

The Significance of Asymptomatic Device-Detected Atrial Arrhythmias

Lessons from the ASSERT Trial
Arrhythmia Winter School, Fe 11th, 2012

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Clinical Case

- 78 year old woman
- History of HTN and diabetes
- **Meds:** Ramipril 10 OD, HCTZ 12.5 OD, Metformin 500 TID, ECASA 80 OD
- Dual-chamber pacemaker implanted 2009 for symptomatic sinus pauses > 5 seconds
- No prior history of Atrial Arrhythmias
- Normal systolic LV fxn, LA diameter 5.0 cm

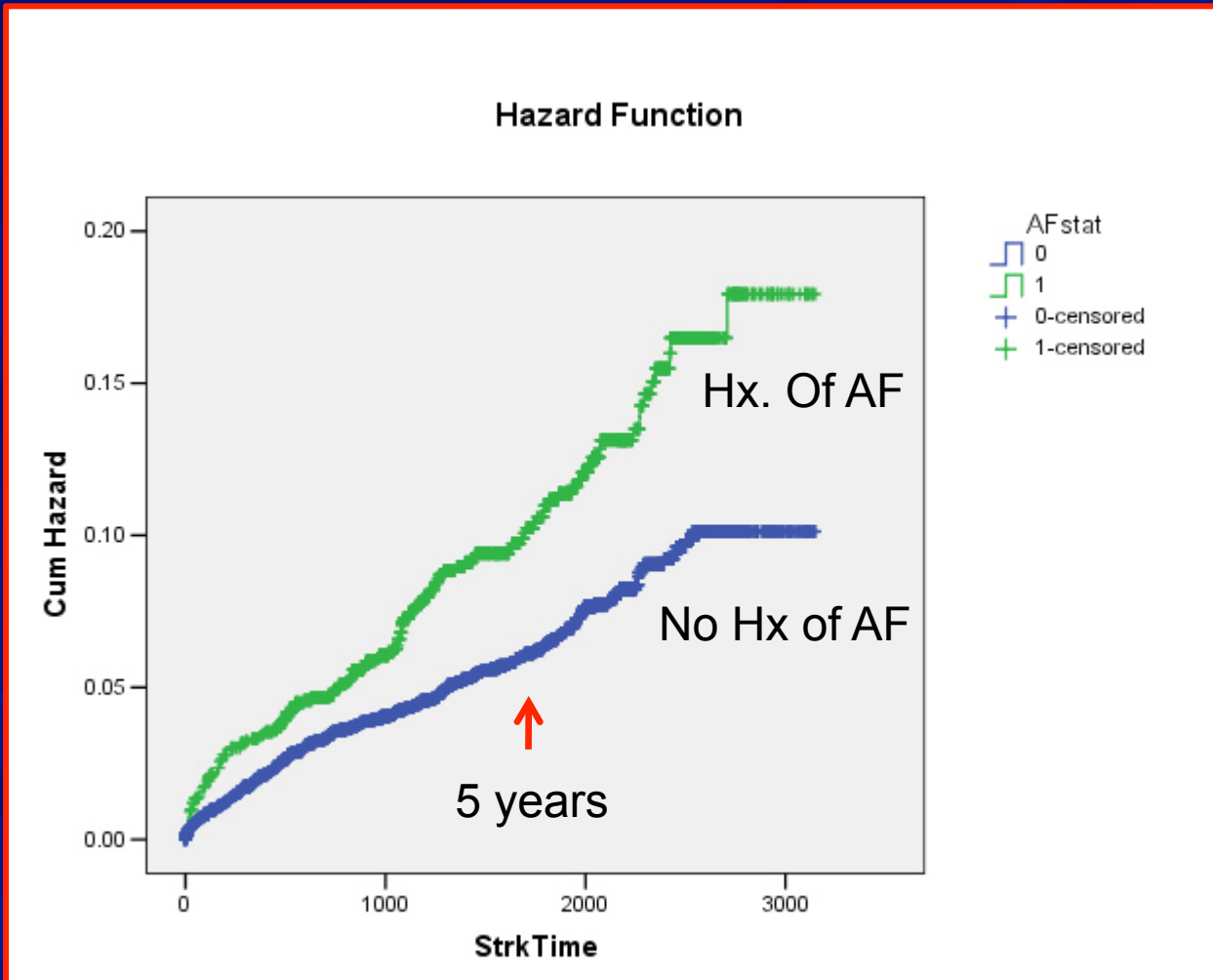
Clinical Case

- Returns to pacemaker clinic for 1-year follow-up
- Atrial and ventricular leads normal
- 0% ventricular paced, 5% atrial paced
- Estimated 10 years of battery life
- 10 episodes of “Atrial High-Rate” $> 190/\text{min}$. Range in length from 30 seconds to 1 hour, NO stored EGMs
- Absolutely no symptoms of arrhythmia

Clinical Questions

- What, if anything should we do for this lady?
- Is this atrial high-rate episode the same as atrial fibrillation?
- Are all atrial high-rate episodes real?
- What is the risk of stroke in patients with atrial high-rate episodes?

