PROTECT AF Trial:
Randomized Prospective Trial of Percutaneous LAA Closure vs Warfarin for Stroke Prevention in AF

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Facts about Atrial Fibrillation (AF)

- AF is the most common cardiac arrhythmia
  - Affects more than 3 million individuals in the US
  - Projected to increase to 16 million by 2050
- Patients with AF have a 5-fold higher risk of stroke
  - Over 87% of strokes are thromboembolic
  - Greater than 90% of thrombus accumulation originates in the Left Atrial Appendage (LAA)
- Stroke is the number one cause of long-term disability and the third leading cause of death in patients with AF

Non-Valvular Atrial Fibrillation Stroke Prevention
Medical Rx

- Warfarin cornerstone of therapy
- Assuming 51 ischemic strokes/1000 pt-yr
  - Adjusted standard dose warfarin prevented 28 strokes at expense of 11 fatal bleeds
  - Aspirin prevented 16 strokes at expense of 6 fatal bleeds
- Warfarin
  - 60-70% risk reduction vs no treatment
  - 30-40% risk reduction vs aspirin

Cooper: Arch Int Med 166, 2006
Lip: Thromb Res 118, 2006

Challenges in Treating AF

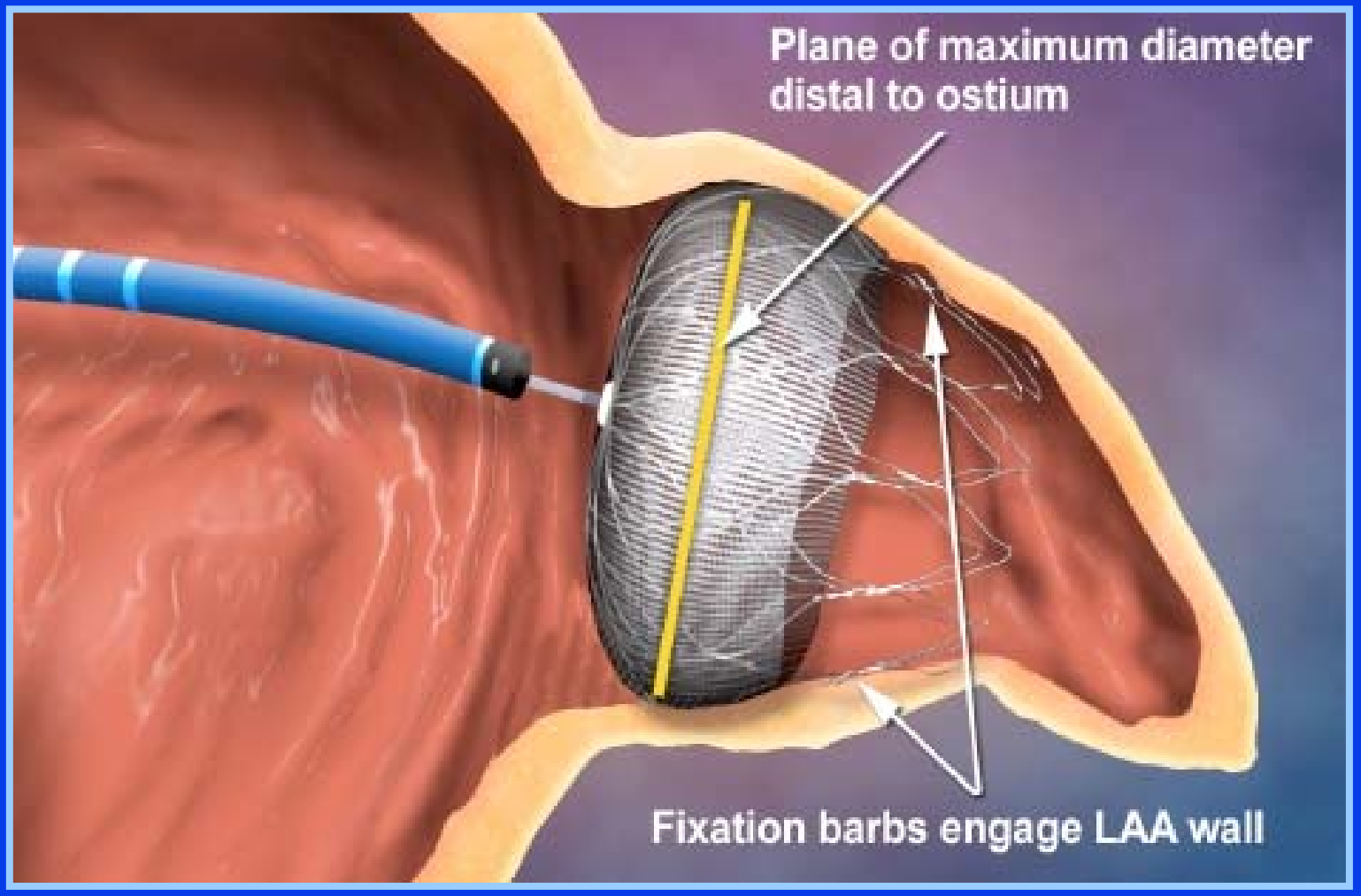
- However warfarin is not always well-tolerated
  - Narrow therapeutic range (INR between 2.0 – 3.0)
  - Effectiveness is impacted by interactions with some foods and medications
  - Requires frequent monitoring and dose adjustments
- Published reports indicate that less than 50% of patients eligible are being treated with warfarin due to tolerance or non-compliance issues
- SPORTIF trials suggest only 60% of patients treated are within a therapeutic INR range, while 29% have INR levels below 2.0 and 15% have levels above 3.0

