Subclinical AF as a Source of Ischemic Stroke: ASSERT Trial

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Introduction

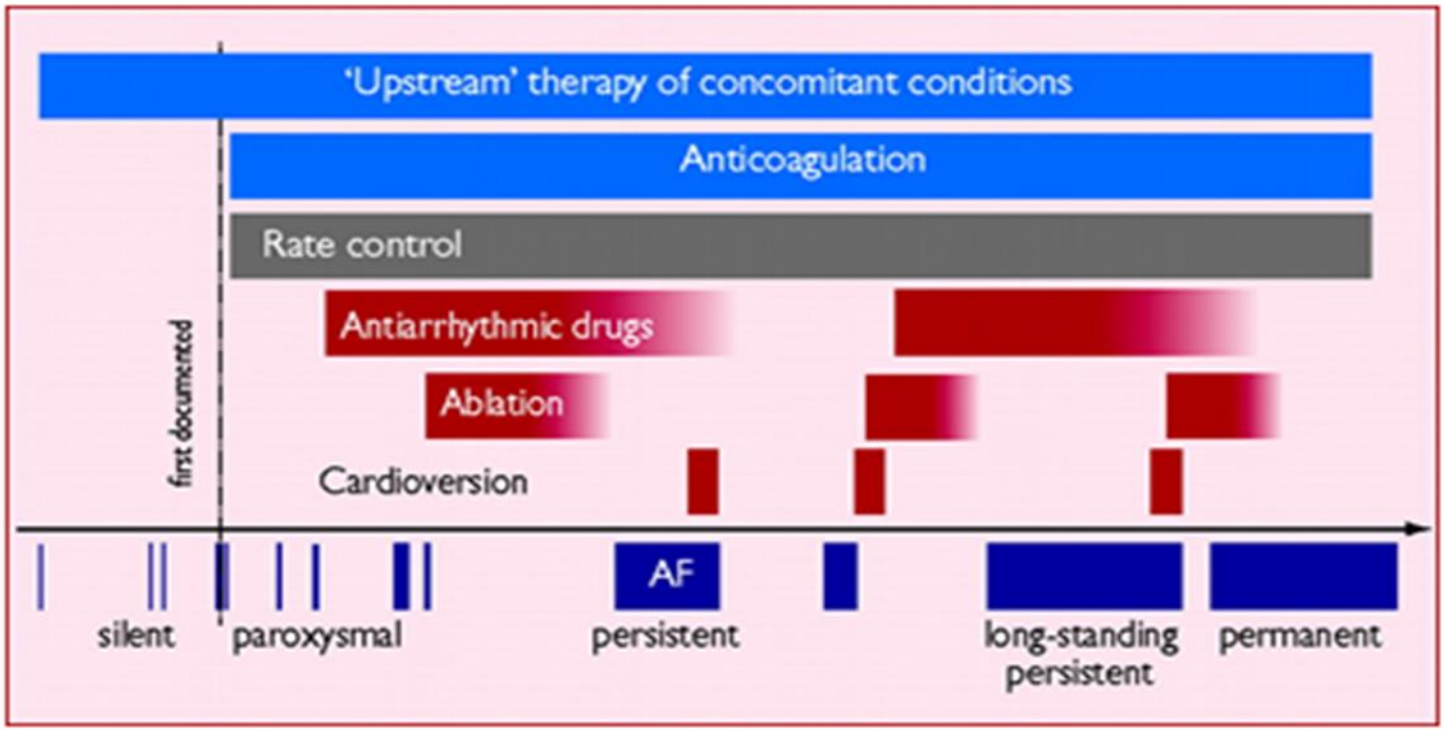
- **Atrial fibrillation (AF)** is responsible for **20% of ischemic strokes**

- **Atrial fibrillation** increases the risk of stroke by a factor of **5** in **non-rheumatic AF** and by a factor of **17** in **rheumatic AF**

- **Anticoagulation** is one of the most effective secondary stroke prophylactic treatment options, which **reduces the risk of stroke** by 2/3

- **Subclinical AF** (asymptomatic AF)
  - 25% of ischemic stroke has **no etiologic factor**
  - Subclinical AF is suspected to be the cause of **cryptogenic stroke**

'Natural' time course of AF. AF = atrial fibrillation.