Stroke Risk in Pacemaker Patients: By History of AF



Healey JS
Circulation 2006

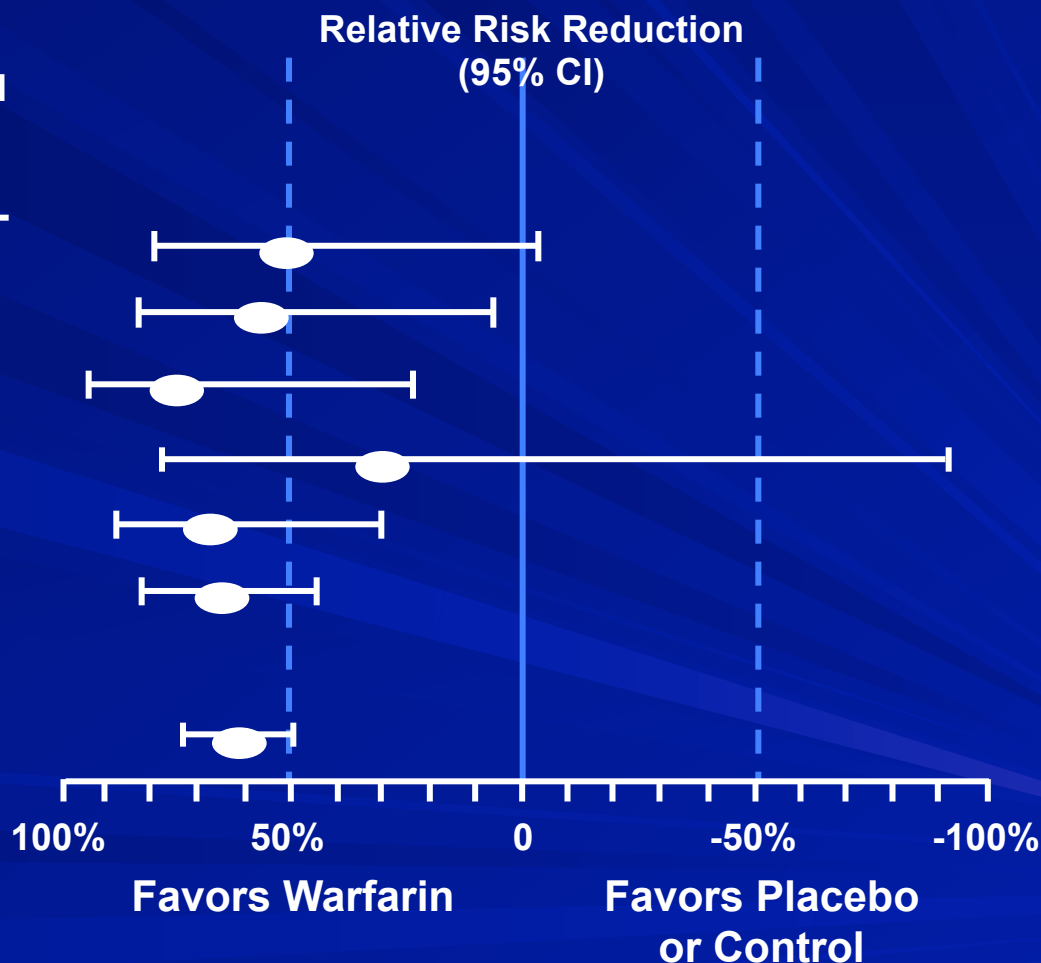
Efficacy of Warfarin

(Compared with Placebo or Control in Six Studies)

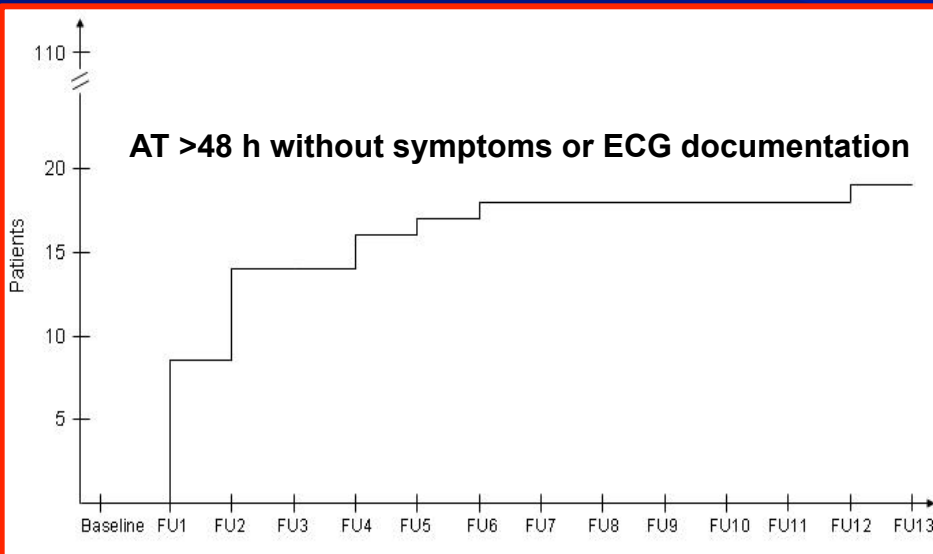
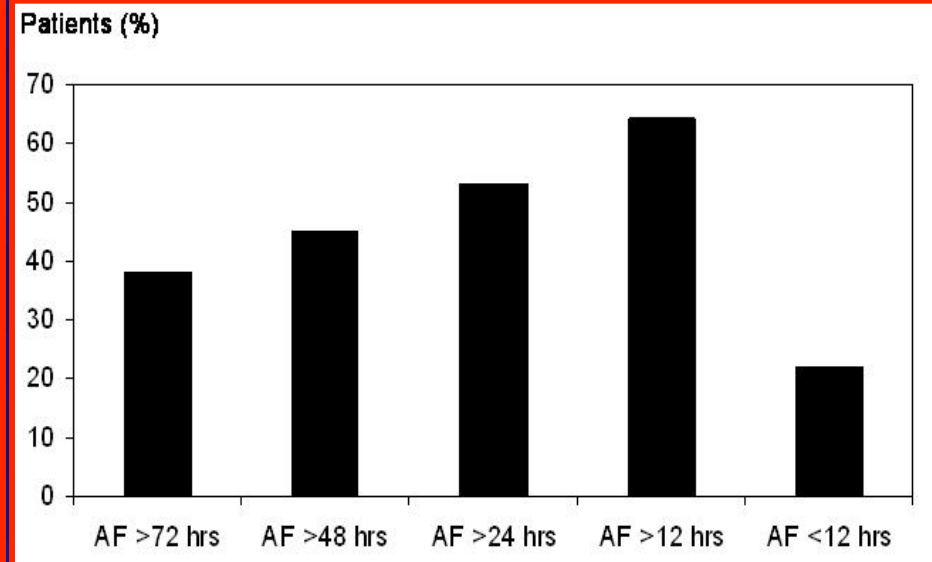
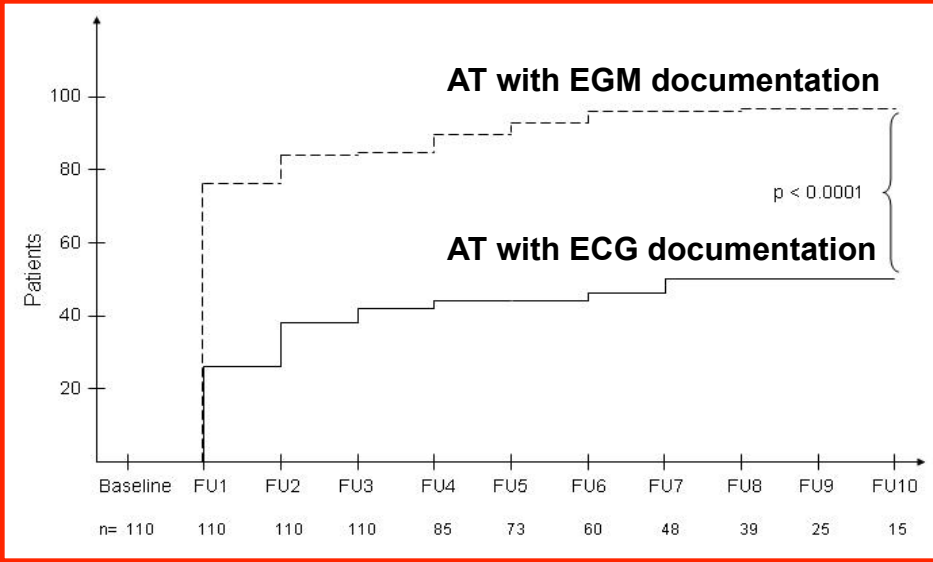
Adjusted-dose warfarin compared with placebo or control

