

**Update on PROTECT AF**  
**Angioplasty Summit – TCTAP 2012**  
**Seoul, Korea**  
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# Presenter Disclosure Information

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

**“Update on PROTECT AF”**

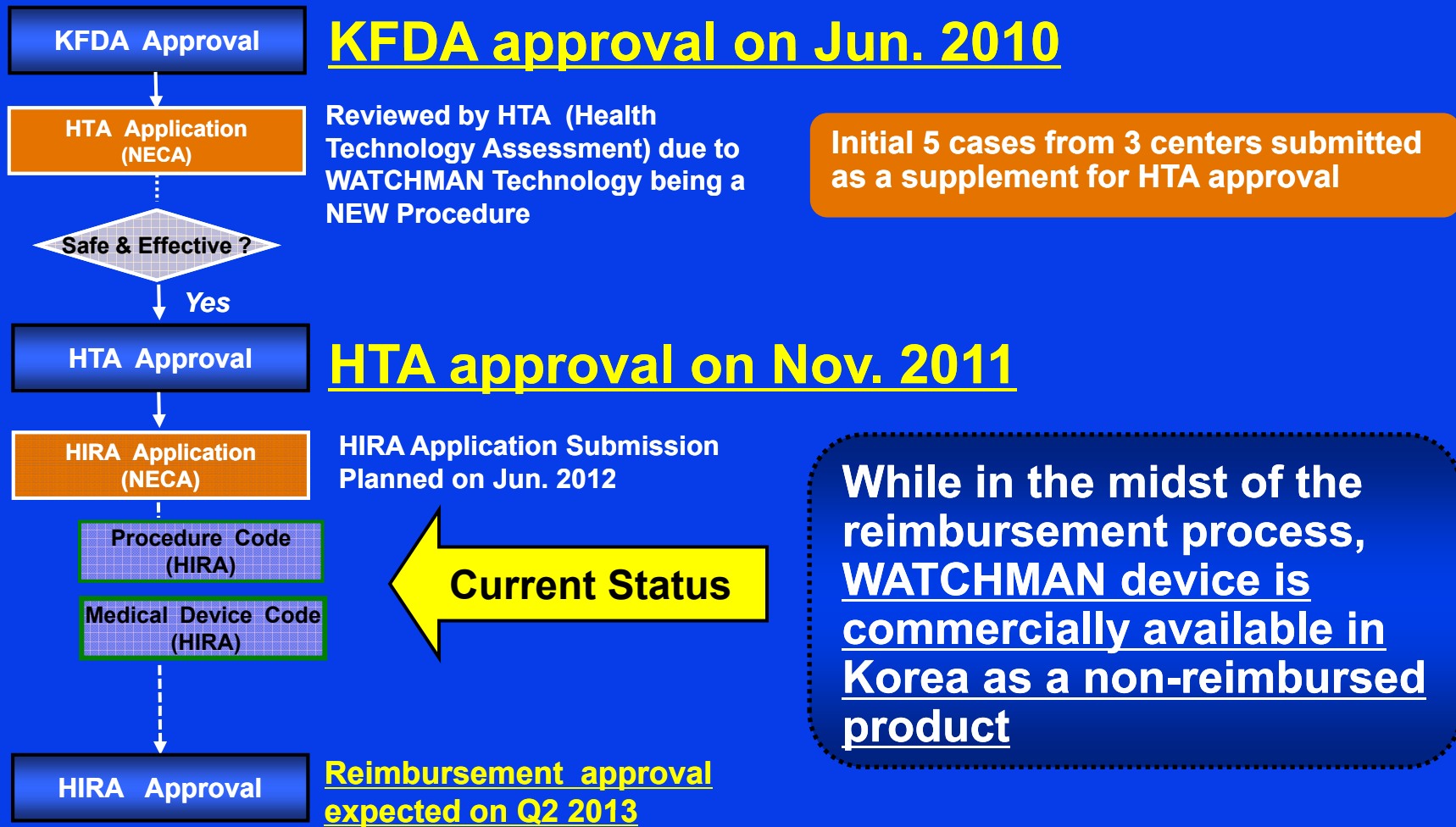
**The following relationships exist related to this presentation:**