Developed with the special contribution of the European Heart Rhythm Association (EHRA) et al. Europace 2010;12:1380-1420

Europace

- Patient often starts with **paroxysmal** AF, but later becomes **persistent** or **permanent** AF

- **The risk of stroke or systemic embolism** is influenced by **cardiovascular risk factors** such as hypertension, diabetes or history of stroke, but **not by type of AF**

- **Most paroxysmal AF** had never showed typical clinical symptoms (clinically **silent disease** during the earlier stages)

- **The first manifestation** of clinical AF is often preceded by **short episodes of 'subclinical' or 'undiagnosed' AF**

- There is a substantial incidence of **subclinical atrial tachyarrhythmias**

: Prevention of Atrial Fibrillation After Cardioversion (PAFAC) trial using transtelephonic transmission

  – 70% of AF episodes were asymptomatic

- **Research interest** has grown in the **clinical relevance of AF** at an even **earlier stage**, before the clinical detection of AF

- These data are mostly derived from patients with implantable **pacemaker devices** which allow a **continuous monitoring** of cardiac rhythm

Does the presence of short episodes of subclinical AF have prognostic significance ?

Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke : report of the Atrial Diagnostics Ancillary Study of the Mode Selection Trial **(MOST)**

Circulation 2003;107:1614-19

Monitored Atrial Fibrillation Duration Predicts Arterial Embolic Events in Patients Suffering From Bradycardia and Atrial Fibrillation Implanted With Antitachycardia Pacemaker

Capucci et al. J Am Coll Cardiol 2005;46:1913-20

TABLE 1

Atrial High Rate Episodes and Thromboembolism

Study	N	Criteria	Result
Glotzer *et al.*[25]	312	220 bpm and > 10 beats (only AHRE > 5 minutes analyzed)	Median 27 months follow-up Presence of (any) AHRE independent predictor of total mortality (CI 2.48, 1.25–4.91); death or nonfatal stroke (CI 2.79, 1.51–5.15)
Capucci *et al.*[26]	725	PR Logic algorithm (prespecified analysis on AF of 5 minutes and 1 day duration)	Median 22 months follow-up AF > 1 day associated with thromboembolism (HR 3.1, 1.1–10.5) AF > 5 minutes not associated with higher risk of thromboembolism Risk of thromboembolism increased with number of risk factors*

AHRE = atrial high rate episodes; AF = atrial fibrillation; CI = confidence interval.

*Risk factors include ischemic heart disease, previous thromboembolism, hypertension, and diabetes.