Study	Year
AFASAK I	1989; 1990
SPAF I	1991
BAATAF	1990
CAFA	1991
SPINAF	1992
EAFT	1993

All trials (n=6)
N=2,900



Potential Clinical Impact of AHRE



In 110 patients with a history of AT

- AT recurred during 19 mo FU in 46% (ECG) versus 88% (device)
- AT >48 h in 50 patients
- 19/50 patients with AT >48 h asymptomatic and in SR at FU

Are all AHRE real? AWARE Trial (N=1642)

■ Appropriate: 73%

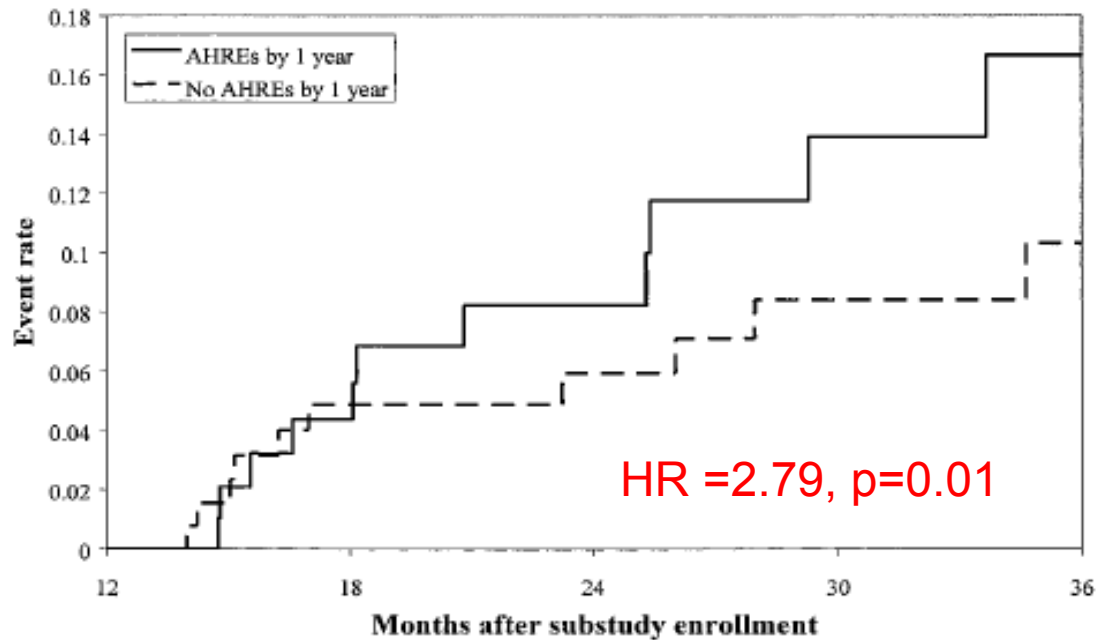
- AF – 42%
- Aflutter – 27%
- Atrial Tachycardia – 4%

■ Inappropriate: 27%

- RNRVAS – 17%
- Noise – 5%
- Farfield R-wave oversensing – 3%
- Sinus tachycardia – 2%

