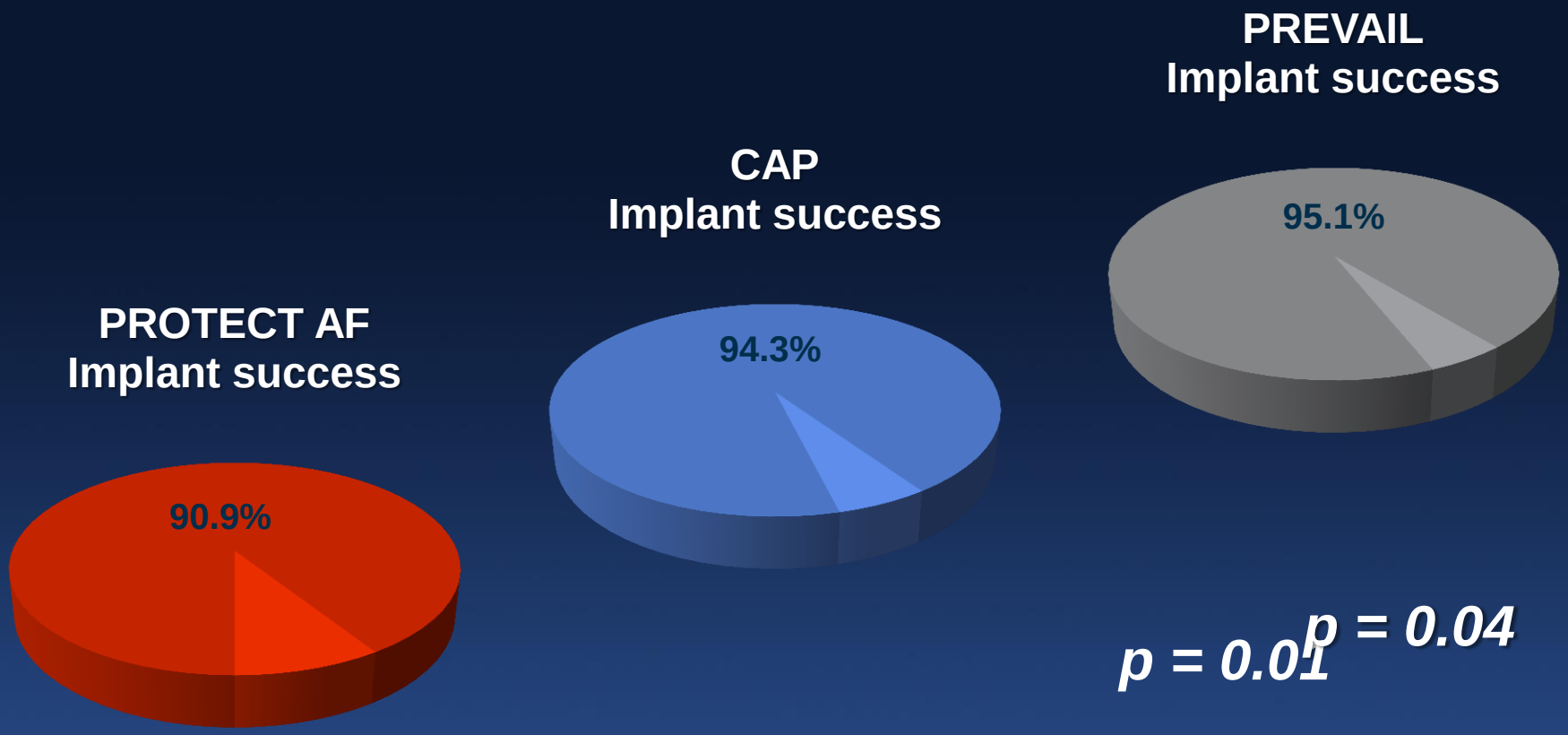
[1] Original protocol allowed 14 days, but was reduced to 7 after a protocol revision
[2] After first 100 study patients, protocol was revised to include roll-in patients for new implanters

