7° AP-HRS Scientific Session, New Dehli, India - Oct 29 to Nov 1, 2014

Causal relationship between AF & stroke

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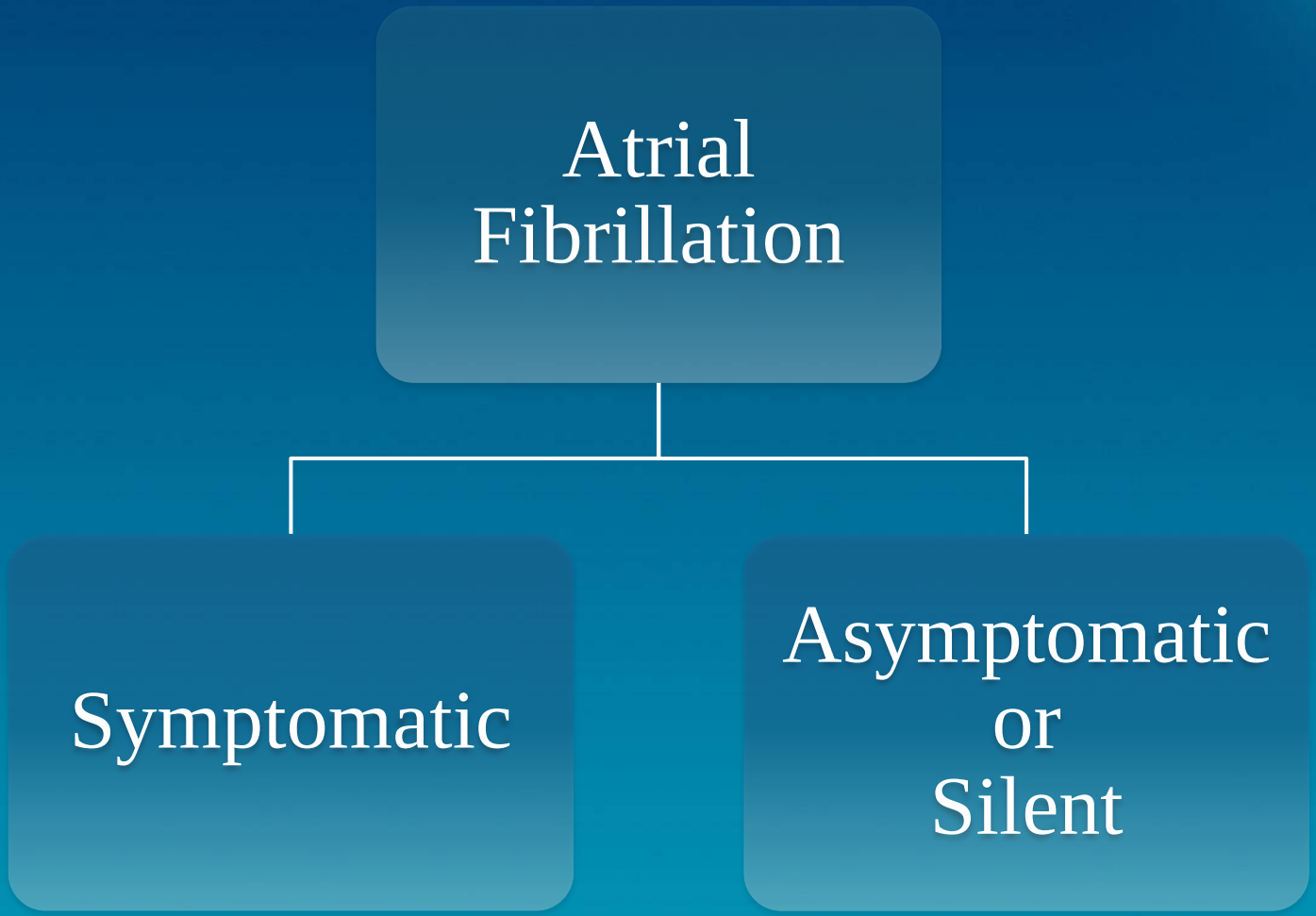
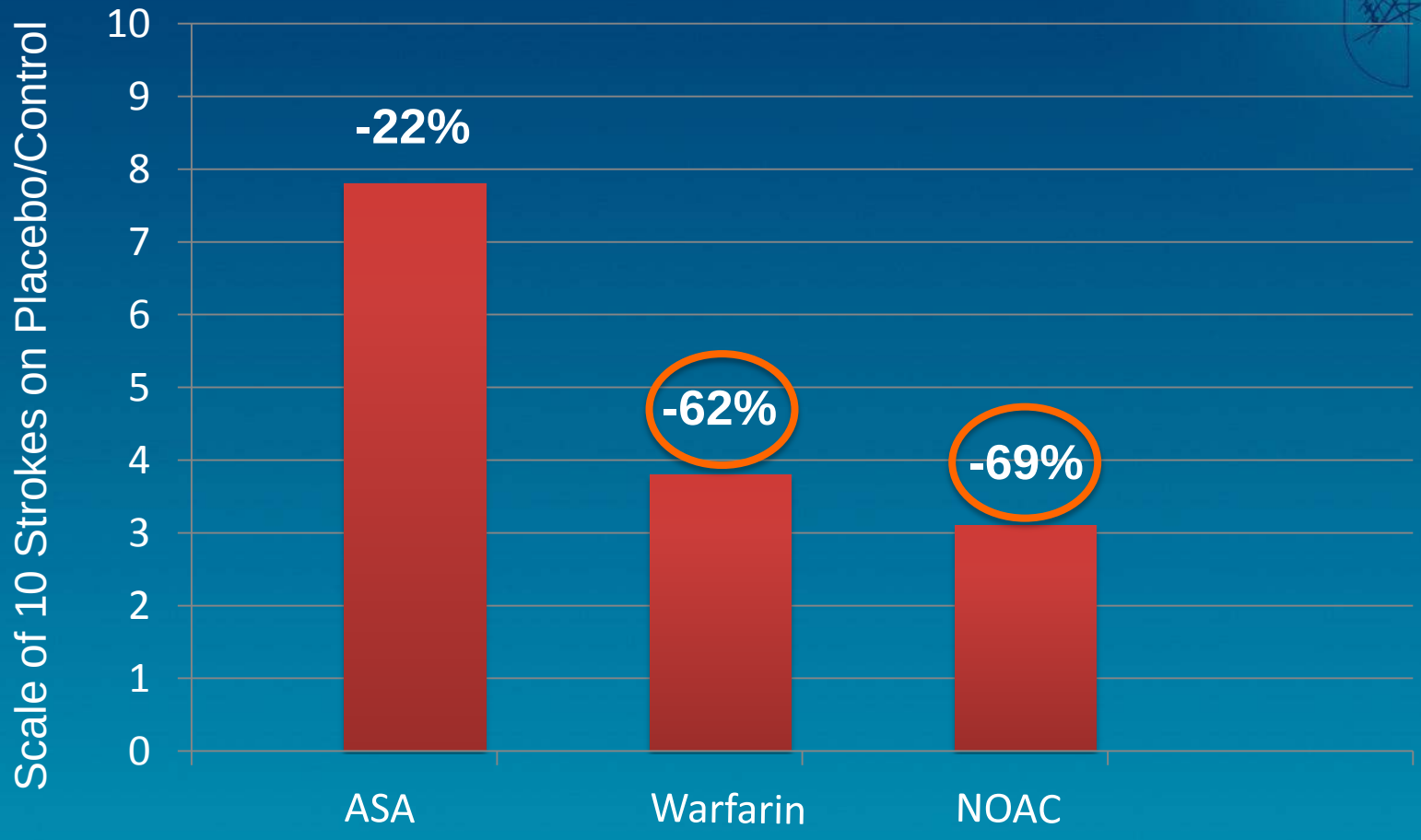
AF & Symptoms