MOST: Death or Stroke

Glotzer, Circulation 2003

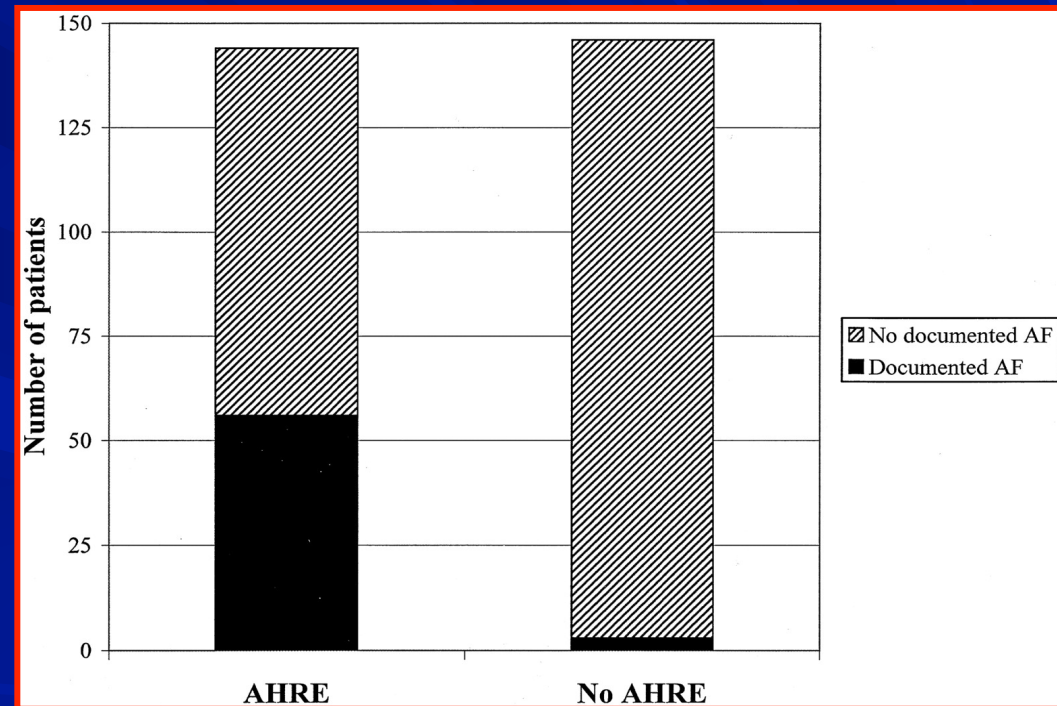


N=312

Figure 2. Kaplan-Meier plot of death or non-fatal stroke after 1 year of ancillary study follow-up in patients with AHREs vs those without AHREs; $P=0.001$. MOST indicates Mode Selection Trial; AHRE, atrial high rate episodes.

Limitations of MOST

- Retrospective
- Composite
- No adjudication of EGMs
- One-third of patients with AHRE had previously documented Atrial Fibrillation



TRENDS: Annualized TE Event Rates

	<u>Annualized Rate</u>	<u>Annualized Rate (Excluding TIAs)</u>
Zero Burden	1.1%/Year	0.5%/Year
Low Burden < 5.5 hours	1.1%/Year	1.1%/Year
High Burden ≥ 5.5 hours	2.4%/Year	1.8%/Year

TRENDS: Results

Cox proportional hazard model adjusting for baseline stroke risk factors & time dependent AT/AF burden & antithrombotic therapy

<u>Variable</u>	<u>Hazard Ratio*</u>	<u>95% Confidence Interval</u>	<u>p-value</u>
Low Burden < 5.5 hours	0.98	0.34 to 2.82	0.97
High Burden ≥ 5.5 hours	2.20	0.96 to 5.05	0.06