Watchman LAA Closure Technology

The WATCHMAN LAA Closure Technology is designed to prevent embolization of thrombi that may form in the LAA.

The WATCHMAN® Left Atrial Appendage Closure Technology is intended as an alternative to warfarin therapy for patients with non-valvular atrial fibrillation.

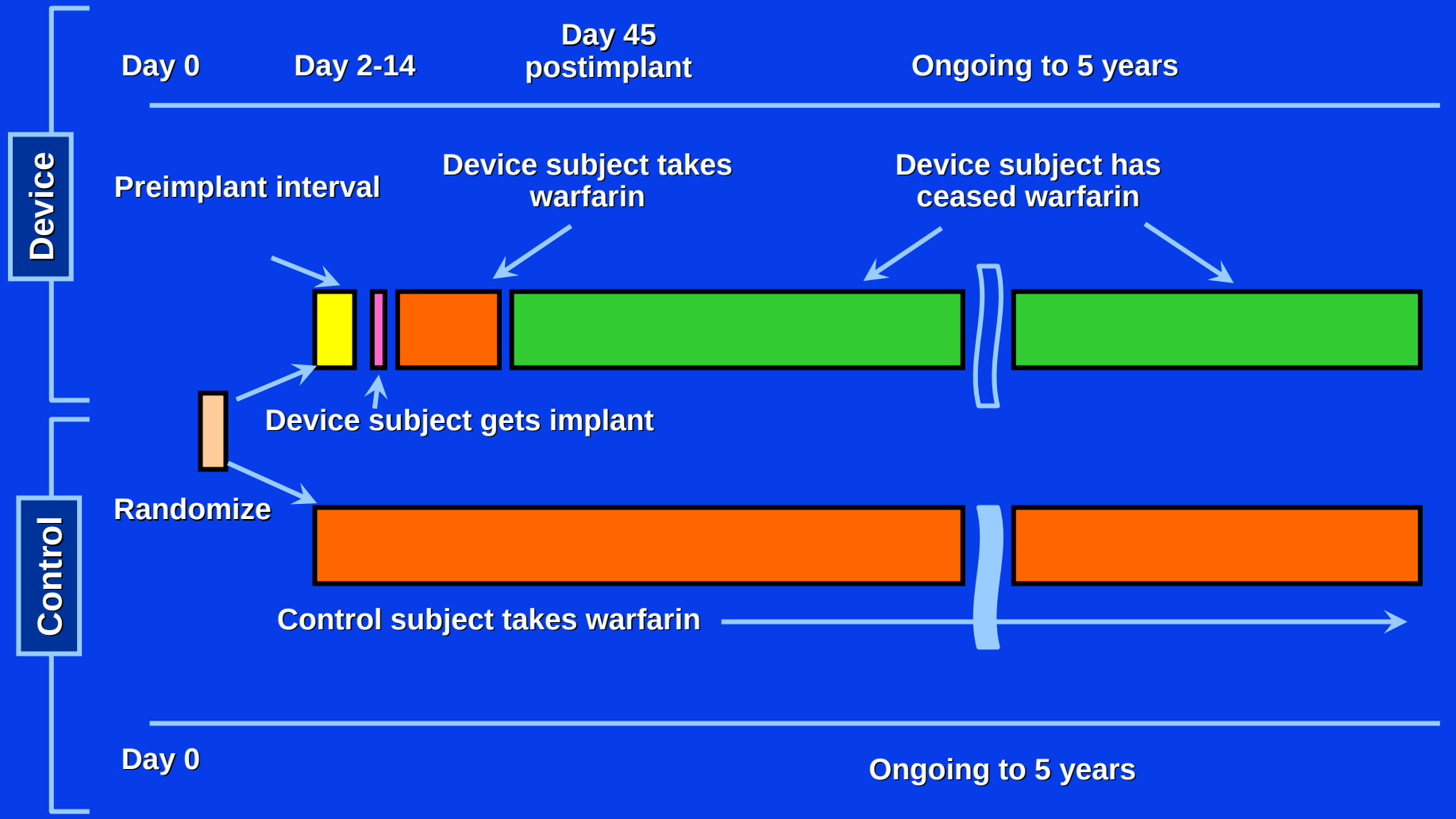
WATCHMAN LAA Closure Device in situ



PROTECT AF Clinical Trial Design

- Prospective, randomized study of WATCHMAN LAA Device vs. Long-term Warfarin Therapy
- 2:1 allocation ratio device to control
- 800 Patients enrolled from Feb 2005 to Jun 2008
  - Device Group (463)
  - Control Group (244)
  - Roll-in Group (93)
- 59 Enrolling Centers (U.S. & Europe)
- Follow-up Requirements
  - TEE follow-up at 45 days, 6 months and 1 year
  - Clinical follow-up biannually up to 5 years
  - Regular INR monitoring while taking warfarin
- Enrollment continues in Continued Access Registry

Patient Study Timeline



Warfarin Discontinuation

87% of implanted subjects were able to cease warfarin at 45 days and the rate further increased at later time points

Visit	Watchman N/Total (%)
45 day	349/401 (87.0)
6 month	347/375 (92.5)
12 month	261/280 (93.2)
24 month	95/101 (94.1)

- Reasons for remaining on warfarin therapy after 45-days:
  - Observation of flow in the LAA (n = 30)
  - Physician Order (n = 13)
  - Other (n = 9)

PROTECT AF Trial Endpoints

- Primary Efficacy Endpoint
  - All stroke: ischemic or hemorrhagic
    - deficit with symptoms persisting more than 24 hours or
    - symptoms less than 24 hours confirmed by CT or MRI
  - Cardiovascular and unexplained death: includes sudden death, MI, CVA, cardiac arrhythmia and heart failure
  - Systemic embolization
- Primary Safety Endpoint
  - Device embolization requiring retrieval
  - Pericardial effusion requiring intervention
  - Cranial bleeds and gastrointestinal bleeds
  - Any bleed that requires $\geq$ 2uPRBC
- NB: Primary effectiveness endpoint contains safety events

PROTECT AF Statistical Overview

PROTECT AF Bayesian sequential design

- Accrue patient-yr up to possible maximum of 1,500
- Analyze at specific time points; 600 patient-yr, then every 150 pt-yr thereafter
- Successful non-inferiority based on first time success criterion met
- Success criterion defined on probability scale

  >97.5% probability that primary efficacy event rate for WATCHMAN is less than two times control

