

Michigan ACC 2010

# Left Atrial Appendage Occlusion For All!

George S. Hanzel, MD, FACC, FSCAI  
Director, Structural Heart Disease  
Beaumont Hospital  
Royal Oak, MI

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## Conflict of Interest Statement

Physician Name

Company/Relationship

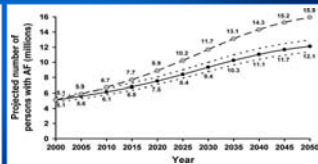
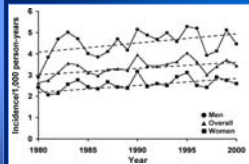
George S. Hanzel, MD

Atritech – Investigator  
No Financial Relationship

## The Atrial Fibrillation Epidemic: Olmsted County

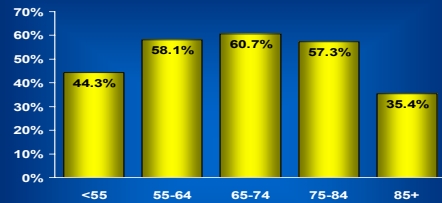
Trends in AF Incidence 1980-2000

Projections for AF Prevalence



Miyasaka Y et al. Circ 2006;114:119

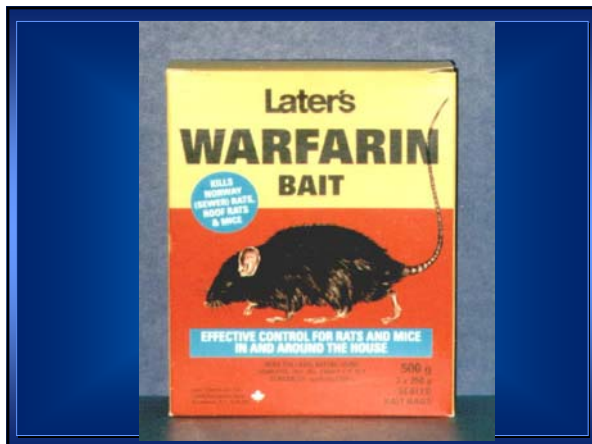
## Warfarin Use in AF Patients by Age



- Only 55% of AF patients with no contraindications to warfarin had evidence of warfarin use in previous 3 months
- Elderly patients with an increased absolute risk of stroke were least likely to be taking warfarin
- Most recent study: 43.5% of 50,551 patients received warfarin within 180 days

Annals of Internal Medicine 1999; 131(12): 927-934

American Journal of Medicine 2006;119:607-615



## Frequency of INR in Target Range

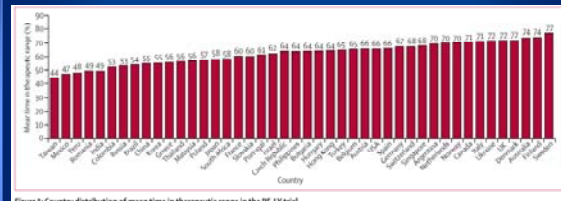


Figure 1: Country distribution of mean time in therapeutic range in the RE-LY trial

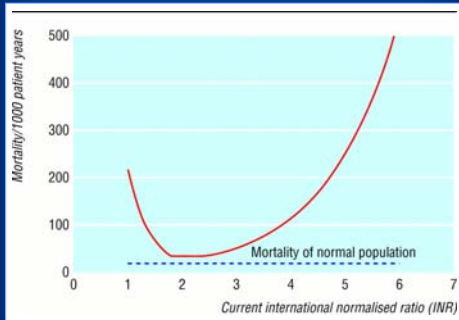
Mean time in therapeutic range = 64%  
Meta-analysis of 14 trials = 54%  
Medicare Database = 35%