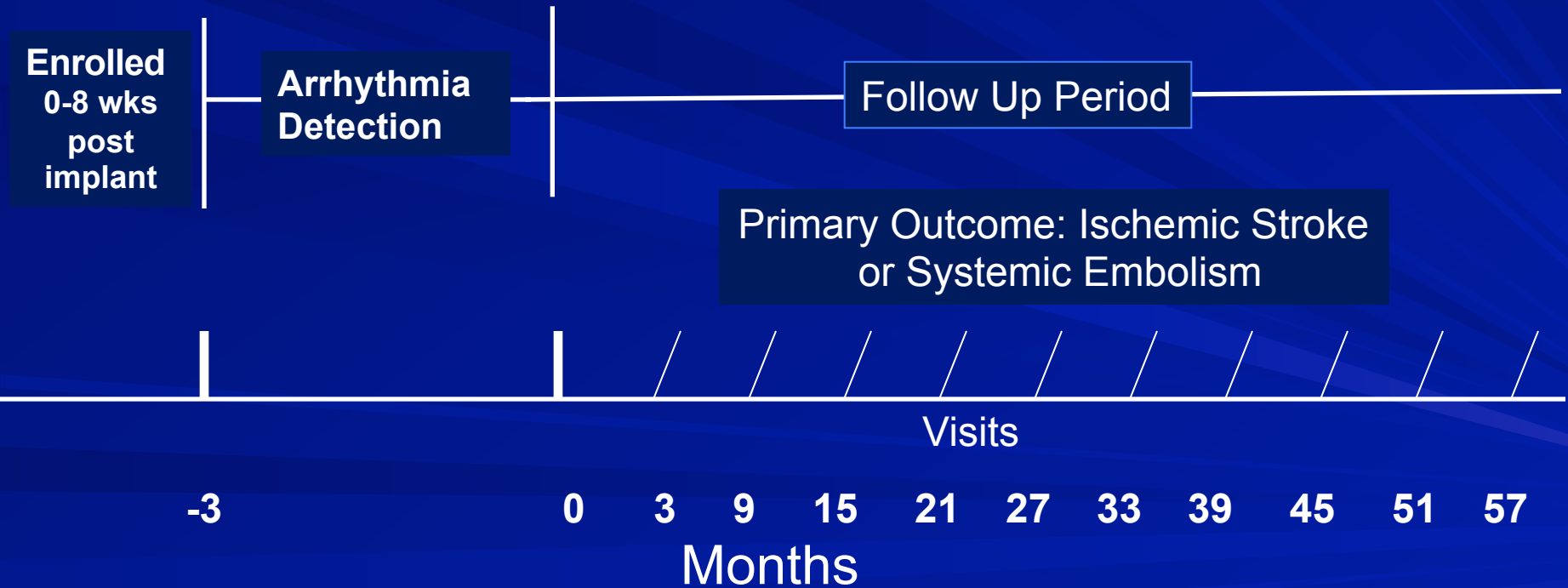
**compared to no AT/AF burden*

Study Design

Prospective Cohort Design

To determine if device-detected atrial tachyarrhythmias are associated with an increased risk of stroke or embolism?

Minimum Follow up	1.75 yrs
Maximum Follow Up	5 yrs
Mean Follow Up	2.8 yrs



ASSERT: Study Design

■ Patient Eligibility

- Enrolled after new dual-chamber pacemaker or ICD
- Age \geq 65 years
- History of hypertension
- Excluded if any history of AF
- Excluded if on Vitamin K antagonist

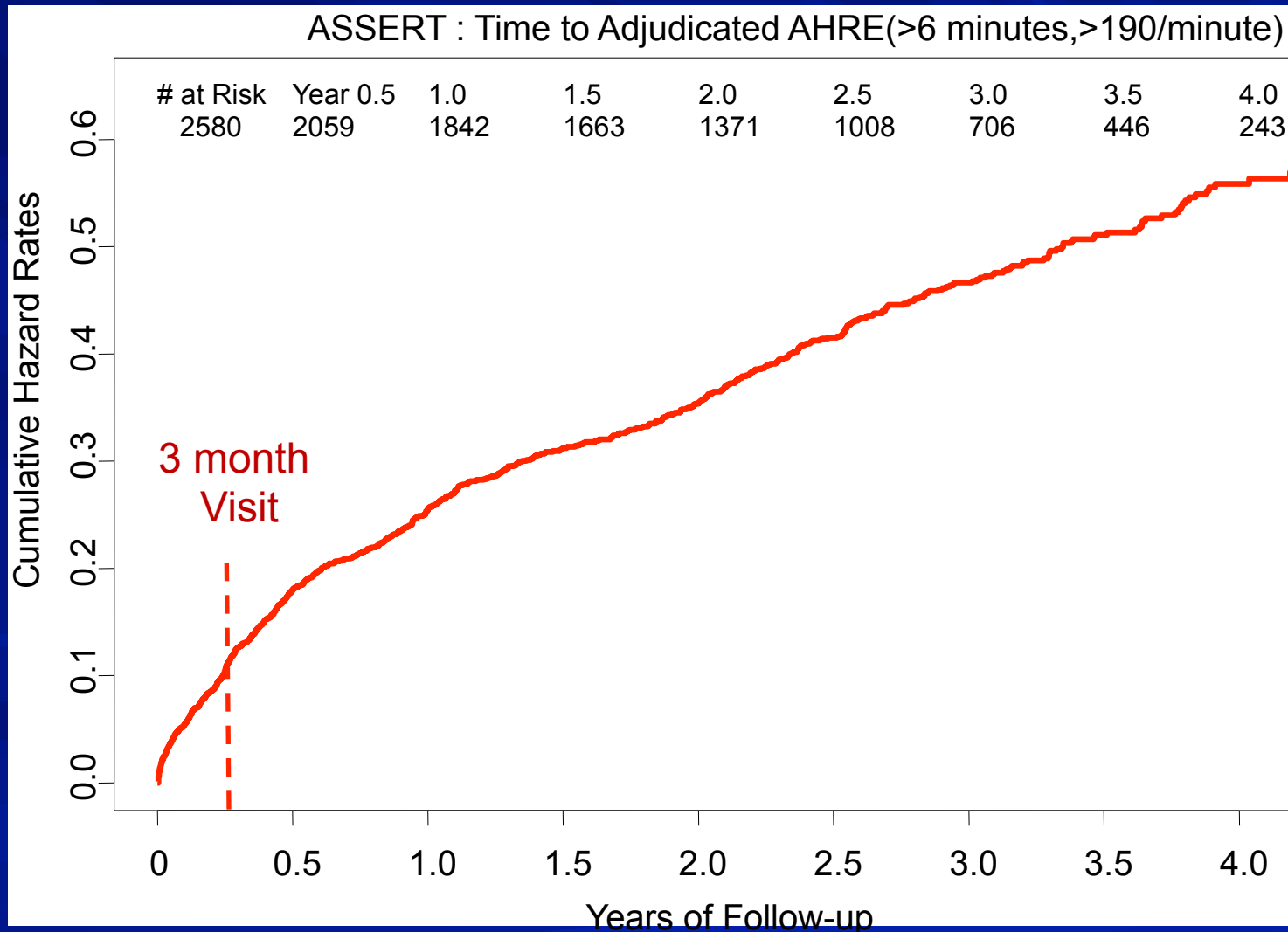
■ Pre-specified primary analysis:

- Monitor from enrolment to 3 month visit for atrial tachyarrhythmia defined as >6 minutes and an atrial rate of >190 bpm
 - Prospective follow up for ischemic stroke or systemic embolism from 3 month visit onwards
- ## ■ Statistical power to detect $\geq 1\%$ per year increase in primary outcome
- ## ■ Adjudication of all available AHRE