  >5% probability that primary efficacy event rate for WATCHMAN is less than control

Key Participation Criteria

- Key Inclusion Criteria
  - Age 18 years or older
  - Documented non-valvular AF
  - Eligible for long-term warfarin therapy, and no other conditions that would require long-term warfarin therapy
  - Calculated CHADS2 score $\geq$ 1
- Key Exclusion Criteria
  - NYHA Class IV Congestive Heart Failure
  - ASD and/or atrial septal repair or closure device
  - Planned ablation procedure within 30 days of potential WATCHMAN Device implant
  - Symptomatic carotid disease
  - LVEF < 30%
  - TEE Criteria: Suspected or known intracardiac thrombus (dense spontaneous echo contract)

Patient Demographics

Baseline Demographics			
Characteristic	**WATCHMAN N= 463**	**Control N= 244**	**P-value**
Age (years)	71.7 ± 8.8 463 (46.0, 95.0)	72.7 ± 9.2 244 (41.0, 95.0)	0.1800
Height (inches)	68.2 ± 4.2 462 (54.0, 82.0)	68.4 ± 4.2 244 (59.0, 78.0)	0.6067
Weight (lbs)	195.3 ± 44.4 463 (85.0, 376.0)	194.6 ± 43.1 244 (105.0, 312.0)	0.8339
Gender Female Male	 137/463 (29.6) 326/463 (70.4)	 73/244 (29.9) 171/244 (70.1)	0.9276