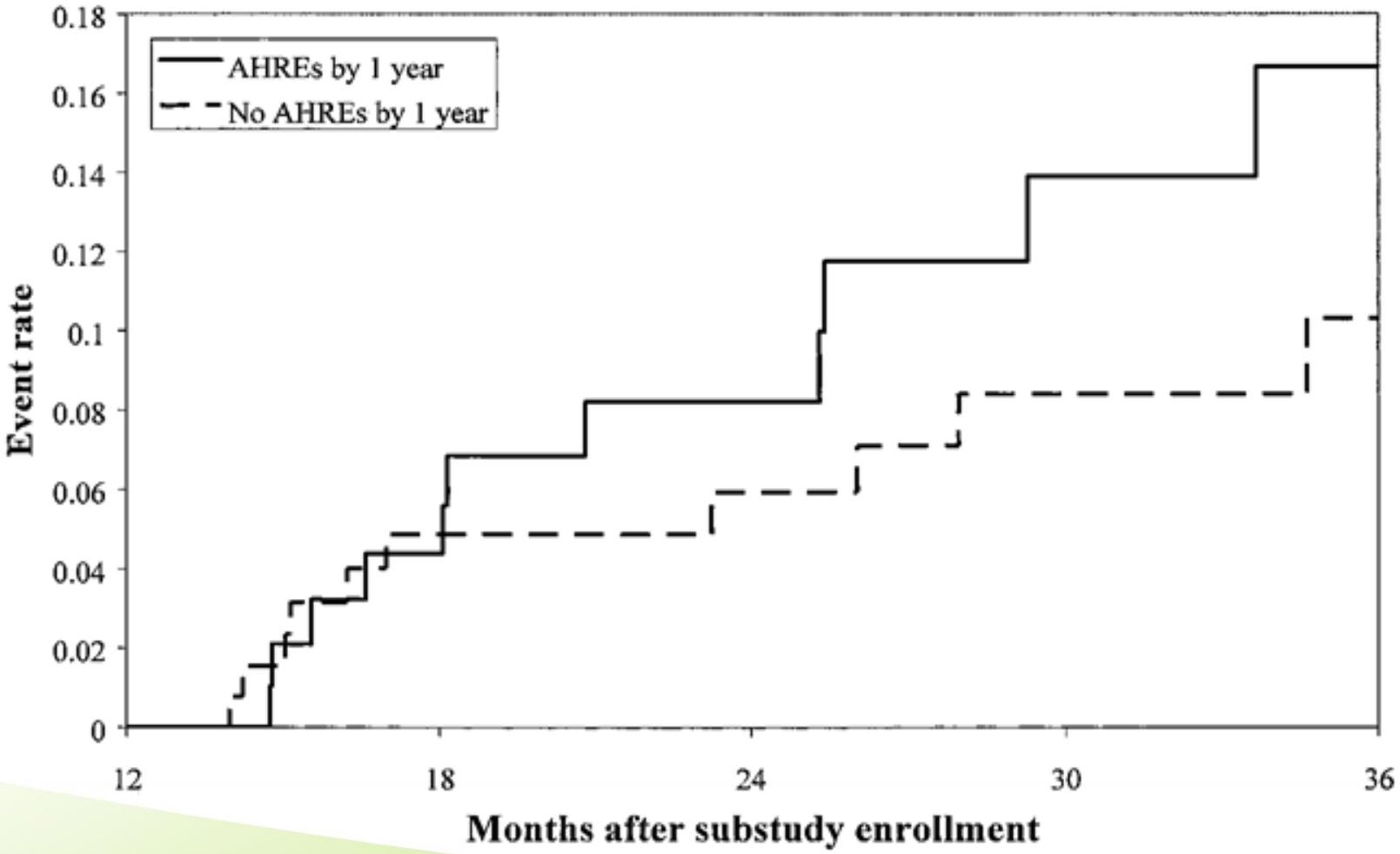
MOST trial

- Pacemaker patients who had at least one episode of atrial tachycardia with more than 220 bpm for at least 5 min (atrial high rate event-AHRE) had a **2.79** fold increase in **the risk of stroke or death**

- AHRE 5 min cutoff : excludes most episodes of oversensing

Pollack WM et al. PACE.2001;24:424-429

MOST trial


AHREs by 1 year
No AHREs by 1 year
Event rate
0.18
0.16
0.14
0.12
0.1
0.08
0.06
0.04
0.02
0
12
18
24
30
36
Months after substudy enrollment

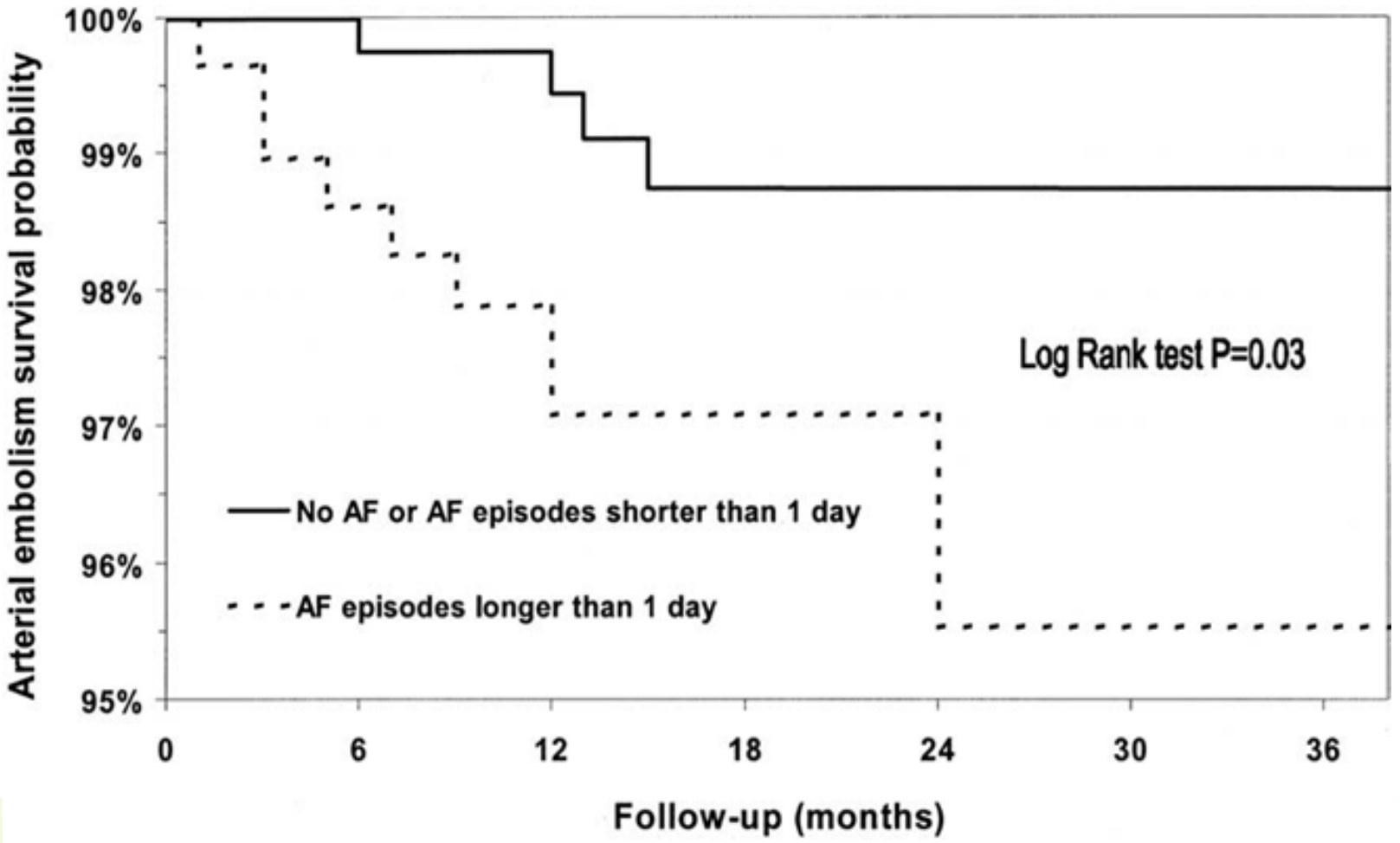
Capucci et al.