ASSERT: Study Results

- 2580 patients enrolled following implant of first pacemaker or ICD (St. Jude Medical)
 - 2451 pacemaker, 129 ICD patients
- 136 participating centres, 23 countries
- Mean follow up 2.8 yrs
- 36% of patients had at least one device-detected atrial tachyarrhythmia
 - >6 min, >190 bpm; at mean FU of 2.8 years
- Cumulative rate of VKA use <2% per year

Time to First Device-Detected Atrial Tachyarrhythmia > 6 min, >190 bpm



Baseline Characteristics

	Device-Detected Atrial Tachyarrhythmia before 3 Month Visit		P-Value
	No N = 2319	Yes N = 261	
Age (years) (mean \pm SD)	76.3 \pm 6.7	77.0 \pm 6.8	0.13
Male	58.7%	54.9%	0.27
History of Prior Stroke	7.2%	6.9%	0.84
History of Heart Failure	14.4%	14.9%	0.83
History of Diabetes Mellitus	29.1%	22.6%	0.03
History of Myocardial Infarction	18.4%	12.3%	0.01
CHADS₂ score (mean \pm SD)	2.26 \pm 1.02	2.21 \pm 1.11	0.47
Sinus Node Disease	42%	50%	0.01
Heart Rate	70.0 \pm 11.6	67.7 \pm 11.7	0.001
Systolic BP (mm Hg)	136.5 \pm 20	137.2 \pm 20	0.60
Baseline use of ASA	61.7%	61.3%	0.91
Baseline use of Clopidogrel	10.7%	9.6%	0.56

Primary and Other Clinical Outcomes

Event	Device-Detected Atrial Tachyarrhythmia				Device-Detected Atrial Tachyarrhythmia Present vs. absent		
	Absent N=2319		Present N= 261		RR	95% CI	p
	events	%/year	events	%/ year			
Ischemic Stroke or Systemic Embolism	40	0.69	11	1.69	2.49	1.28 – 4.85	0.007
Vascular Death	153	2.62	19	2.92	1.11	0.69 – 1.79	0.67
Stroke / MI / Vascular Death	206	3.53	29	4.45	1.25	0.85 – 1.84	0.27
Clinical Atrial Fibrillation or Flutter	71	1.22	41	6.29	5.56	3.78 – 8.17	<0.001

Clinical Outcomes Censored if Clinical Atrial Fibrillation/Flutter Occurs

Event	Device-Detected Atrial Tachyarrhythmia				Device-Detected Atrial Tachyarrhythmia Present vs. absent		
	Absent N= 2319		Present N= 261		RR	95% CI	p
	events	%/ year	events	%/year			
Ischemic Stroke or Systemic Embolism	40	0.70	10	1.67	2.41	1.21 – 4.83	0.01
Vascular Death	153	2.67	19	3.17	1.18	0.73 – 1.90	0.50
Stroke / MI / Vascular Death	206	3.59	29	4.84	1.32	0.90 – 1.95	0.16

Clinical Outcomes Adjusted for Baseline Risk of Stroke

Event	Device-Detected Atrial Tachyarrhythmia				Device-Detected Tachyarrhythmia Present vs. absent		
	Absent N= 2319		Present N= 261		RR	95% CI	p
	events	%/ year	events	%/year			
Ischemic Stroke or Systemic Embolism	40	0.69	11	1.69	2.50	1.28 – 4.89	0.008
Vascular Death	153	2.62	19	2.92	1.14	0.71 – 1.84	0.59
Stroke / MI / Vascular Death	206	3.53	29	4.45	1.27	0.86 – 1.88	0.23
Clinical Atrial Fibrillation or Flutter	71	1.22	41	6.29	5.75	3.89 – 8.47	<0.001

Clinical Outcomes by CHADS₂

CHADS ₂ Score	Total Pts.	Sub-clinical Atrial Tachyarrhythmia between enrollment and 3 months						Sub-clinical Atrial Tachyarrhythmia Present vs. absent		
		Present			Absent			HR	95% CI	P (trend)
		Pts.	events	%/year	Pts.	events	%/year			
1	600	68	1	0.56	532	4	0.28	2.11	0.23 – 18.9	0.35
2	1129	119	4	1.29	1010	22	0.77	1.83	0.62 – 5.40	
>2	848	72	6	3.78	776	18	0.97	3.93	1.55 – 9.95	

Conclusions

- Over 2.8 years mean follow up, device-detected atrial tachyarrhythmias (>6 min, >190 bpm) are present in 36% of pacemaker patients with hypertension; but no prior history of AF
- Device-detected atrial tachyarrhythmias are associated with a 2.5-fold increased risk of ischemic stroke or systemic embolism
- In patients with CHADS₂ score > 2, device-detected atrial tachyarrhythmias increase the absolute risk of stroke or systemic embolism to 4% per year