**Immediate Past President ACC.**

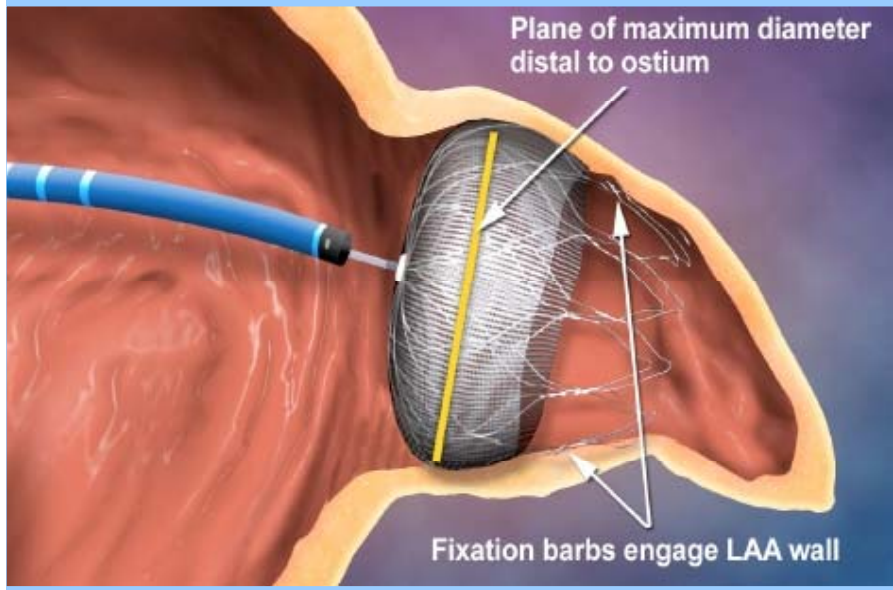
**Mayo Foundation and I have licensed some of this technology to Atritech**

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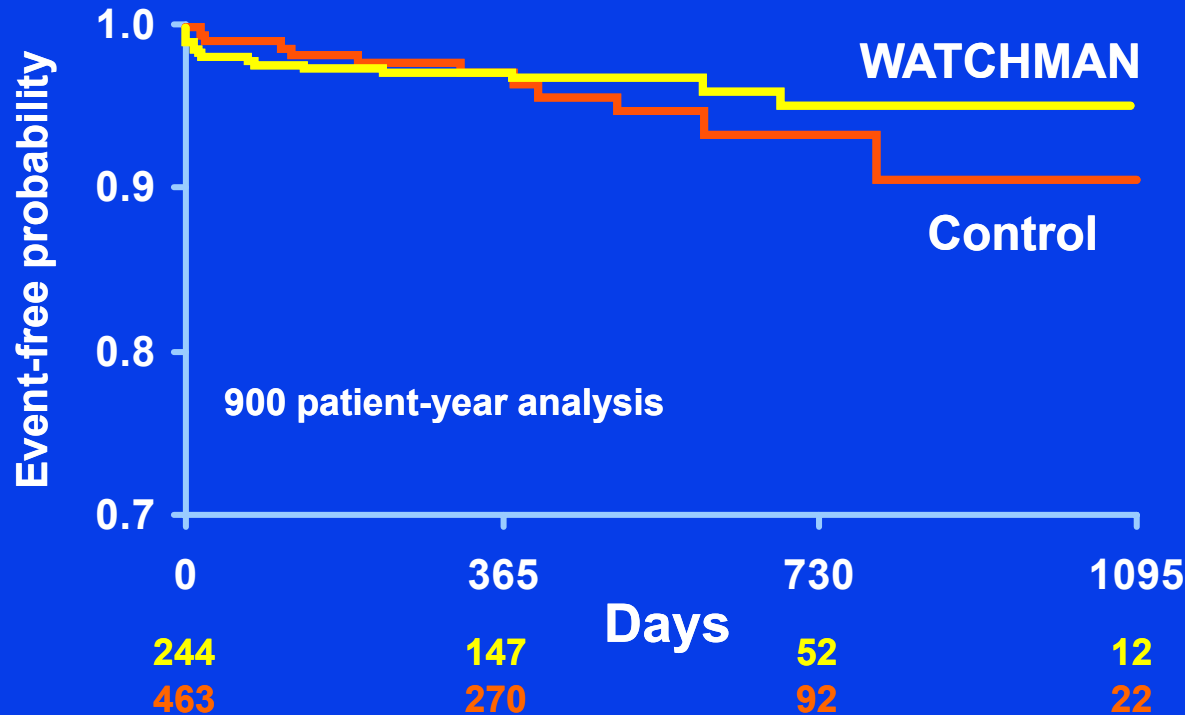
# WM Commercial Launch Milestones in Korea