- The risk of embolism was **3.1 times** increased in patients with device-detected **AF episodes longer than one** day during follow-up

Table 3. Percentage of Patients With AF Episodes of Given Duration for the Group of Patients With and Without Arterial Embolic Events

	711 Patients With No Embolic Events	14 Patients With Embolic Events	p Value
Percentage of patients with AF episodes > 5 min	73.8%	78.6%	1.00*
Percentage of patients with AF episodes > 1 day	41.2%	71.4%	0.03*

*Fisher exact test.
AF = atrial fibrillation.


Arterial embolism survival probability
100%
99%
98%
97%
96%
95%
0
6
12
18
24
30
36
Follow-up (months)
Log Rank test P=0.03
No AF or AF episodes shorter than 1 day
AF episodes longer than 1 day

The TRENDS study

Circ Arrhythmia Electrophysiol 2009;2:474-480

- 2486 patients with >1 stroke risk factor (heart failure, hypertension, age >65 years, diabetes, or prior TE) receiving pacemakers or defibrillators

- Patients with a **daily burden** of atrial tachycardia of **more than 5.5 h** have a **2.4 fold** increase in the **risk** of thromboembolism, compared with patients with no atrial tachycardia

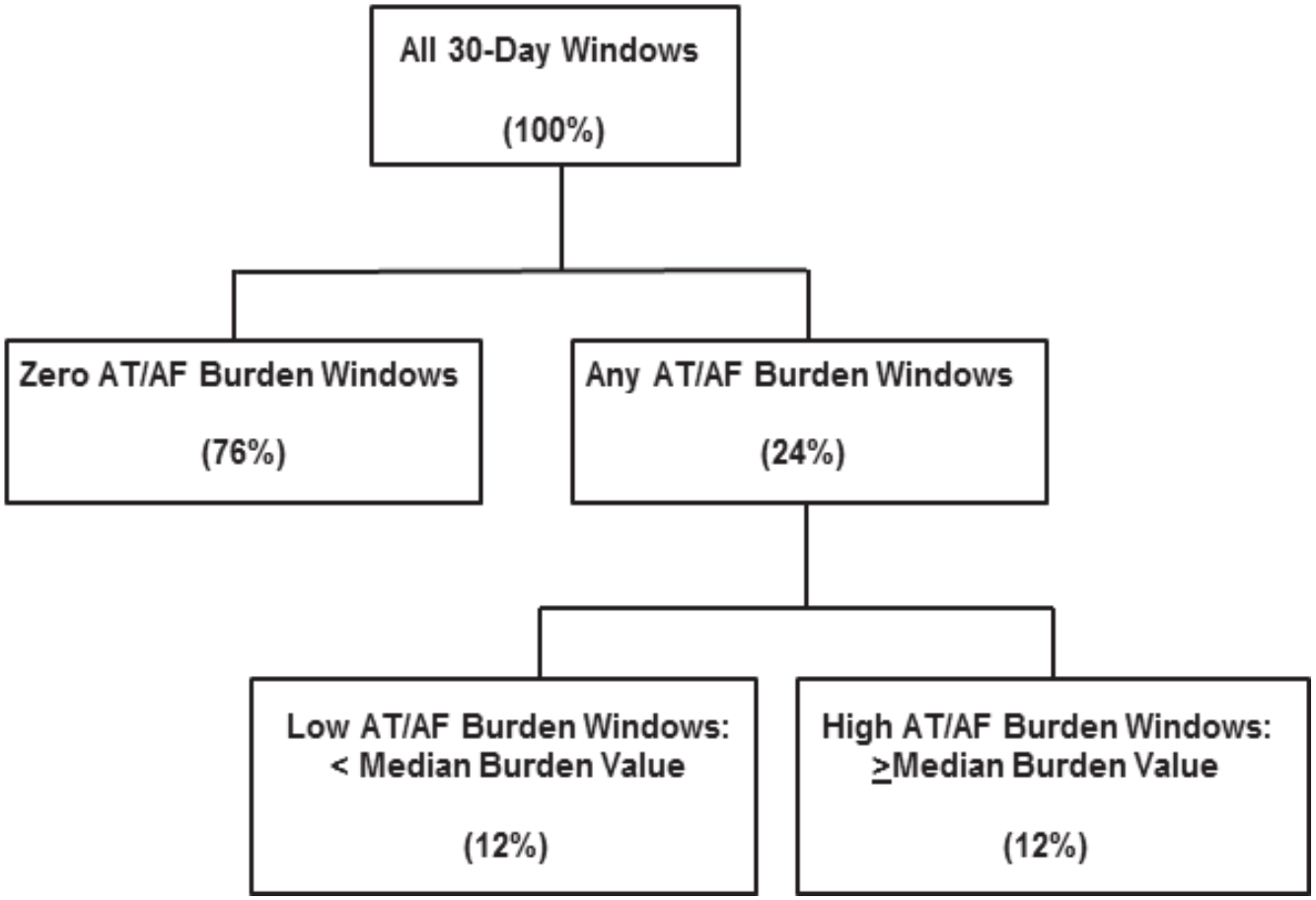

All 30-Day Windows
(100%)
Zero AT/AF Burden Windows
(76%)
Any AT/AF Burden Windows
(24%)
Low AT/AF Burden Windows:
< Median Burden Value
(12%)
High AT/AF Burden Windows:
≥Median Burden Value
(12%)

Table 2. TE Rates for the Overall Study Group (Unadjusted)

AT/AF Burden Subset	Annualized TE Rate (95% CI), %	Annualized TE Rate Excluding TIAs (95% CI), %
Zero AT/AF burden	1.1 (0.8–1.6)	0.5 (0.3–0.9)
Low AT/AF burden (< 5.5 h)	1.1 (0.4–2.8)	1.1 (0.4–2.8)
High AT/AF burden (5.5 h)	2.4 (1.2–4.5)	1.8 (0.9–3.8)

Table 3. Hazard Ratios for Thromboembolic Events Associated With AT/AF Burden Adjusted for Stroke Risk Factors and Antithrombotic Therapy

Category	Variable	Hazard Ratio (95% CI)*	*P* Value
AT/AF burden	Low burden vs zero burden	0.98 (0.34, 2.82)	0.97
	High burden vs zero burden	2.20 (0.96, 5.05)	0.06

High and low burden are separated by the median value of 30-day windows having nonzero AT/AF burden; that is, high corresponds to a burden of > 5.5 hours, low corresponds to a burden of 20 seconds to < 5.5 hours.