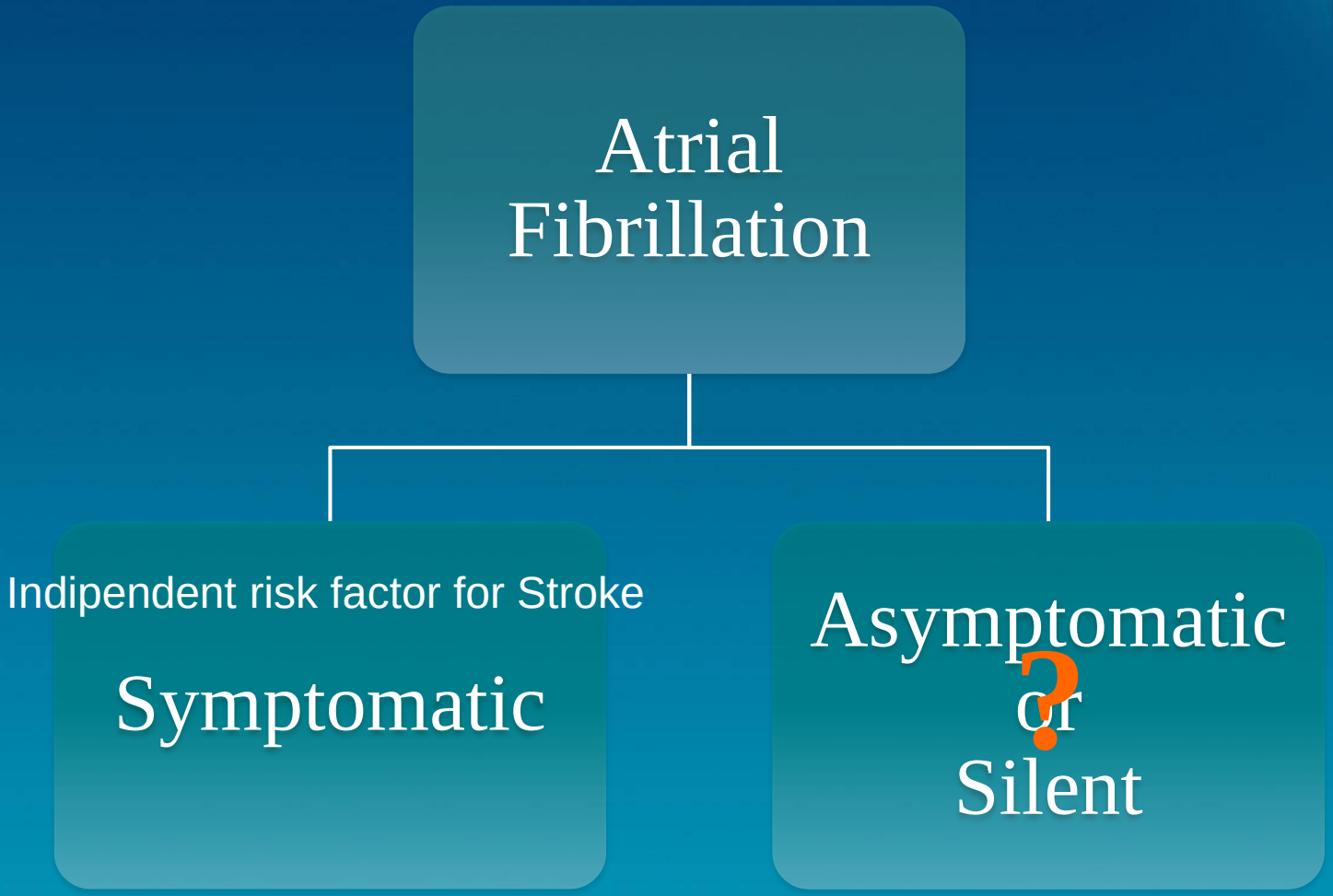
Risk of Thromboembolic Events / Stroke

(The SPAF Investigators. Ann Intern Med 1992; 116: 1 – 5)

Stroke risk reductions from randomized trials of antithrombotic agents in atrial fibrillation.