# Proof of Concept



Intent-to-Treat  
**All Stroke**



Randomization allocation  
(2 device:1 control)

**Key Implication:  
Confirms Role  
of LAA in CVA**

# Interpretation

- **“The efficacy of percutaneous closure of the LAA with this device was non-inferior to that of warfarin therapy. Although there was a higher rate of adverse safety events in the intervention group than in the control group, events in the intervention group were mainly a result of periprocedural complications. Closure of the LAA ... an alternative strategy to chronic warfarin therapy for stroke prophylaxis.” Lancet 2009:374; 534-42**



*My wife said "Watcha doin' today?"*

*I said "Nothing"*

*She said, "You did that yesterday"*

*I said "I wasn't finished."*

# 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

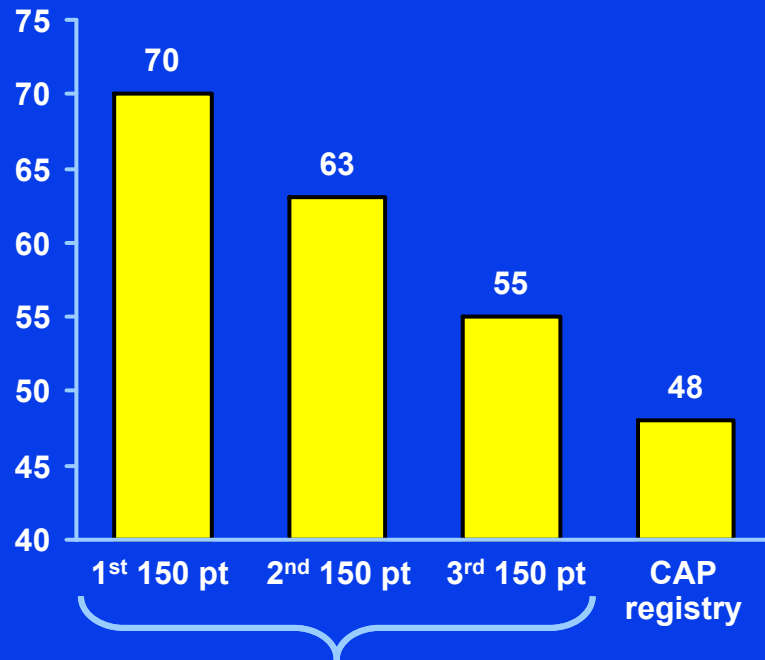
\*From tests comparing the PROTECT AF cohort with CAP

±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

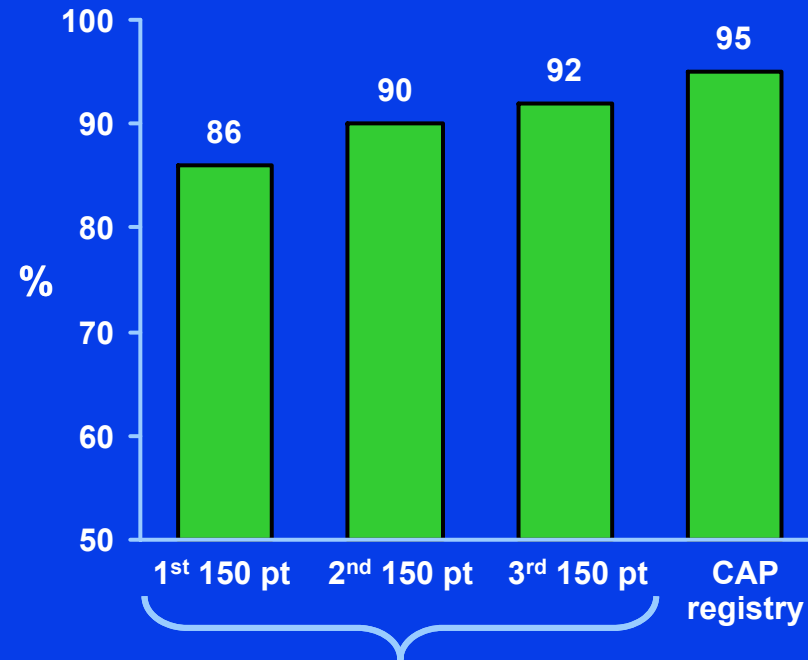
# Learning Curve: Tertiles by Enrollment Date and CAP