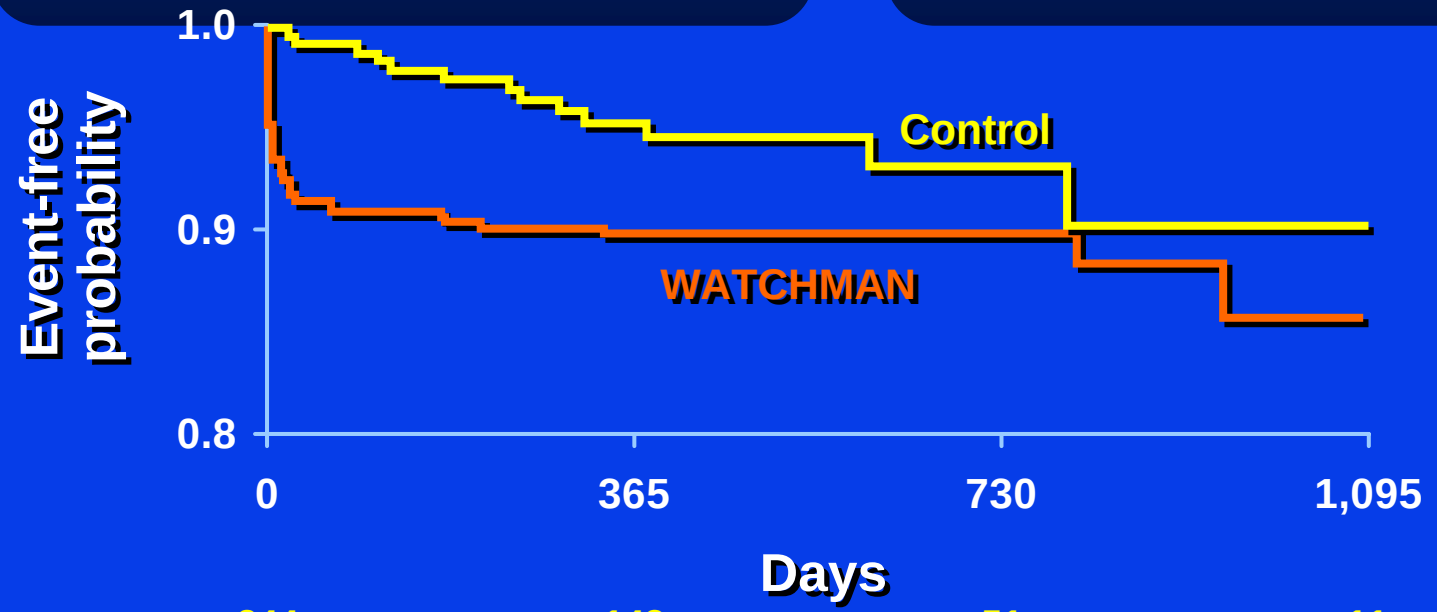
Patient Demographics

Baseline Risk Factors			
	WATCHMAN N= 463	Control N= 244	P-value
CHADS2 Score			
1	158/463 (34.1)	66/244 (27.0)	0.3662
2	157/463 (33.9)	88/244 (36.1)	
3	88/463 (19.0)	51/244 (20.9)	
4	37/463 (8.0)	24/244 (9.8)	
5	19/463 (4.1)	10/244 (4.1)	
6	4/463 (0.9)	5/244 (2.0)	
AF Pattern			
Paroxysmal	200/463 (43.2)	99/244 (40.6)	0.7623
Persistent	97/463 (21.0)	50/244 (20.5)	
Permanent	160/463 (34.6)	93/244 (38.1)	
Unknown	6/463 (1.3)	2/244 (0.8)	