AF & Risk of Stroke



Asymptomatic AF / Detection Methods

Intermittent ambulatory ECG monitoring

- **Standard-12 lead ECG**
- **24-h / 7-d Holter monitoring**
- **In-hospital telemetry**
- **Mobile continuous outpatient telemetry**
- **Event recorder / Intermittent TTEM**

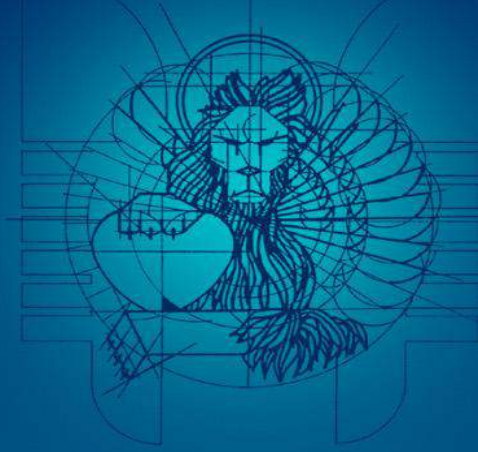
Continuous ambulatory ECG monitoring

- **PM - ICD Device memory**
- **External & Implantable loop recorder**

Prevalence of Asymptomatic AF

Clinical Settings	Percent
Incidental finding at standard ECG **ECG**	**16-25**
Pts treated with AADs **TTEM**	**56-70**
PM – ICD recipients **Device memory**	**51-74**
Pts with criptogenetic ischemic stroke **HM - ILR**	**4-20**
Pts after AF ablation **HM - MCOT - PM/ICD - ILR**	**0-31**

Silent AF / Main Issues



- **Clinical / prognostic significance**
- **Causal relationship with stroke**
- **Therapeutical implications**

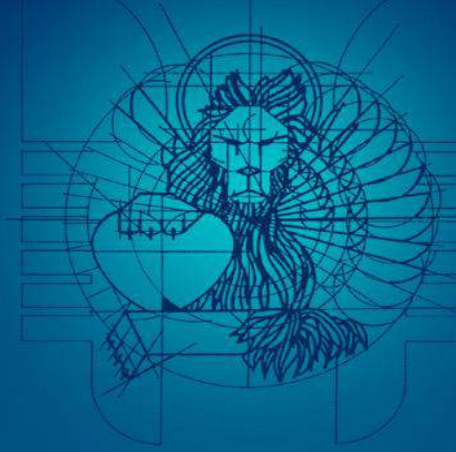
Table 4 Summary of studies on AF detected by dual-chamber cardiac implantable electronic devices and thromboembolic risk

Year	Trial	No. of patients	Duration of follow-up	Atrial rate cutoff	AF burden threshold	Hazard ratio for TE event	TE event rate (below vs above AF burden threshold)
2003	Ancillary MOST[47]	312	27 months (median)	>220 bpm	5 minutes	6.7 ($P = .020$)	3.2% overall (1.3% vs 5%)
2005	Italian AT500 Registry[49]	725	22 months (median)	>174 bpm	24 hours	3.1 ($P = .044$)	1.2% annual rate
2009	Botto et al[50]	568	1 year (mean)	>174 bpm	$CHADS_2$ + AF burden	N/A	2.5% overall (0.8% vs 5%)
2009	TRENDS[51]	2486	1.4 years (mean)	>175 bpm	5.5 hours	2.2 ($P = .060$)	1.2% overall (1.1% vs 2.4%)
2012	Home Monitor CRT[52]	560	370 days (median)	>180 bpm	3.8 hours	9.4 ($P = .006$)	2.0% overall
2012	ASSERT[31]	2580	2.5 years (mean)	>190 bpm	6 minutes	2.5 ($P = .007$)	(0.69% vs 1.69%)

AF = atrial fibrillation; TE = thromboembolic event.