*Estimates based on Cox model with time-varying AT/AF burden and antithrombotic therapy.

The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT)

N England J Med 2012;366:120-9

- The ASSERT study recruited 2580 patients above 65 years of age, with hypertension and with **no history of AF**

- The patients had undergone the implantation of dual-chamber pacemakers or implantable cardioverter–defibrillators (ICDs) in the preceding 8 weeks

- Subclinical atrial tachyarrhythmias (episodes of atrial rate **>190 beats per minute for longer than 6 min**) were detected for 3 months following the enrollment

- Patients were followed for 2.5 years with regards to clinical events

- Patients with pacemakers were randomly divided into two intervention/treatment arms: with or without continuous atrial overdrive pacing

Patient Eligibility

- Recent Pacemaker Implant or generator replacement (< 8 weeks) St. Jude Medical IDENTITY ®ADx DR (Model 5386/5380)
- Primary indication sinus or AV node disease.
- History of hypertension requiring pharmacological therapy (≥ 4 weeks of therapy)
- Age ≥ 65 years

↓

Enrollment -Baseline Clinical Assessment 4-8 Weeks post implant

- Written Informed Consent obtained (may be obtained at pacemaker implant)
- Baseline data collected; Clinical Assessment/Medical History/Concomitant Medications/Implant details
- Pacemaker programmed to collect AHRE data

↓

Randomization 3 Months (12 weeks) after enrollment

- Clinical Assessment/ Concomitant Medications/Pacemaker Complications and other Adverse Signs and Symptoms/Outcome Event Assessment
- Assessment of AHRE
- Mechanisms of AF Evaluation-Atrial electrical remodeling parameters measured

↓

®

↙ AF Suppression Algorithm

↘ No AF Suppression Algorithm

↓

6 Monthly Clinic Follow-up Assessments (min 30 month, max 42 month)

- Clinical Assessment/ Concomitant Medications/Pacemaker Complications and other Adverse Signs/Symptoms
- Pacemaker Interrogation/Programming
- Outcome Event Assessment
- Mechanisms of AF Evaluation-Atrial electrical remodeling parameters measured at Month 12 and 24.