## Procedure Time (Minutes)



PROTECT-AF: tertiles of enrollment

## Implant Success



PROTECT-AF: tertiles of enrollment

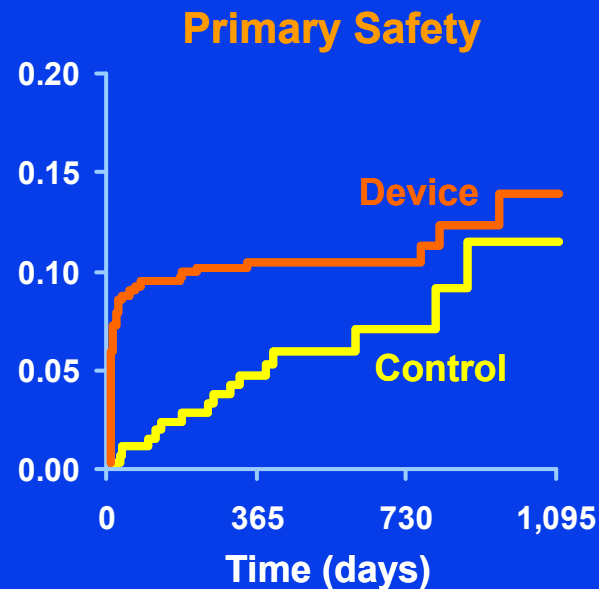
Reddy et al: Circulation 123:417, 2011





# Primary Safety Results: Intent-To-Treat

Cohort 1,050 pt yr	WATCHMAN Rate (events/100 pt yr)		Control Rate (events/100 pt yr)		Relative risk	95% CI
Intention-to-treat	7.4	49/658.8	4.4	16/364.2	1.69	0.96, 2.97



## Pericardial effusion/tamponade

- 22 requiring Tx (4.8% of pt)
  - 15 treated percutaneously
  - 7 underwent surgical intervention
- Extended hospitalization
- **No** death or long-term disability

## Effect of operator experience

- ~2% (CAP registry)

Reddy et al: Circulation 123:417, 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 7d	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

# Functional Impact of Events: Disability & Death

	<b>WATCHMAN Group Event Rate, % (n per 100 pt yrs)</b>	<b>Warfarin Group Event Rate, % (n per 100 pt yrs)</b>	<b>Relative Risk (95% CI)</b>
<b>MRS increase ≥ 1 or death</b>	<b>1.8 (19/1042.2)</b>	<b>4.3 (24/559.5)</b>	<b>0.43 (0.24 – 0.82)</b>
<b>MRS increase ≥ 2 or death</b>	<b>1.5 (16/1047.1)</b>	<b>3.7 (21/563.9)</b>	<b>0.41 (0.22 – 0.82)</b>
<b>MRS increase ≥ 3 or death</b>	<b>1.4 (15/1048.5)</b>	<b>3.3 (19/567.5)</b>	<b>0.43 (0.22 – 0.88)</b>

The WATCHMAN had a statistically improved outcome compared to the Warfarin group in all categories

# Intent-to-Treat: Primary Efficacy Results

Cohort	WATCHMAN Rate (95% CI)	Control Rate (95% CI)	Rel risk (95% CI)	Posterior probabilities	
				Noninferiority	Superiority
600 pt-yr	4.4 (2.6-6.7)	5.8 (3.0-9.1)	0.76 (0.39-1.67)	0.992	0.734
900 pt-yr	3.4 (2.1-5.2)	5.0 (2.8-7.6)	0.68 (0.37-1.41)	0.998	0.837
1,065 pt-yr	3.0 (1.9-4.5)	4.9 (2.8-7.1)	0.62 (0.35-1.25)	>0.999	0.900
1,350 pt-yr	2.9 (2.0-4.3)	4.2 (2.5-6.0)	0.69 (0.42-1.37)	>0.999	0.830
1,500 pt-yr	3.0 (2.1-4.3)	4.3 (2.6-5.9)	<b>0.71 (0.44-1.30)</b>	<b>&gt;0.999</b>	0.846

- **Noninferiority criteria met**
- **29% lower relative risk in WATCHMAN group**