*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

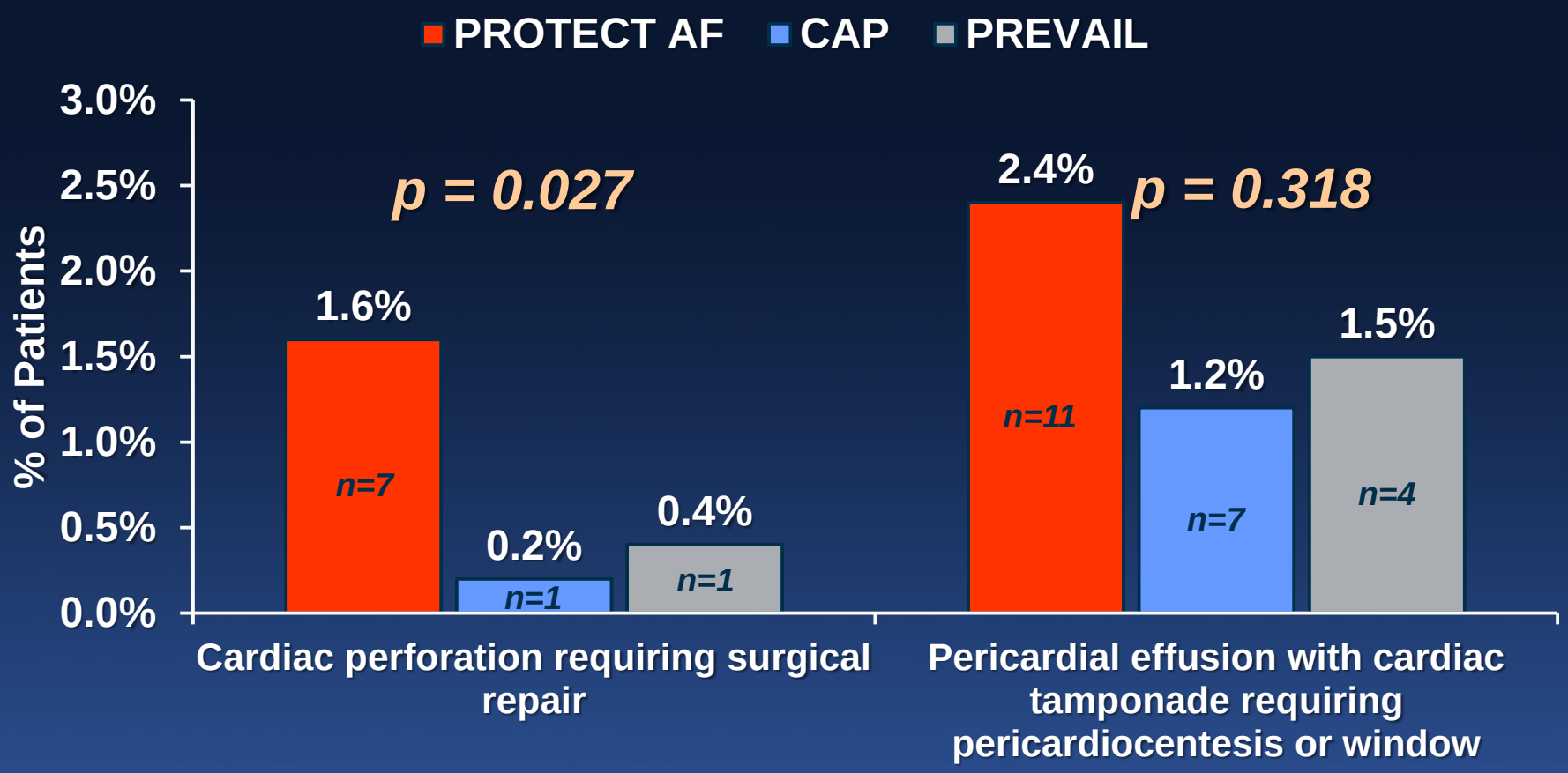
Procedure Implant Success