LVEF %	57.3 ± 9.7	56.7 ± 10.1	0.4246
	460 (30.0, 82.0)	239 (30.0, 86.0)	

Intent-to-Treat
Primary Safety Results

Randomization allocation (2 device : 1 control)

Cohort	Device Events (no.)	Device Total pt-yr	Device Rate (95% CI)	Control Events (no.)	Control Total pt-yr	Control Rate (95% CI)	Rel. Risk (95% CI)
900 pt-yr	48	554.2	8.7 (6.4, 11.3)	13	312.0	4.2 (2.2, 6.7)	2.08 (1.18, 4.13)



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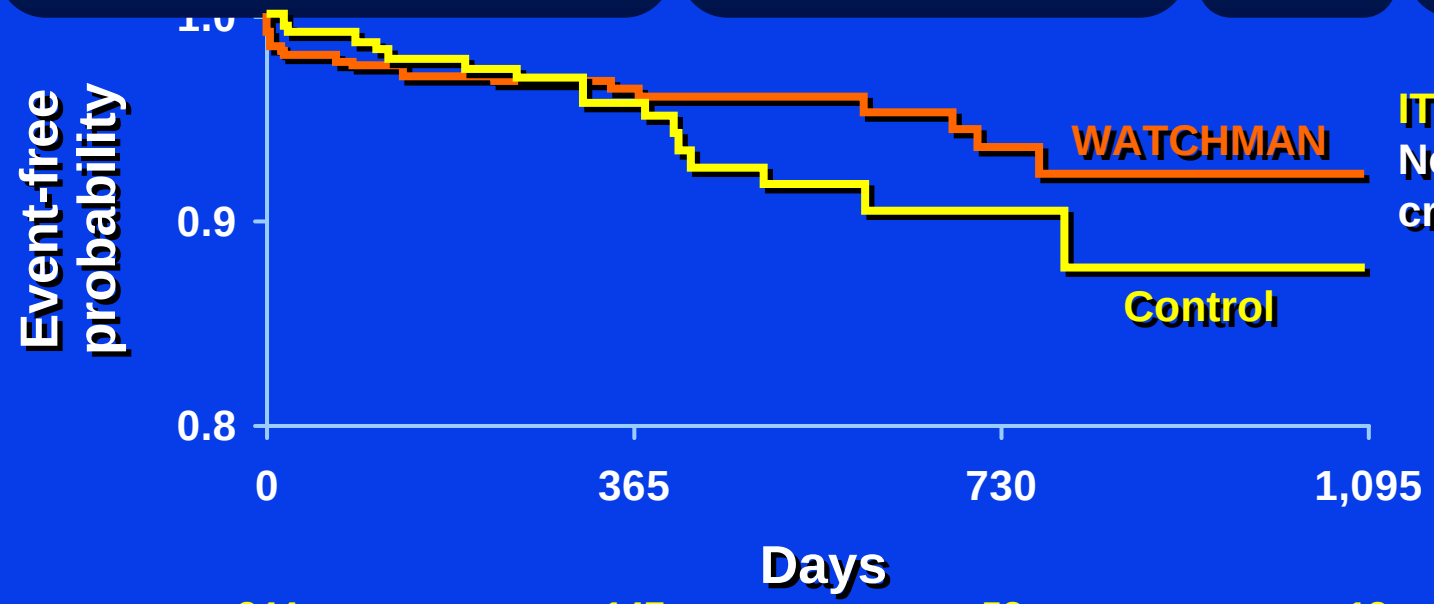
Intent-to-Treat
Primary Efficacy Results