# Intent-to-Treat: All-Cause Mortality

Cohort	WATCHMAN Rate (95% CI)	Control Rate (95% CI)	Rel risk (95% CI)	Posterior probabilities*	
				Noninferiority	Superiority
600 pt-yr	3.4 (1.8-5.4)	4.9 (2.3-7.8)	0.69 (0.33-1.66)	0.991	0.779
900 pt-yr	2.9 (1.7-4.4)	4.7 (2.5-7.1)	0.61 (0.32-1.32)	0.999	0.889
1,065 pt-yr	3.0 (1.9-4.5)	4.8 (2.8-7.1)	0.62 (0.34-1.24)	>0.999	0.907
1,350 pt-yr	3.1 (2.1-4.4)	4.4 (2.6-6.1)	0.70 (0.43-1.36)	>0.999	0.823
1,500 pt-yr	3.2 (2.3-4.5)	4.5 (2.8-6.2)	<b>0.71 (0.46-1.28)</b>	>0.999	0.852

- **29% lower relative risk in WATCHMAN group**

\*No adjustment made for multiple comparisons

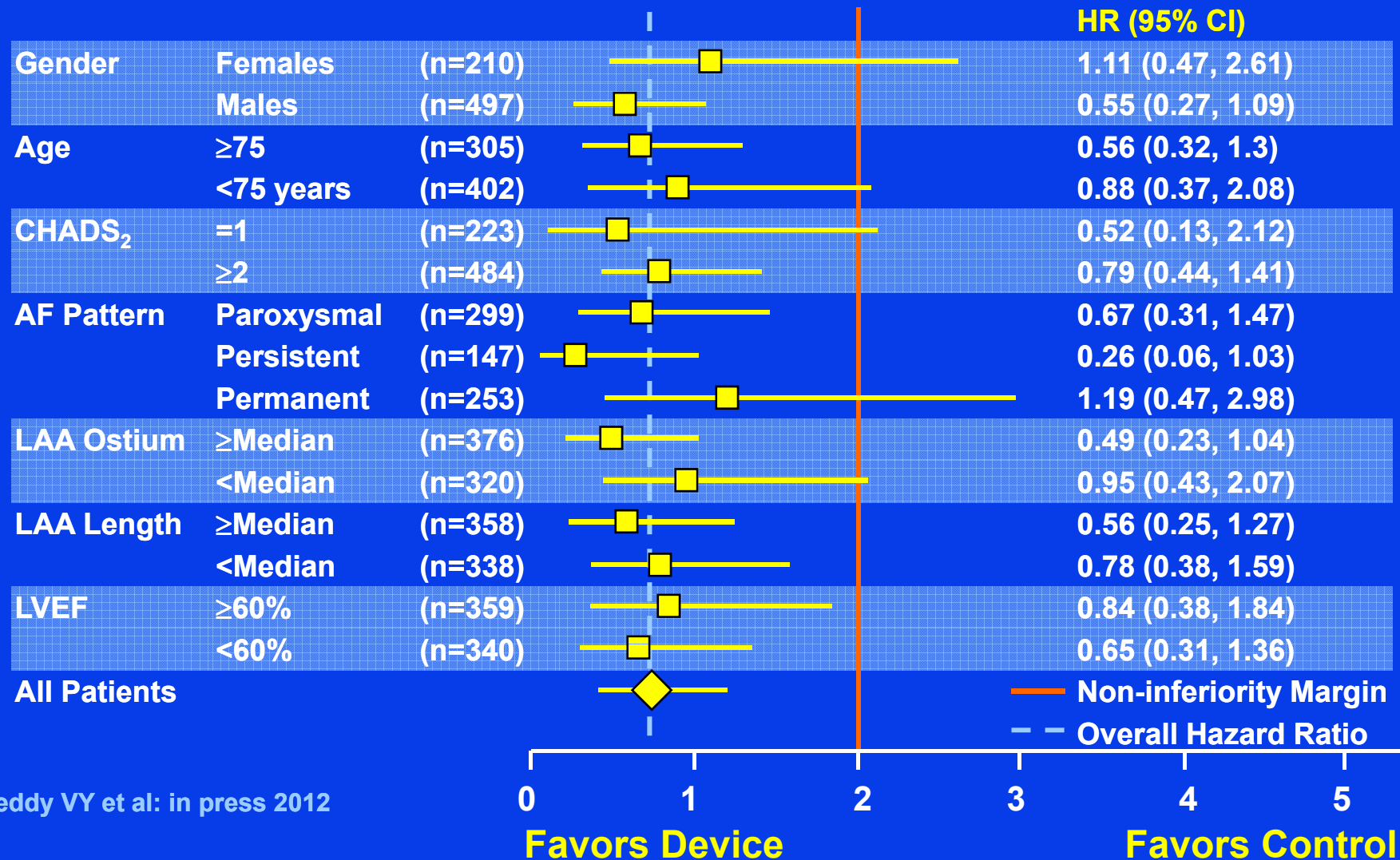
# Intent-to-Treat: All Stroke

Cohort	WATCHMAN Rate (95% CI)	Control Rate (95% CI)	Rel risk (95% CI)	Posterior probabilities*	
				Noninferiority	Superiority
600 pt-yr	3.4 (1.9-5.5)	3.6 (1.5-6.3)	0.96 (0.43-2.57)	0.927	0.488
900 pt-yr	2.6 (1.5-4.1)	3.5 (1.7-5.7)	0.74 (0.36-1.76)	0.998	0.731
1,065 pt-yr	2.3 (1.3-2.6)	3.2 (1.6-5.2)	0.71 (0.35-1.64)	0.993	0.769
1,350 pt-yr	2.1 (1.3-3.3)	2.7 (1.4-4.3)	0.78 (0.41-1.75)	0.989	0.685
1,500 pt-yr	2.0 (1.3-3.1)	2.7 (1.5-4.1)	0.77 (0.42-1.62)	0.995	0.728

- **23% lower relative risk in WATCHMAN group**

\*No adjustment made for multiple comparisons