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

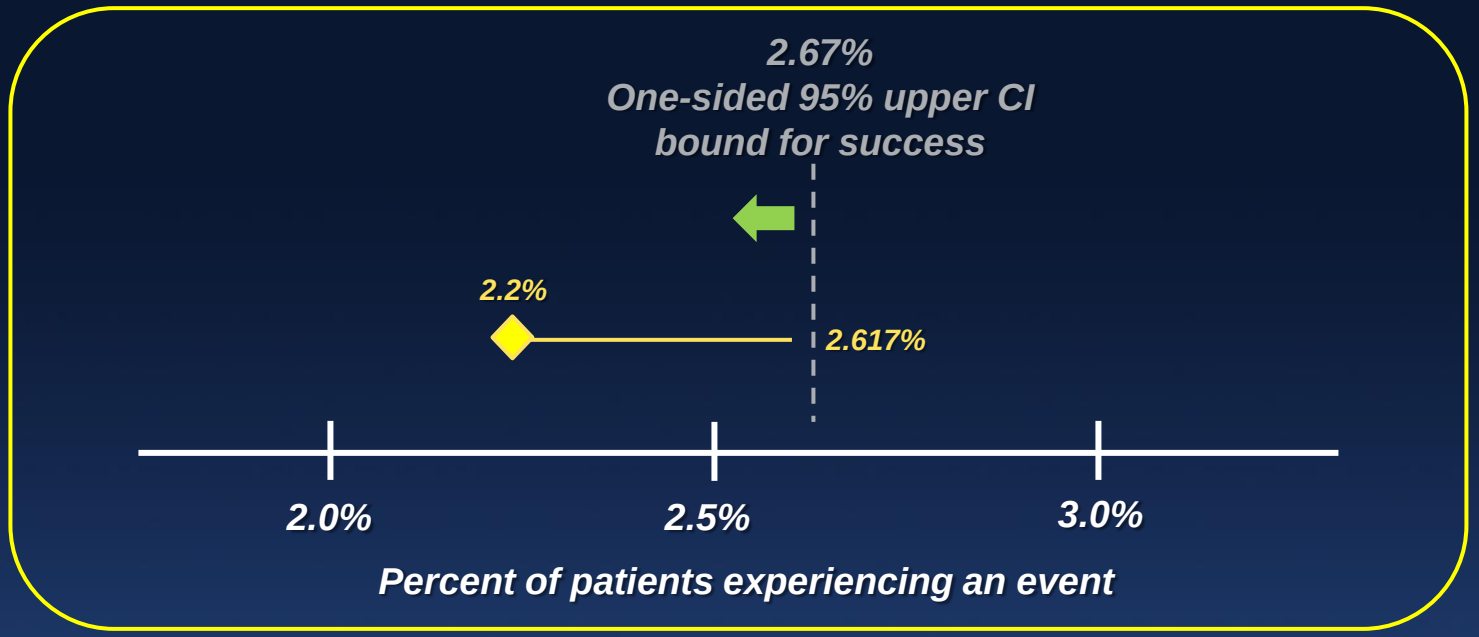
PROTECT AF and CAP data from Reddy, VY et al. Circulation. 2011;123:417-424