Randomization allocation (2 device : 1 control)

	Device			Control				Posterior Probabilities	
Cohort	Events (no.)	Total pt-yr	Rate (95% CI)	Events (no.)	Total pt-yr	Rate (95% CI)	Rel. Risk (95% CI)	Non-inferiority	Superiority
900 pt-yr	20	582.3	3.4 (2.1, 5.2)	16	318.0	5.0 (2.8, 7.6)	0.68 (0.37, 1.41)	0.998	0.837



ITT Cohort:
Non-inferiority criteria met

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PROTECT AF Trial
What are the Analysis Issues

1. How do you deal with safety endpoints which are also primary efficacy endpoints?
2. How do you deal with early procedural safety risks (seen with all invasive interventional procedures) vs late primary efficacy endpoints?
3. How do you deal with a strategy of warfarin started immediately and indefinitely versus an invasive approach that also requires 45 days of warfarin (?double jeopardy)
4. How do you factor in procedural learning curve?

Potential Safety Endpoints
Device

- Procedural complications
  - Pericardial effusion
  - Stroke – ischemic
- Bleeding during 45 days of Warfarin

Intent-to-Treat
Primary Safety Results

Cohort	Device			Control			RR (95% CI)
	Events (no.)	Total pt-yr	Rate (95% CI)	Events (no.)	Total pt-yr	Rate (95% CI)	
600 pt-yr	45	386.4	11.6 (8.5, 15.3)	9	220.4	4.1 (1.9, 7.2)	2.85 (1.48, 6.43)
900 pt-yr	48	554.2	8.7 (6.4, 11.3)	13	312.0	4.2 (2.2, 6.7)	2.08 (1.18, 4.13)

- Pericardial effusions – largest fraction of safety events in device group
- Stroke events – most serious fraction of safety events in control group
- Bleeding events were also frequent

Pericardial Effusions by Experience

- Pericardial effusions – most common safety issue
- Throughout PROTECT AF Trial, procedural modifications and training enhancements were implemented
- Procedural events would be expected to decrease over time

Site implant group	Any		Serious	
	No.	%	No.	%
Early patients (1-3)	13/154	8.4	10/154	6.5
Late patients (≥4)	27/388	7.0	17/388	4.4
Total	40/542	7.2	27/542	5.0