# Primary Efficacy By Patient Subgroup



Reddy VY et al: in press 2012

# Quality of Life in PROTECT AF Trial

## SF-12v2 Quality Of Life Summary: All Subjects

		Treatment			Control			
		Baseline	12 month	Change	Baseline	12 month	Change	P*
General health	Mean ± SD Median [Range]	43.1±9.6 40.4 [18.9, 62.0]	44.3±10.1 40.4 [18.9, 62.0]	0.9±8.8 0.0 [-21.6, 32.3]	42.7±9.8 40.8 [18.9, 62.0]	42.6±9.7 40.4 [18.9, 62.0]	-0.2±9.6 0.0 [-43.1, 32.3]	0.0601
Total physical score	Mean ± SD Median [Range]	42.5±10.1 43.0 [9.2, 64.3]	43.3±11.0 45.1 [12.3, 64.2]	0.4±9.0 0.0 [-27.0, 24.4]	42.9±10.1 43.4 [11.6, 64.2]	41.2±10.4 41.9 [16.7, 61.8]	-2.0±8.5 -1.2 [-24.7, 23.4]	0.0015
Physical function	Mean ± SD Median [Range]	43.2±11.5 47.9 [22.1, 56.5]	43.6±12.0 47.9 [22.1, 56.5]	0.1±11.7 0.0 [-34.4, 34.4]	43.2±11.3 47.9 [22.1, 56.5]	40.7±11.4 39.3 [22.1, 56.5]	-2.9±10.9 0.0 [-34.4, 34.4]	0.0009
Physical limitation	Mean ± SD Median [Range]	44.3±10.3 43.4 [20.3, 57.2]	45.2±10.7 48.0 [20.3, 57.2]	0.3±9.9 0.0 [-36.9, 36.9]	45.4±10.8 48.0 [20.3, 57.2]	43.3±10.8 48.0 [20.3, 57.2]	-2.6±10.0 0.0 [-36.9, 32.2]	0.0027

\*P-values compare the randomized groups for the change in QOL component, adjusted for the baseline value