Pericardial Effusions Requiring Intervention



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

First Primary Endpoint
Acute (7-day) Procedural Safety

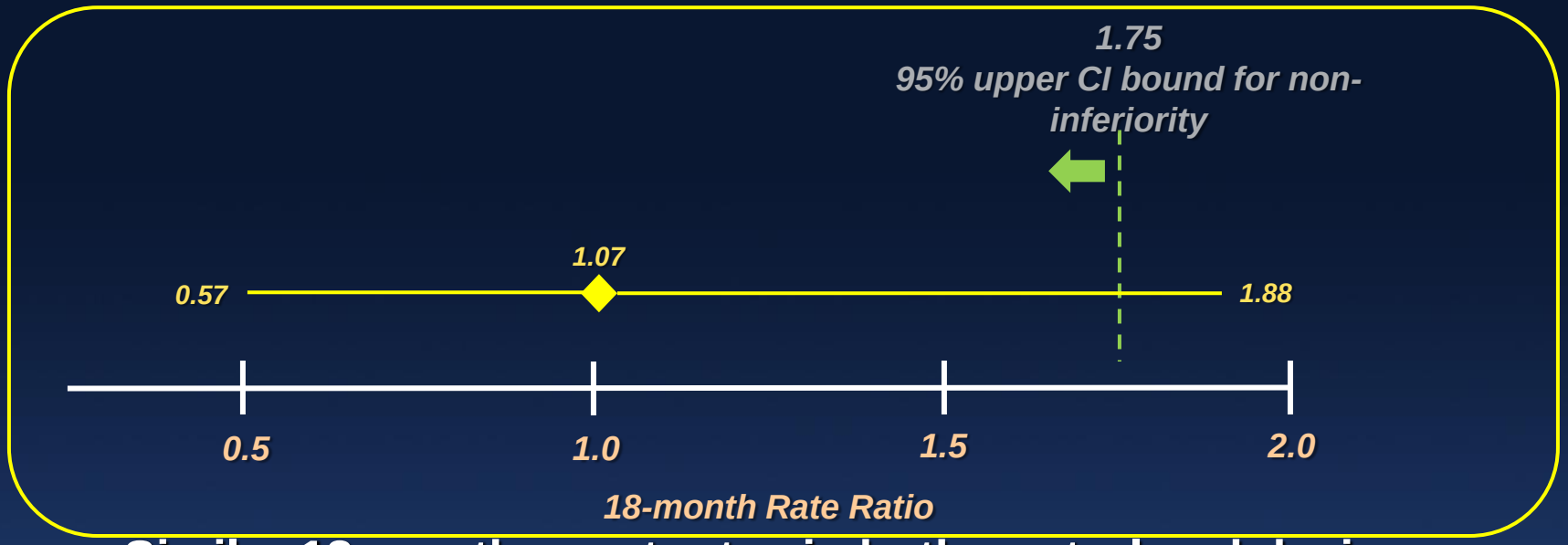


- 6 events in device group = 2.2% (6/269)
- Pre-specified criterion met for first primary endpoint (95% Upper confidence bound < 2.67%)
  - 95% CI = 2.618%

[1] CI is one-sided

Results are preliminary; final validation not yet complete

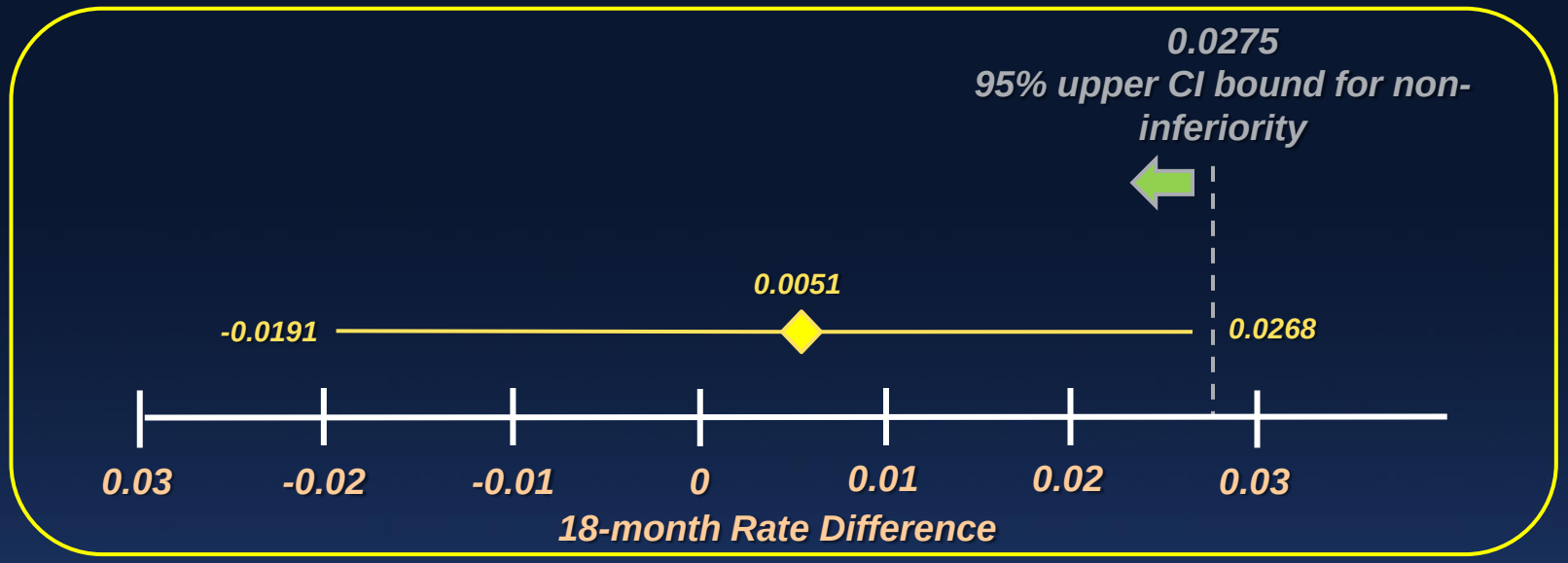
Second Primary Endpoint
Composite 18-month Efficacy