Wallentin L, et al. Lancet 2010;376:975

Heneghan C, et al. Lancet 2006;367:404

Birman-Deych E, et al. Stroke 2006;37:1070

## INR Range and Mortality



42,451 patients, 3533 deaths

Odén A et al. *BMJ* 2002;325:1073

## RELY: Dabigatran vs Warfarin

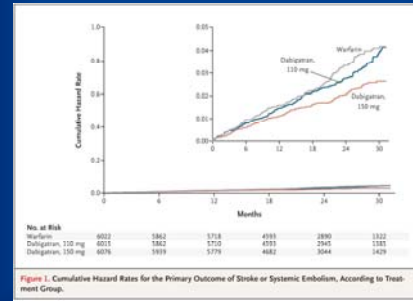


Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

Connolly S, et al. *NEJM* 2009;361:1139-51

## RELY: Dabigatran vs Warfarin

	Warfarin	Dabigatran 110	Dabigatran 150
Stroke and Embolization	1.69%/yr	1.53%/yr	1.11%/yr
ICH	0.38%/yr	0.12%/yr	0.19%/yr
Death	4.13%/yr	3.75%/yr	3.64%/yr
Major Bleed	3.36%/yr	2.71%/yr	3.11%/yr
MI	0.53%/yr	0.72%/yr	0.74%/yr
Net Benefit	7.64%/yr	7.09%/yr	6.91%/yr

	Warfarin	Dabigatran 110	Dabigatran 150
Dyspepsia	5.8%	11.8%	11.3%
Discontinuation Rate at 2 Years	16.6%	20.7%	21.2%

Connolly S, et al. *NEJM* 2009;361:1139-51

## COST!!!

- Dabigatran 110 mg: \$ 235.50 Canadian = \$ 231.40 US
- Patented drug prices 35-45% lower in Canada c/w the United States
- Likely cost of Dabigatran in US ~360.00-460.00 per month

## The Left Atrial Appendage: "Our Most Lethal Attachment"



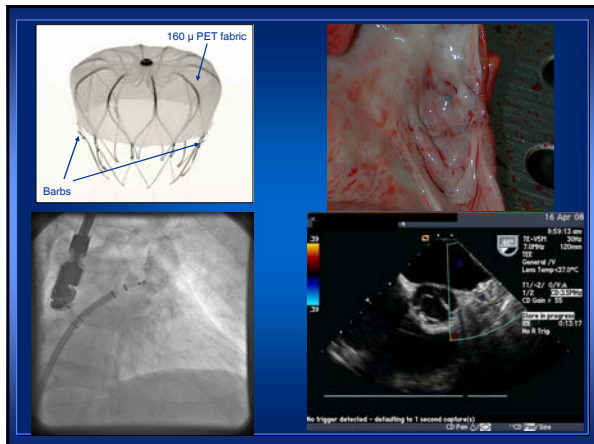
## Left Atrial Appendage Is A Major Source Of Thrombus that Cause Stroke In AF Patients

- 91% of all thrombus in patients with AF is found in the left atrial appendage (LAA)
- The four largest TEE studies comprising 1,181 patients showed that 98% of thrombi were found in the LAA

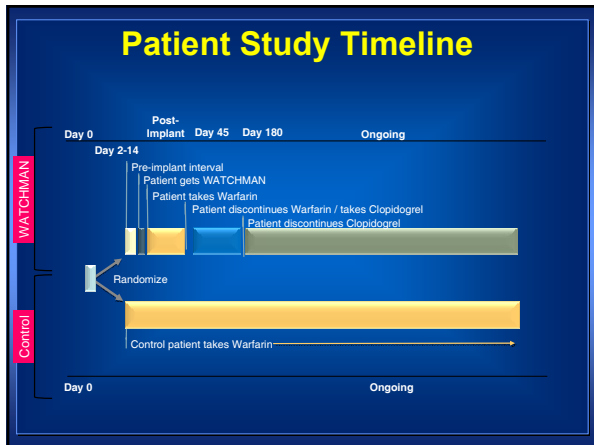
### Location of thrombi in non-rheumatic Atrial-Fib