Glotzer TV et al. Heart Rhythm 2014; Epub before Print

Silent AF / Significance



- It is not yet known what is the length of asymptomatic episodes or the amount of asymptomatic burden that convey a substantial risk.

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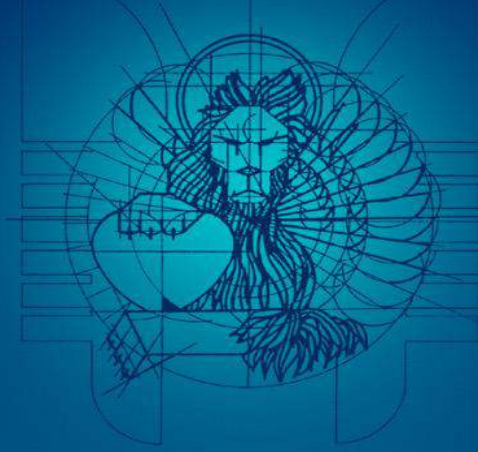
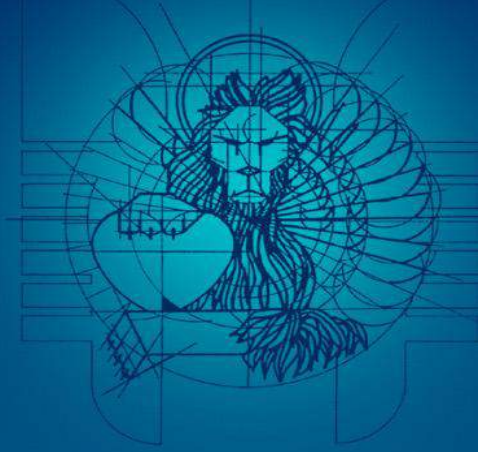


- The duration of the longest episode and the burden of asymptomatic AF that are the best predictors for subsequent stroke are still matter of debate.

Silent AF / Main Issues



- **Clinical / prognostic significance**
- **Causal relationship with stroke**
- **Therapeutical implications**

Silent AF & Stroke

- Direct cause of stroke ?
- Marker of an increased risk ?

Table 5 Temporal relationship of device-detected AF to thromboembolic events

Year	Trial	No. of patients with TE event	Definition of AF episode	Any AF detected before TE event	AF detected only after TE event	No AF in 30 days before TE event	Any AF in 30 days before TE event
2011	TRENDS[53]	40	5 minutes	20/40 (50%)	6/40 (15%)	29/40 (73%)	11/40 (27%)
2014	ASSERT[54]	51	6 minutes	18/51 (35%)	8/51 (16%)	47/51 (92%)	4/51 (8%)
2014	IMPACT[55]	69	36/48 atrial beats ≥200 bpm	20/69 (29%)	9/69 (13%)	65/69 (94%)	4/69 (6%)

AF = atrial fibrillation; TE = thromboembolic event.

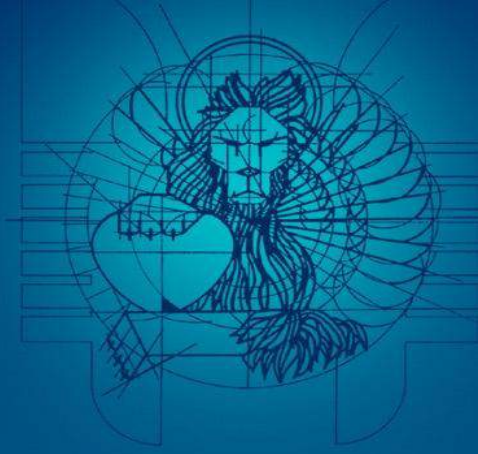
Glotzer TV et al. Heart Rhythm 2014; Epub before Print

Silent AF & Stroke

- These results indicate that a proximate temporal relationship does not exist between asymptomatic AF and stroke occurrence and suggest that silent AF is not the direct cause of the stroke in the majority of patients with device-detected AF.

- They also call into question our current understanding of how AF causes embolic events.