- The primary outcome was **ischemic stroke** or **systemic embolism**

- Secondary outcomes were **vascular death, myocardial infarction, stroke from any cause, and atrial tachyarrhythmias** documented by surface electrocardiography.

- **The primary outcome** of the randomized trial of continuous **atrial overdrive pacing** was symptomatic or asymptomatic **atrial tachyarrhythmia** lasting **more than 6 minutes**, documented by surface ECG

- 261 (**10.1%**) patients had **subclinical atrial tachyarrhythmias** detected by an implanted device within 3 months

- **Clinical atrial tachyarrhythmias** on ECGs
  : 41 (**15.7%**) of patients with subclinical atrial tachyarrhythmias before the 3-month visit
  : 71 (**3.1%**) of the patients without subclinical atrial tachyarrhythmias

  (hazard ratio: 5.56; 95% CI: 3.78–8.17; $p < 0.001$)

Table 1. Baseline Characteristics of the Patients. *

Characteristic	Device-Detected Subclinical Atrial Tachyarrhythmia			Continuous Atrial Overdrive Pacing†	
	Yes (N=261)	No (N=2319)	P Value	On (N=1164)	Off (N=1179)
Age — yr	77±7	76±7	0.13	76±7	76±7
Male sex — no. (%)	147 (56.3)	1359 (58.6)	0.48	687 (59.0)	658 (55.8)
Systolic blood pressure while sitting — mm Hg	137±20	138±19	0.38	139±20	138±19
Heart rate — beats/min	68±12	70±12	0.001	70±11	69±12
Body-mass index‡	28±5	27±5	0.43	27±5	27±5
Risk factors for stroke — no. (%)					
Prior stroke	18 (6.9)	168 (7.2)	0.84	80 (6.9)	88 (7.5)
Prior transient ischemic attack	13 (5.0)	113 (4.9)	0.94	52 (4.5)	60 (5.1)
History of heart failure	39 (14.9)	335 (14.4)	0.83	142 (12.2)	162 (13.7)
Diabetes mellitus	59 (22.6)	674 (29.1)	0.03	329 (28.3)	325 (27.6)
Prior myocardial infarction	32 (12.3)	427 (18.4)	0.01	175 (15.0)	200 (17.0)
$CHADS_2$ score§	2.2±1.1	2.3±1.0	0.47	2.2±1.0	2.3±1.1
Sinus-node disease, with or without atrioventricular-node disease — no. (%)	130 (49.8)	964 (41.6)	0.01	519 (44.6)	498 (42.2)
Atrioventricular-node disease, without sinus-node disease — no. (%)	132 (50.6)	1279 (55.2)	0.16	648 (55.7)	686 (58.2)
Atrial lead in septal position — no. (%)	101 (38.7)	972 (41.9)	0.32	492 (42.3)	498 (42.2)
Duration of hypertension >10 yr — no. (%)	115 (44.1)	965 (41.6)	0.45	486 (41.8)	505 (42.8)
Left ventricular hypertrophy on ECG — no. (%)	6 (2.3)	105 (4.5)	0.09	46 (4.0)	50 (4.2)
Time from implantation of pacemaker or ICD to enrollment — days	25±22	29±40	0.04	28±39	29±39
Medications — no. (%)					
Aspirin	160 (61.3)	1430 (61.7)	0.91	721 (61.9)	705 (59.8)
Beta-blocker	94 (36.0)	849 (36.6)	0.85	398 (34.2)	400 (33.9)
Statin	113 (43.3)	1112 (48.0)	0.15	544 (46.7)	537 (45.5)

- During the follow-up period, 51 patients experienced ischemic stroke or SE.

- 40 events (0.69 per 100 patient-years) in the subgroup **without** subclinical atrial tachyarrhythmias

- 11 events (1.69 per 100 patient-years) occurred in the subgroup **with** at least one episode of subclinical atrial tachyarrhythmia.