Setting	Total # of thrombi found in LAA and atrium	Found LAA		Found in left atrium		Reference
		#	%	#	%	
TEE	67	66	99	1	1.5	Stoddard, JACC '95
TEE	35	34	97	1	2.9	Manning, Circ '94
Autopsy	47	35	74	12	25.5	Alborg, Acta Med. Scan. '69
TEE	4	2	50	2	50.0	Tsai, JFMA '90
TEE	13	12	92	1	7.7	Klein, Int. J. Card. Imag. '93
TEE & Operation	11	8	73	3	27.3	Manning, Circ '94
SPAF III & TEE	20	19	95	1	5.0	Klein, Circ '94
TEE	19	19	100	0	0	Leung, JACC '94
TEE	6	6	100	0	0	Hart, Stroke '94
<b>Total</b>	<b>222</b>	<b>201</b>	<b>91%</b>	<b>21</b>	<b>9.5%</b>	

The Annals of Thoracic Surgery, 1996;61:755-9



- ## PROTECT AF Clinical Trial
- Prospective, randomized study of WATCHMAN LAA Device vs. Long-term warfarin Therapy
  - 2:1 allocation ratio device to control
  - 800 patients enrolled from February 2005 to June 2008
    - 93 roll-in; 707 randomized
  - 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
    - INR monitoring every 2 weeks for 6 months and monthly thereafter



### Patient Risk Factors

Baseline Risk Factors					
	WATCHMAN N= 463		Control N= 244	P-value	
CHADS <sub>2</sub> Score:	1	157/463 33.9%	66/244 27.0%	0.39	
	2	158/463 34.1%	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%	0.76	
	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	30.0, 82.0	56.7 ± 10.1	30.0, 86.0	0.42
	460		239		

### Warfarin Discontinuation: WATCHMAN Group

- 76% of randomized patients discontinued warfarin at 45 days
- 87% of implanted patients discontinued warfarin at 45 days

Visit	Warfarin Discontinuation N / Total Implanted (%)	
45 day	348/401	86.7%
6 month	355/385	92.2%
12 month	345/370	93.2%
24 month	293/311	94.2%

Reason for Continuation / Re-initiation	At 45 days N / Total (%)	At 6 months N / Total (%)
Observation of Flow in the LAA	30 7.5%	14 3.6%
Physician Discretion	23 5.7%	16 4.2%

- ### PROTECT AF Trial Endpoint: Efficacy
- Primary Efficacy Endpoint (Non-inferiority hypothesis)
    - 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
    - Systemic thromboembolism
  - If a patient experienced a stroke followed by death, the primary endpoint was the stroke (time-to-first event Bayesian analysis)
  - Significant safety events are part of this Efficacy Endpoint

## Intent-to-Treat: Primary Efficacy Results

Cohort	WATCHMAN		Control		Relative Risk (95% CI)		Posterior Probabilities	
	Rate (95% CI)		Rate (95% CI)		Rate (95% CI)		Non-inferiority	Superiority
600 pt-yrs	4.4	(2.6, 6.7)	5.8	(3.0, 9.1)	0.76	(0.39, 1.67)	0.992	0.734
900 pt-yrs	3.4	(2.1, 5.2)	5.0	(2.8, 7.6)	0.68	(0.37, 1.41)	0.998	0.837
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
1350 pt-yrs	2.9	(2.0, 4.3)	4.2	(2.5, 6.0)	0.69	(0.42, 1.37)	>0.999	0.830
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

- Non-inferiority criteria met
- 29% lower relative risk in WATCHMAN Group

## PROTECT AF Trial Endpoint: Safety

- Primary Safety Endpoint (No pre-specified hypothesis)
  - Events considered life-threatening by CEC, including
    - Device embolization requiring retrieval
    - Pericardial effusion requiring intervention
    - Cranial bleeds and gastrointestinal bleeds
  - Any bleed that requires transfusion  $\geq$  2 units Packed Red Blood Cells
- Safety Endpoint Emphasis
  - Periprocedural events including procedure-related stroke
  - Long-term bleeding or device embolization events