- Continued ACCESS Registry

Any		Serious	
No.	%	No.	%
1/88	1.1	1/88	1.1

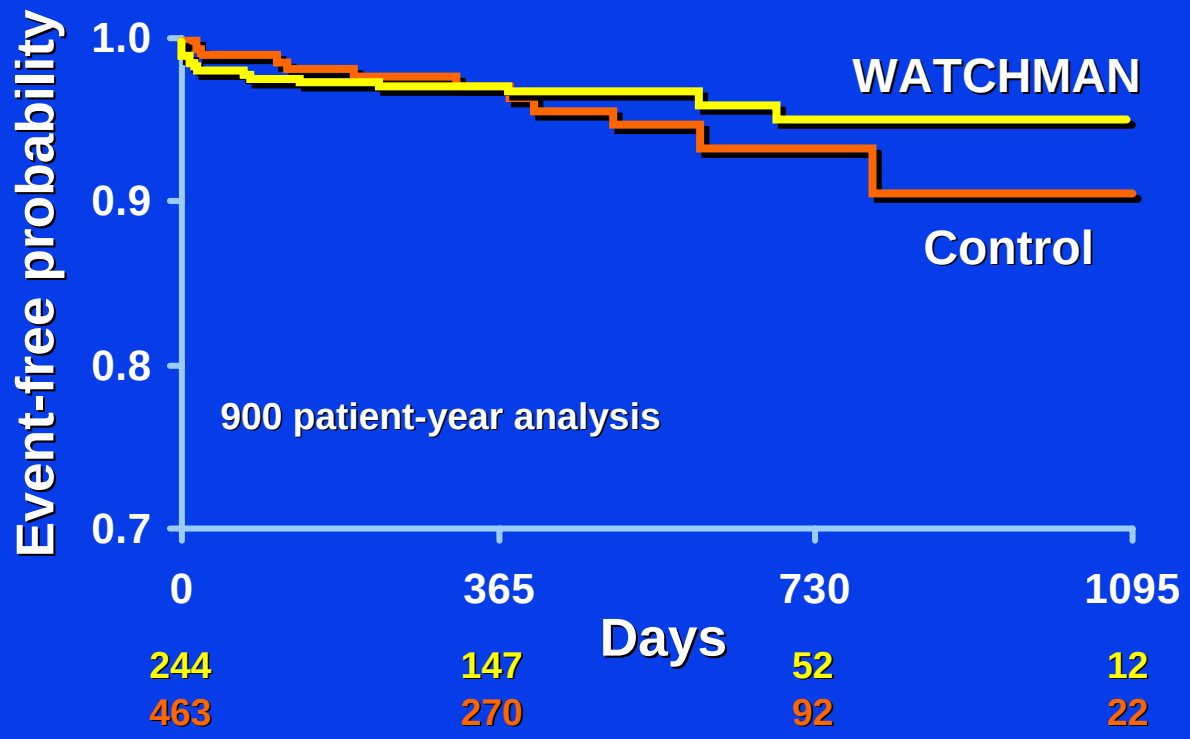
Safety Events
Stroke

Safety stroke events

- Also counted as efficacy events in efficacy analyses
- 5 events in device group classified as “ischemic stroke”
  - All periprocedural: extended hospitalization by 7 days
  - 3 were related to air embolism
- 1 hemorrhagic stroke in device group vs 6 in control group
  - Device event occurred 15 days post implant while patient was on warfarin
  - 4/6 stroke events in control group patients resulted in death

Intent-to-Treat
All Stroke

	Device			Control				Posterior probabilities	
Cohort	Events eve	Total pt-yr	Rate (95% CI)	Events (no.)	Total pt-yr	Rate (95% CI)	RR (95% CI)	Non-inferiority	Superiority
600 pt-yr	14	409.3	3.4 (1.9, 5.5)	8	223.6	3.6 (1.5, 6.3)	0.96 (0.43, 2.57)	0.927	0.488
900 pt-yr	15	582.9	2.6 (1.5, 4.1)	11	318.1	3.5 (1.7, 5.7)	0.74 (0.36, 1.76)	0.998	0.731