- subclinical atrial tachyarrhythmias were independent risk factor for stroke and clinical AF

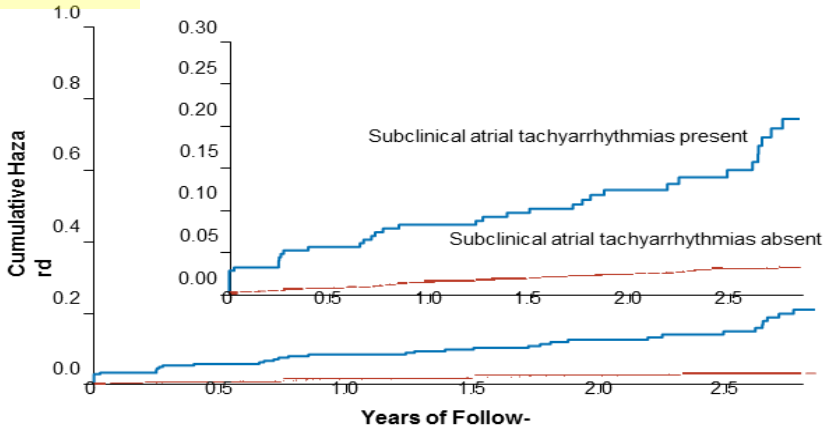
  : an increase by a factor of 2.5

- The population-attributable risk of ischemic stroke or SE associated with subclinical atrial tachyarrhythmia was 13%.

Table 2. Clinical Outcomes Occurring after the 3-Month Visit, According to Whether Subclinical Atrial Tachyarrhythmias Were or Were Not Detected between Enrollment and the 3-Month Visit.

Clinical Outcome	Subclinical Atrial Tachyarrhythmias between Enrollment and 3 Months				Hazard Ratio with Subclinical Atrial Tachyarrhythmias (95% CI)	P Value
	Present (N = 261)		Absent (N = 2319)			
	no. of events	*%/yr*	*no. of events*	*%/yr*		
Ischemic stroke or systemic embolism	11	1.69	40	0.69	2.49 (1.28–4.85)	0.007
Ischemic stroke	10	1.54	36	0.62	2.52 (1.25–5.08)	0.01
Systemic embolism	1	0.15	4	0.07	2.24 (0.25–20.10)	0.47
Myocardial infarction	7	1.07	39	0.67	1.52 (0.68–3.42)	0.31
Death from vascular causes	19	2.92	153	2.62	1.11 (0.69–1.79)	0.67
Stroke, myocardial infarction, or death from vascular causes	29	4.45	206	3.53	1.25 (0.85–1.84)	0.27
Hospitalization for heart failure	20	3.07	131	2.24	1.36 (0.85–2.19)	0.20
Clinical atrial fibrillation or flutter on surface electrocardiogram	41	6.29	71	1.22	5.56 (3.78–8.17)	<0.001

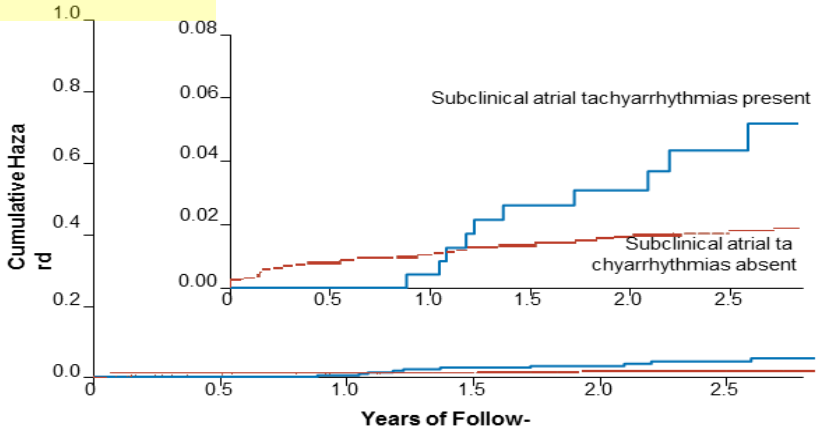
A Risk of Clinical Atrial Tachyarrhythmias



up No. at Risk

Subclinical atrial tachyarrhythmias present	261	236	222	205	160	110
Subclinical atrial tachyarrhythmias absent	2319	2146	2064	1911	1544	1176

B Risk of Ischemic Stroke or Systemic Embolism



up No. at Risk

Subclinical atrial tachyarrhythmias present	261	249	238	218	178	122
Subclinical atrial tachyarrhythmias absent	2319	2145	2070	1922	1556	1197

Figure 1. The Risk of Clinical Atrial Tachyarrhythmias and of Ischemic Stroke or Systemic Embolism, According to the Presence or Absence of Subclinical Atrial Tachyarrhythmias.

Panel A shows the risk of electrocardiographically documented clinical atrial tachyarrhythmias after the 3-month visit, according to whether subclinical atrial tachyarrhythmias were or were not detected between enrollment and the 3-month visit. Panel B shows the risk of ischemic stroke or systemic embolism after the 3-month visit, according to whether subclinical atrial tachyarrhythmias were or were not detected between enrollment and the 3-month visit. The insets show the same data on an enlarged y axis.