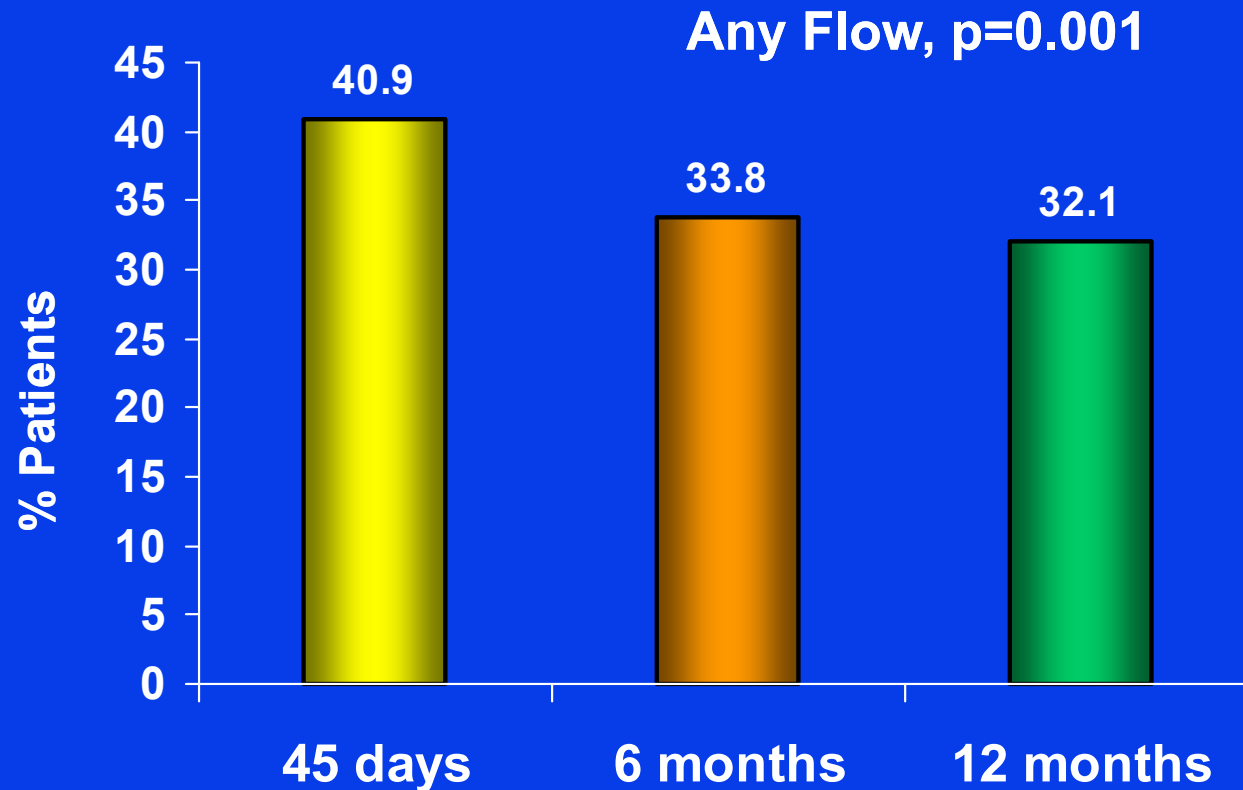


# Watchman Protocol

- TEE at 45 days, 6 months and 12 months
- Warfarin discontinued if 45 day TEE documented either minimal or no peri-device flow (jet  $\leq$  5 mm width)
- Post hoc analysis of peri-device flow on clinical outcome

# Peri-device Flow and Watchman

## 419/445 Patients Core Lab Evaluation



TEE

# Peri-device Flow and Watchman

	45 days	6 months	12 months	P
<b>TEE evaluations</b>	<b>445</b>	<b>414</b>	<b>389</b>	
<b>Flow around device filter</b>				
Yes (%)	182 (40.9)	140 (33.8)	125 (32.1)	0.001
No (%)	237 (53.3)	253 (61.1)	249 (64.0)	
Unable to evaluate	18 (4.0)	19 (4.6)	15 (3.9)	
Field not completed	8 (1.8)	2 (0x5)	0 (0.0)	
<b>If leak present</b>				
<b>Flow severity</b>				
Minor < 1 mm (%)	14 (7.7)	4 (2.9)	1 (0.8)	0.275
Moderate 1-3 mm (%)	109 (59.9)	84 (60.0)	78 (62.4)	
Major > 3 mm (%)	59 (32.4)	52 (37.1)	46 (36.8)	
<b>Flow measurement (mm)</b>				
Mean (standard deviation)	2.8 (1.0)	2.9 (1.1)	2.9 (1.0)	0.902
Minimum, maximum	0.9, 6.2	0.8, 6.8	1.1, 6.0	

# Peri-device Flow and Watchman

	Any Residual Flow	No Flow	P
Efficacy	9/182 (5%)	18/263 (7%)	0.572
Ischemic stroke/ Systemic embolism	5/182 (3%)	11/263 (4%)	0.669

Viles-Gonzalez, JACC  
2012;10:923-29

# LAA Occlusion Residual Leaks

**Conclusions:** These data indicate that residual peri-device flow into the LAA after percutaneous closure with the Watchman device was common, and is not associated with an increased risk of thromboembolism. These data corroborate the safety of Warfarin discontinuations after Watchman implantation regardless of the presence of the residual peri-device flow provided it is  $< 5$  mm width