ASSERT Adjudication

J. Healey, Europace, 2011

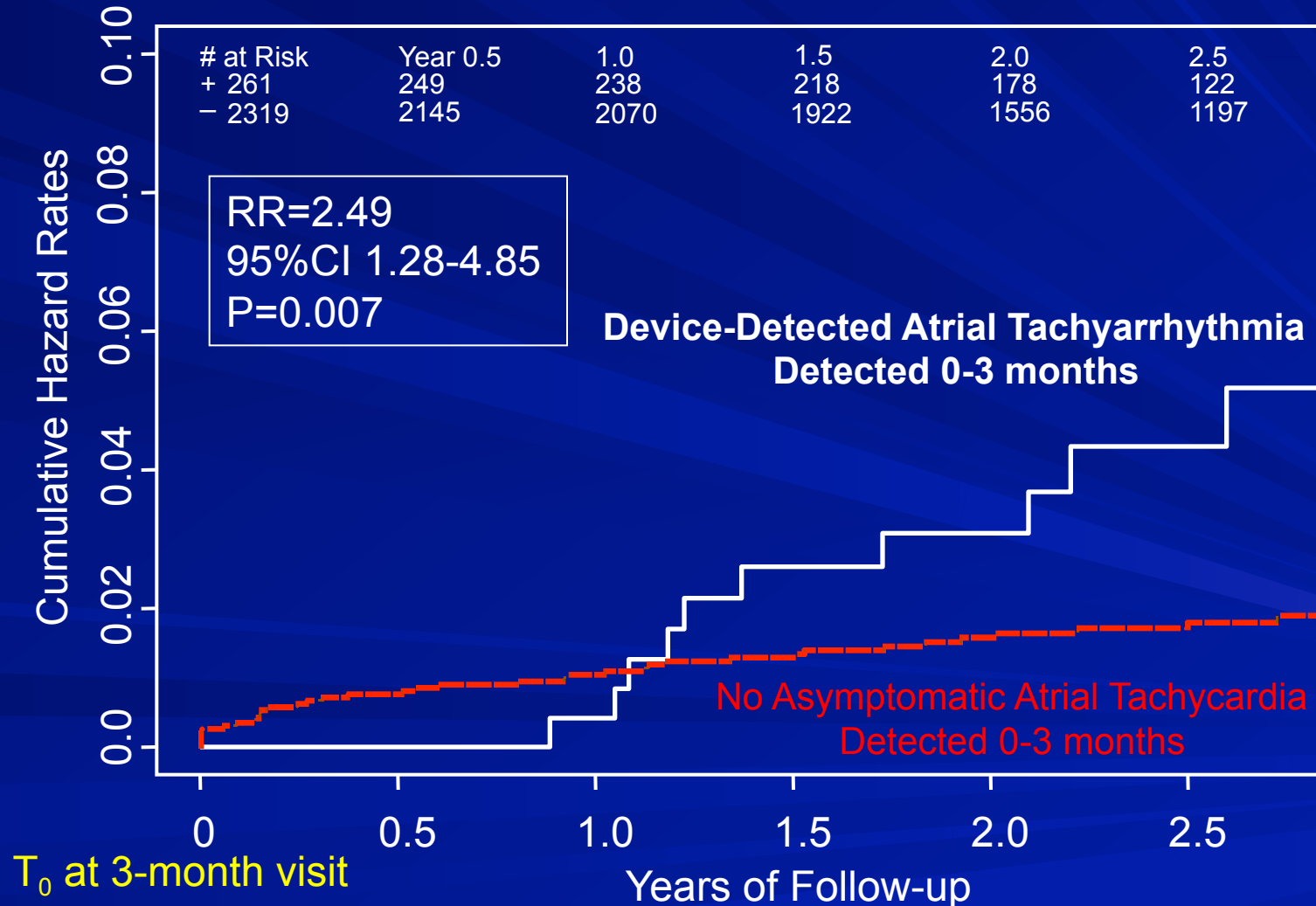
AHRE Type	Appropriate (N)	Inappropriate (N)	Positive-Predictive Value
> 6 min, > 190 bpm	7751	1584	83.0%
> 6 min, > 250 bpm	6658	712	90.3 %
> 30 min, > 190 bpm	5400	408	93.0%
> 30 min, > 250 bpm	4810	214	95.7%
> 6 hrs, > 190 bpm	2325	69	97.1%
> 6 hrs, > 250 bpm	2092	46	97.8%
> 24 hrs, > 190 bpm	1174	22	98.2%

17,000 AHRE episodes double-adjudicated
PPV for AHRE < 6 min: 48%

ASSERT RESULTS: Using un- adjudicated AHRE

	RR of clinical AT	P	RR of Primary Outcome* (Ischemic Stroke and Non-CNS Embolism)	P
AHRE > 6min	5.25	<0.001	2.04	0.04
AHRE > 30 min	5.37	<0.001	2.10	0.04
AHRE > 6 hrs	7.83	<0.001	4.32	<0.001

ASSERT: Ischemic Stroke or Systemic Embolism



ASSERT: Time-Dependent Analysis

Duration of AT ≥ 190 Beats per Minute	Ischemic Stroke or Embolism: Atrial Tachyarrhythmia Present vs. Absent		
	RR	95% CI	P-Value
≥ 6 minutes	1.77	1.01-3.10	0.047
≥ 30 minutes	1.87	1.06-3.28	0.03
≥ 6 hours	2.01	1.14-3.54	0.02
≥ 12 hours	1.86	1.05-3.29	0.02
≥ 24 hours	1.98	1.13-3.49	0.02
≥ 48 hours	1.93	1.09-3.42	0.02
Duration of Risk Associated with AT ≥ 6 minutes			
Lifelong	1.77	1.01-3.10	0.047
1 month	2.31	0.92-5.79	0.07
1 week	1.44	0.20-10.4	0.72
1 day	4.11	0.57-29.8	0.16
Delay between AT and Risk of Stroke			
Zero delay	1.77	1.01-3.10	0.047
3 months	1.58	0.85-2.91	0.15
6 months	2.04	1.08-3.88	0.029
12 months	2.91	1.46-5.81	0.002