- 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

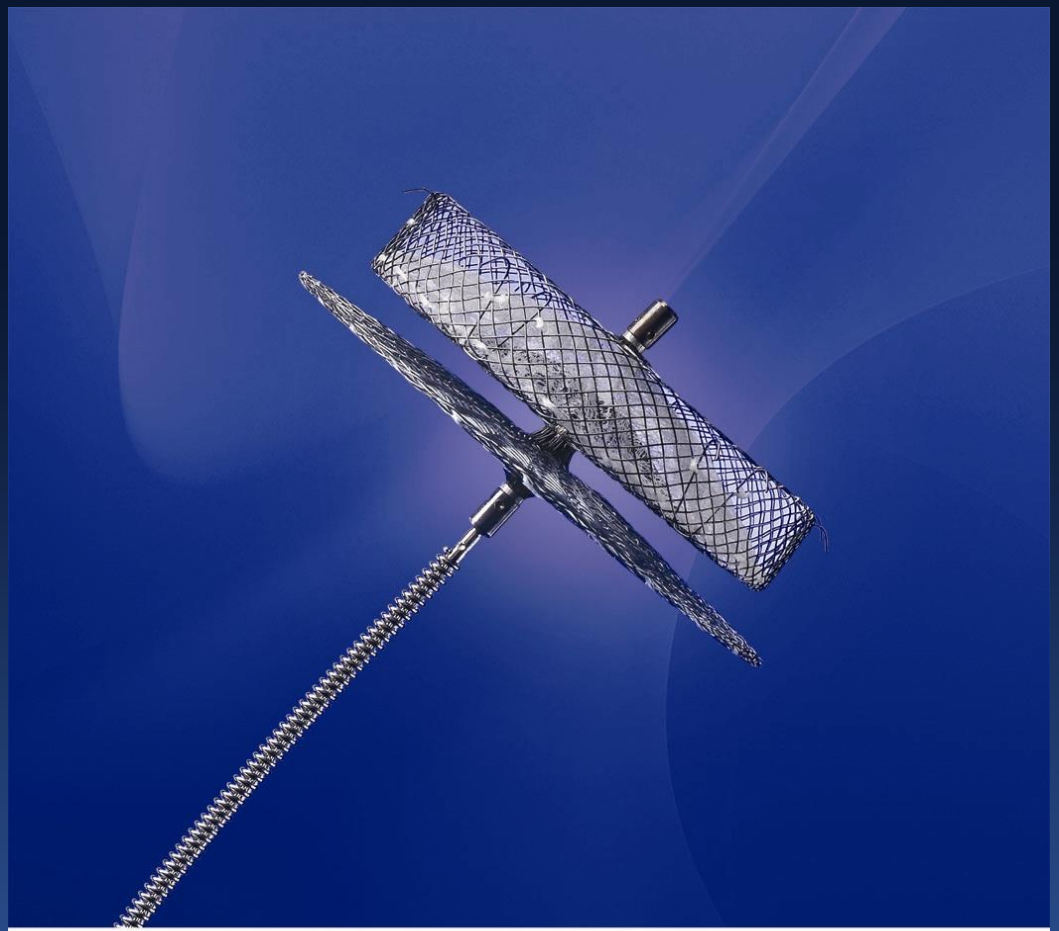
- Pre-specified non-inferiority criterion met for third primary endpoint (95% CI Upper Bound < 0.0275%)