# Pivotal Trial #2

## PREVAIL

- Multicenter randomized trial of 475 patients with nonvalvular AF and similar inclusion criteria to PROTECT AF
- 2:1 randomization
- Primary endpoint:
  - Hemorrhagic stroke
  - Ischemic stroke
  - Systemic embolism
  - CV/unexplained death
- Adaptive study design, Bayesian piecewise exponential model, noninferiority

# **LAA Occlusion**

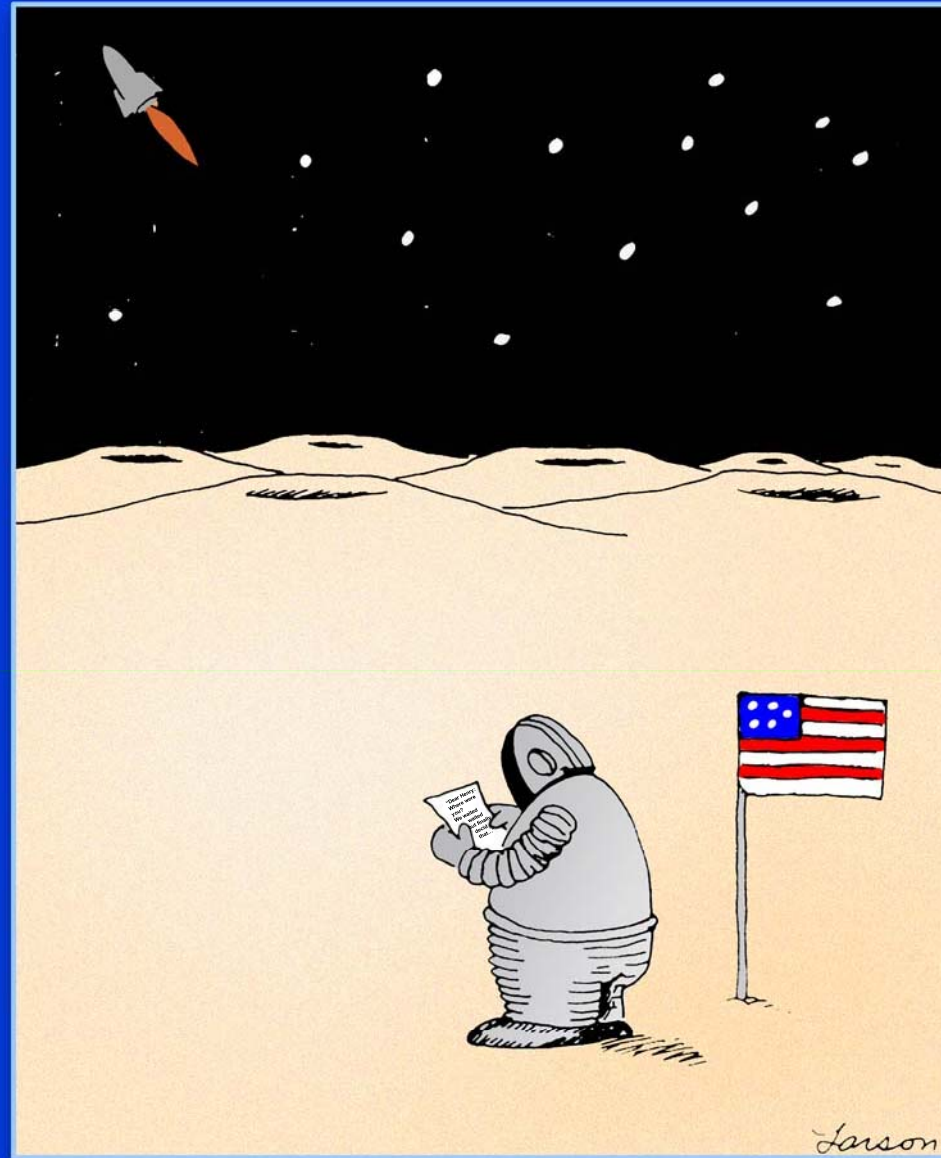
## **NICE Guidance**

**June 2010**

**“Percutaneous occlusion of LAA is efficacious in reducing the risk of thrombo-embolic complications associated with non-valvular AF. Patients should be selected by a multidisciplinary team including a cardiologist and other appropriate clinicians experienced in the management of patients with AF at risk of stroke.”**

**Jain AK, Heart 97:762-765, 2011**





**“Dear Henry: Where were you?  
We waited and waited but finally decided that...”**