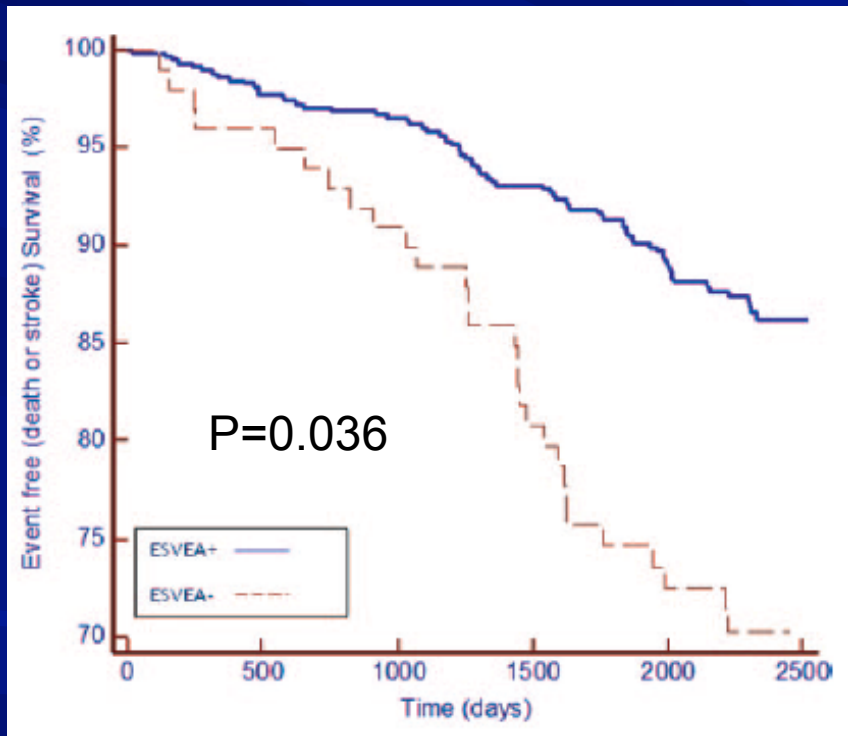
ASSERT: Relationship between AHRE and Stroke

- In ASSERT, 59 patients had stroke or SE
- 30 had no AHRE
 - 9 had AHRE but only AFTER their stroke
- 20 patients had at least one AHRE > 6 minutes prior to their stroke or SE
 - 3 developed persistent AF at least one month before, but only recognized clinically in 1 pt.
 - 2 patients had 9-day long episodes 1-2 weeks prior
 - 1 patient had 2.7 hour episode beginning 48 hours prior
 - None of remaining 14 pts. had ANY AHRE > 6 minutes in 30 days before stroke or SE

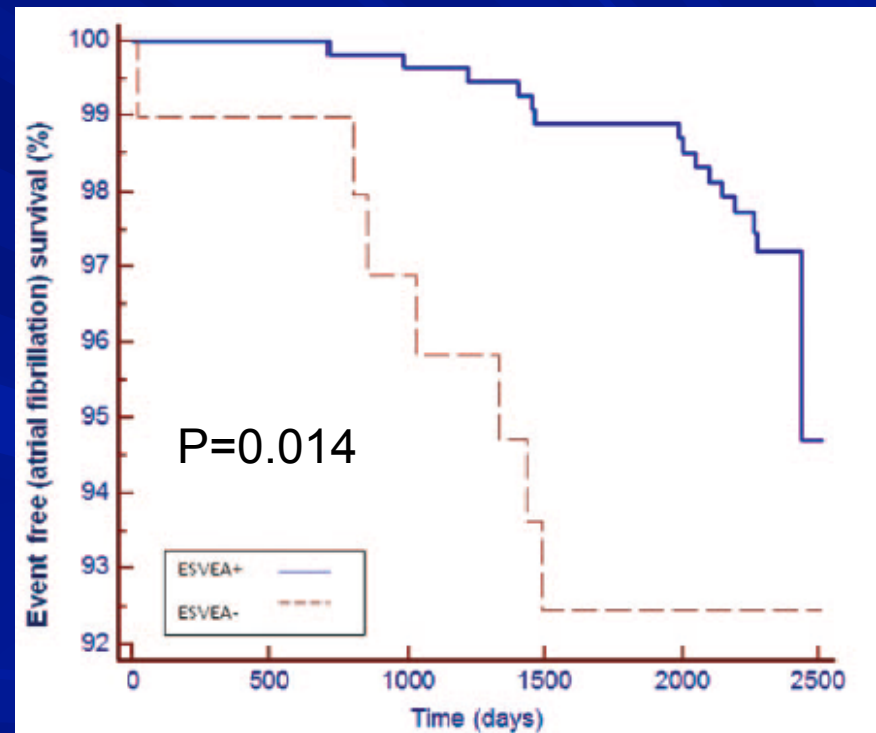
Beyond the Pacemaker Population

- Copenhagen Holter Study
 - Circulation 2010; 121
 - 678 healthy men and women
 - 55-75 years old
- One 48 hour holter
- Positive defined as > 30 PACs per hour or any run ≥ 20 beats
- Mean follow-up of 6.3 years

Outcomes of Cohort Study



Death or Stroke



Hospitalization for AF

Absolute Event Rates

Table 2. Event Numbers and Events per 1000 Patient-Years for Up to 7 Years of Follow-Up in All Participants and in Participants With and Without ESVEA

	All (n=678)	ESVEA		<i>P</i> *
		Yes (n=99)	No (n=579)	
Atrial fibrillation	22 (5.5)	7 (12.8)	15 (4.3)	0.008
Stroke	27 (6.7)	10 (18.8)	17 (4.9)	0.0002
Total mortality	87 (21.4)	21 (37.2)	66 (18.9)	0.005

Unanswered Questions?

- Clear association between AHRE and stroke, but no intervention study
 - Risk of stroke similar to AF for patient with 1 fewer CHADS-2 points
 - Temporal association of AHRE and stroke?
- Should atrial leads be implanted in all patients (and have AHRE storage activated)?
- Should devices be implanted to detect AF in high-risk non-pacemaker patient groups?