## Intent-to-Treat: Primary Safety Results

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

## Intent-to-Treat: All Cause Mortality

Cohort	WATCHMAN		Control		Relative Risk (95% CI)	Posterior Probabilities*		
	Rate (95% CI)		Rate (95% CI)			Non-inferiority	Superiority	
600 pt-yrs	3.4	(1.8, 5.4)	4.9	(2.3, 7.8)	0.69	(0.33, 1.66)	0.991	0.779
900 pt-yrs	2.9	(1.7, 4.4)	4.7	(2.5, 7.1)	0.61	(0.32, 1.32)	0.999	0.889
1065 pt-yrs	3.0	(1.9, 4.5)	4.8	(2.8, 7.1)	0.62	(0.34, 1.24)	>0.999	0.907
1350 pt-yrs	3.1	(2.1, 4.4)	4.4	(2.6, 6.1)	0.70	(0.43, 1.36)	>0.999	0.823
1500 pt-yrs	3.2	(2.3, 4.5)	4.5	(2.8, 6.2)	0.71	(0.46, 1.28)	>0.999	0.852

- 29% lower relative risk in WATCHMAN Group

## Performance Metrics PROTECT AF vs CAP

	PROTECT AF	PROTECT AF		CAP	p-value*	p-value $\pm$
		Early	Late			
Procedure Time (Mean $\pm$ SD)	62 $\pm$ 34	67 $\pm$ 36	58 $\pm$ 33	50 $\pm$ 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

- Shorter implant time, higher implant success rate, higher warfarin discontinuation rate

Pericardial Effusion Rate: 5% vs 1.2%

## ASAP Study Synopsis

- To characterize the performance of the WATCHMAN LAA Closure Device in non-valvular AF patients for which long-term warfarin therapy is contraindicated
- Contraindicated definition: history of hemorrhagic & bleeding tendencies, hypersensitivity to warfarin
- Multicenter, prospective non-randomized feasibility study
  - Up to 150 patients @ 4 sites in Europe
  - Follow up @ 3, 6, 12, 18 & 24 months
  - TEE at 3 and 12 months
- Post procedure anti-platelet regimen
  - Clopidogrel through 6 months
  - ASA indefinitely

## ASAP Results

- 64 patients enrolled @ 4 centers in Europe – (80 now)
- Average CHADS<sub>2</sub> = 2.6
- Successful implantation in 59/64 pts (92%)
- 1 serious pericardial effusion
- Follow-up
  - 37 patients @ 3 months
  - 25 patients @ 6 months
  - 7 patients @ 1 year
- 1 patient with device related thrombus @ 3 mo TEE follow up
  - Resolved w/ 2 mo SQ heparin
- No strokes or TIA's

Poster presented at  
2010 HRS by Dr.  
Vivek Reddy

## PREVAIL

- 475 patients
- 2:1 randomization Watchman vs Warfarin
- CHADS<sub>2</sub> ≥ 2
- Primary Endpoint: stroke, systemic embolization, cv or unexplained death

## Conclusions

- Warfarin is grossly underutilized and can be difficult to manage
  - And patients hate it!
- Dabigatran is very promising
  - Likely expensive
  - Risk of major hemorrhage continues to accrue over years with continued therapy
- LAA Occlusion
  - Very promising initial data suggesting reduced cv death, total stroke, and systemic embolization
  - Complications are frontloaded
    - Pericardial effusion rates dramatically reduced as learning curve surmounted
    - New devices may enhance safety

## LAA Occlusion for Whom?

- Warfarin/Dabigatran contraindications?
- High-risk for major bleeding?
- Refusal/preference to avoid warfarin/dabigatran?

**Table 4** Bleeding Risk Assessment in AF: HAS-BLED Bleeding Risk Score

Letter	Clinical Characteristic*	Points Awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points