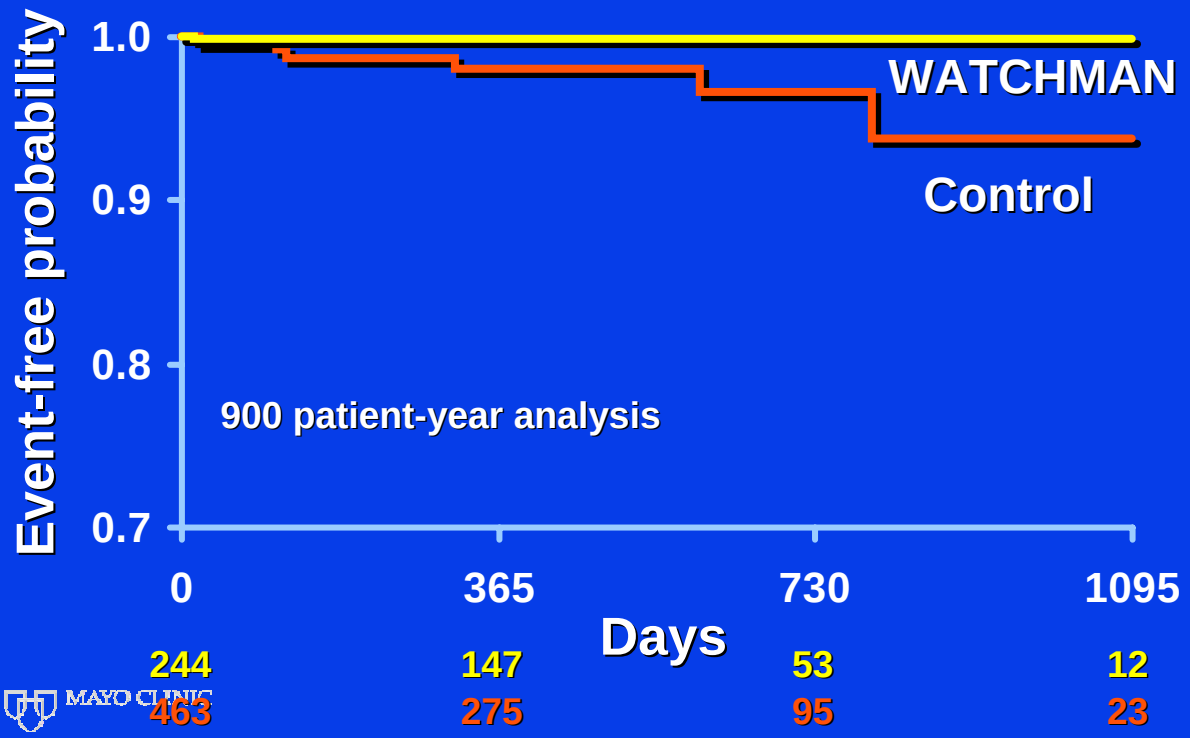


Randomization allocation (2 device:1 control)

ITT cohort: Non-inferiority criteria met

Intent-to-Treat
Hemorrhagic Stroke

	Device			Control				Posterior probabilities	
Cohort	Events (no.)	Total pt-yr	Rate (95% CI)	Events (no.)	Total pt-yr	Rate (95% CI)	RR (95% CI)	Non-inferiority	Superiority
600 pt-yr	1	416.7	0.2 (0.0, 0.9)	4	224.7	1.8 (0.5, 3.9)	0.13 (0.00, 0.80)	0.998	0.986
900 pt-yr	1	593.6	0.2 (0.0, 0.6)	6	319.4	1.9 (0.7, 3.7)	0.09 (0.00, 0.45)	>0.999	0.998



Randomization allocation
(2 device:1 control)

ITT cohort: Superiority criteria met

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Risk/Benefit Analysis

- **Intent-to-treat analysis**
- Primary endpoint (intent to treat) achieved
- Other statistically significant endpoint findings
  - Noninferiority for the primary efficacy event rate – 32% lower in device group
  - Noninferiority for all strokes – 26% lower in device group
  - Superiority for hemorrhagic stroke – 91% lower in device group
  - Noninferiority for mortality rate – 39% lower rate in device group
- Increased rate of primary safety events for the device group relative to the control group
  - Most events in the device group were procedural effusions that decreased over the course of the study
- 87% of patients were able to discontinue warfarin at 45 days

Summary

- Long-term warfarin treatment of patients with AF has been found effective, but presents difficulties and risk
- PROTECT AF trial was a randomized, controlled, statistically valid study to evaluate the WATCHMAN device compared to warfarin
- In PROTECT AF, hemorrhagic stroke risk is significantly lower with the device.
  - When hemorrhagic stroke occurred, risk of death was markedly increased
- In PROTECT AF, all cause stroke and all cause mortality risk are non-inferior to warfarin
- In PROTECT AF, there are early safety events, specifically pericardial effusion; these events have decreased over time

Conclusion

The WATCHMAN LAA Technology offers a safe and effective alternative to warfarin in patients with non-valvular atrial fibrillation at risk for stroke and who are eligible for warfarin therapy