A patient had a CHADS2 score of higher than 2, the risk of ischemic stroke or systemic embolism associated with a subclinical atrial tachyarrhythmia was nearly 4% per year

Table 3. Risk of Ischemic Stroke or Systemic Embolism after the 3-Month Visit, According to Baseline $CHADS_2$ Score and According to Whether Subclinical Atrial Tachyarrhythmias Were or Were Not Detected between Enrollment

$CHADS_2$ Score	No. of Patients	Subclinical Atrial Tachyarrhythmias between Enrollment and 3 Months						Hazard Ratio for Ischemic Stroke or Systemic Embolism with Subclinical Atrial Tachyarrhythmias (95% CI)*
		Present			Absent			
		no. of patients	*no. of events*	*%/yr*	*no. of patients*	*no. of events*	*%/yr*	
1	600	68	1	0.56	532	4	0.28	2.11 (0.23–18.9)
2	1129	119	4	1.29	1010	18	0.70	1.83 (0.62–5.40)
>2	848	72	6	3.78	776	18	0.97	3.93 (1.55–9.95)

* The P value for trend is 0.35.

Table 4. Effect of Continuous Atrial Overdrive Pacing on Clinical Outcomes.

Outcome	Continuous Atrial Overdrive Pacing Turned On (N=1164)		Continuous Atrial Overdrive Pacing Turned Off (N=1179)		Hazard Ratio with Continuous Atrial Overdrive Pacing Turned On	P Value
	No. of Patients	Annual Rate*	No. of Patients	Annual Rate*		
Atr						.10
						.29
Asymptomatic	36	1.17	28	0.90	1.31 (0.80–2.16)	0.29
Device-detected atrial tachyarrhythmia with duration >24 hr	134	4.37	125	4.01	1.11 (0.87–1.41)	0.42
Stroke, systemic embolism, myocardial infarction, death from vascular causes, or hospitalization for heart failure	160	5.22	146	4.69	1.13 (0.90–1.41)	0.29
Stroke	21	0.68	25	0.80	0.85 (0.48–1.52)	0.59
Systemic embolism	3	0.10	2	0.06	1.52 (0.25–9.12)	0.64
Myocardial infarction	22	0.72	20	0.64	1.13 (0.62–2.08)	0.69
Death from vascular causes	82	2.67	80	2.57	1.05 (0.77–1.42)	0.78
Hospitalization for heart failure	77	2.51	59	1.89	1.34 (0.95–1.88)	0.09

The results of this study did not show a benefit of continuous atrial overdrive pacing

In all these trials

- There is a substantial incidence of subclinical atrial tachyarrhythmias among **elderly patients with pacemakers** who are free from clinical AF

- **Subclinical AF** increased the risk of clinical AF **5–6 fold**, which suggests that subclinical AF could be regarded as **a precursor to clinical AF**

- **Subclinical AF** increased the **risk of ischemic stroke or systemic embolism**

The best predictor for subsequent stroke ?

- **Subclinical AF burden**, together with **CHADS2** or **CHA2DS2-VASC** scores, would provide the opportunity for early thromboprophylaxis in patients **without clinical AF**

- **'burden' of AF**
  - percentage of time spent in AF divided by total time
  - the duration of the longest AF episode

Subclinical AF in patients without pacemaker

- The prevalence of subclinical AF in a more **general population** may be smaller than in these **pacemaker trials**

- The use of an **implantable loop recorder** currently investigated in the CRYSTAL-AF study (CRYptogenic STroke And underLying Atrial Fibrillation)

Methods to predict subclinical AF

- Clinical information scoring system

  : Score for Targeting Atrial Fibrillation (STAF)

  Stroke 2009;40:2866-8

- Radiological indicators that could predict paroxysmal AF

  : increasing numbers of chronic brain lesions on CT or MRI and acute cortical infarcts

  Stoke 2010;41:2596-600

- Echocardiographic parameters
  : left atrial volume and left atrial pump function
  Hypertension. 2010 May;55(5):1150-6

- Biomarkers
  : brain natriuretic peptide level >99 pg/ml
  PLOS one 2012;7:e34351

- The number of atrial premature beats, which can easily be derived from 24 h-Holter ECG

  : more than 70 premature atrial beats in 24 h were associated with a 6.6 fold increase in the risk of paroxysmal AF

Stroke 2007;38:2292-4

summary

- There is a **substantial incidence** of subclinical atrial tachyarrhythmias
- **Subclinical AF** emerges as a **precursor of clinical AF** and a **risk factor for stroke**
- **Subclinical AF burden**, together with **CHADS2** or **CHA2DS2-VASC** scores, would be a predictor for subsequent stroke

summary

- The **early detection** of subclinical AF and **effective treatment** may be a **promising strategy** for primary and secondary stroke prevention