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

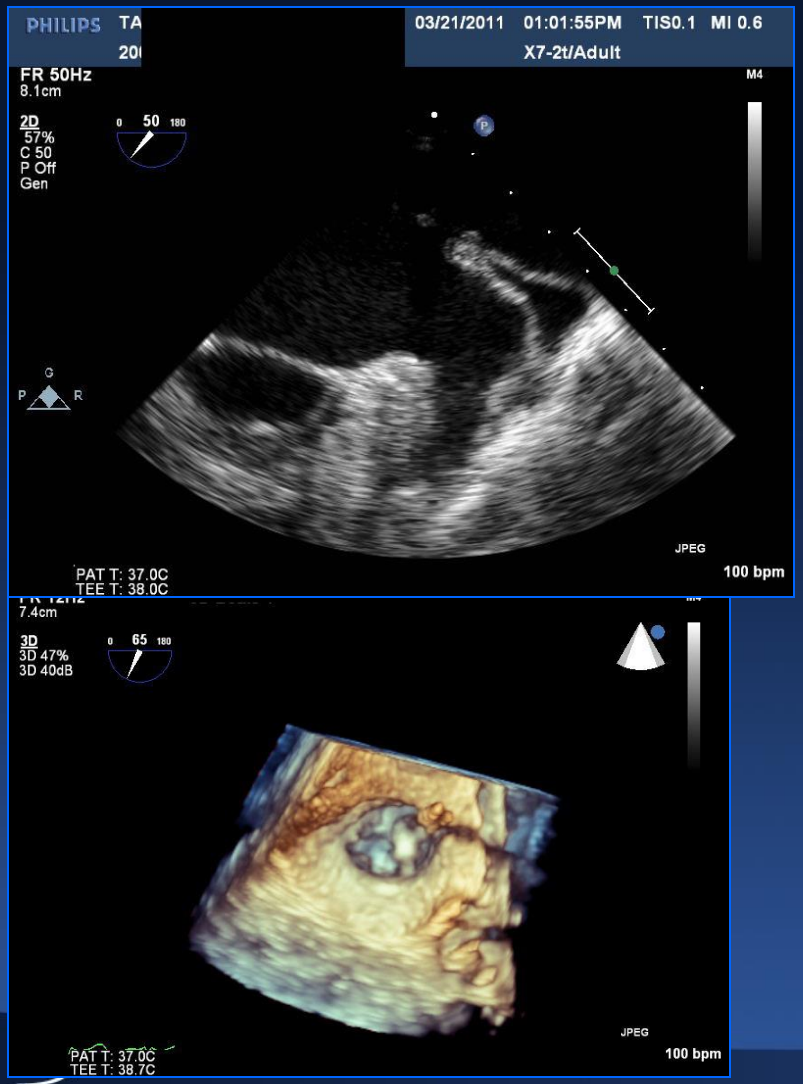
AMPLATZER® Cardiac Plug



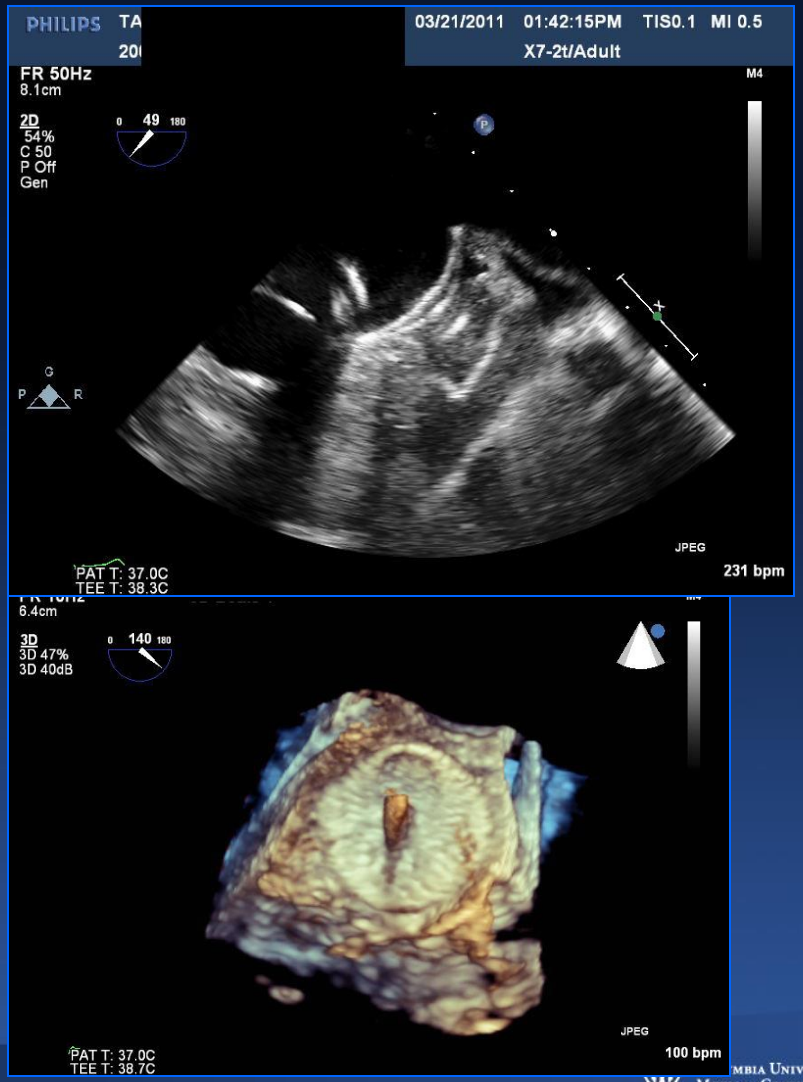
- **CE Mark – 2008**
  > 400 implants WW
- **U.S. – 2010**
  Limited to investigational use under approved clinical protocol

LAA occlusion with ACP plug

Before



After



CARDIOVASCULAR RESEARCH FOUNDATION
A Passion for Innovation

COLUMBIA UNIVERSITY MEDICAL CENTER
NewYork-Presbyterian
The University Hospital of Columbia and Cornell

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

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**

PROTECT AF:
Limitations

- Now novel OACs (Factor II/Xa Inhibitors)
  - Despite advent of new OACs, Warfarin still remains the #1 OAC prescribed for stroke prevention in AF
- Post-Implant Anticoagulation regimen
  - ASAP Registry (ASA/Clopidogrel for 6 mo) suggests that the regimen can be simplified
- Data demonstrates that LAA closure with the Watchman is efficacious for stroke prophylaxis
  - But inappropriate to directly extrapolate to other LAA closure devices / strategies
  - Need RCTs comparing to either OACs or Watchman

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. • Gastrointestinal Bleeding, Dyspepsia, Myocardial Infarction (higher with Dabigatran) • 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%)

Conclusions

- LAA occlusion is an alternative to long term antithrombotic therapy in patients with chronic non rheumatic AF
  - Safe
  - Superior to Coumadin at long term
  - Procedure is successful even with new operators
  - No Data available comparing LAA occlusion versus the new oral anticoagulant agents

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