Silent AF & Stroke



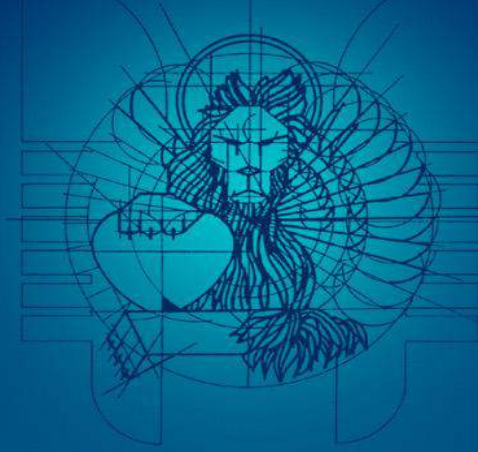
- It is likely that multiple mechanisms contribute to stroke in patients with asymptomatic AF.

- In some cases stroke may be, indeed, due to stasis from an actual AF episode;
  in other cases to chronic atrial and endothelial changes caused by multiple prior AF episodes;
  in other more cases to non-AF mechanisms.

Silent AF & Stroke

- In these latter cases, AF probably represents simply a marker of increased stroke from any cause because of its relationship to other comorbidities, such as presence of HF, hypertension, diabetes, occult atrial myopathy, endothelial dysfunction, and/or other vascular disease risk factors summarized by the CHA2DS2-VASc scoring system.

Silent AF / Main Issues



- **Clinical / prognostic significance**
- **Causal relationship with stroke**
- **Therapeutical implications**

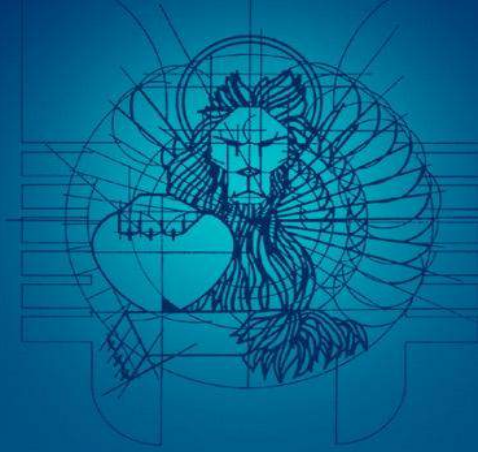
Asymptomatic AF / Therapy

- Need for Oral Anticoagulation

Asymptomatic AF / Need for OAC

- Detection of silent AF, especially in PM-ICD recipients and in patients with critpogenetic stroke, theoretically could allow for early initiation of OAC, assuming that device-detected AF imparts a stroke risk similar to symptomatic AF.

Asymptomatic AF / Need for OAC



- However, whether pts with subclinical AF have to be anticoagulated currently remains an unanswered question.
- Indeed, no prospective randomized trials using OAC have been performed in this field so far.

Temporal Relationship Between Subclinical Atrial Fibrillation and Embolic Events

Michela Brambatti, MD; Stuart J. Connolly, MD; Michael R. Gold, MD; Carlos A. Morillo, MD; Alessandro Capucci, MD; Carmine Muto, MD; Chu P. Lau, MD; Isabelle C. Van Gelder, MD; Stefan H. Hohnloser, MD; Mark Carlson, MD; Eric Fain, MD; Juliet Nakamya, PhD; Georges H. Mairesse, MD; Marta Halytska, BSc; Wei Q. Deng, MSc; Carsten W. Israel, MD; Jeff S. Healey, MD; on behalf of the ASSERT Investigators

LACK OF PROXIMATE TEMPORAL RELATIONSHIP

Background—Among patients with implantable pacemakers and defibrillators, subclinical atrial fibrillation (SCAF) is associated with an increased risk of stroke; however, there is limited understanding of their temporal relationship.

Methods and Results—The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) enrolled 2580 pacemaker and defibrillator patients aged ≥65 years with a history of hypertension but without a history of atrial fibrillation. Pacemakers and implantable cardioverter-defibrillators precisely logged the time and duration of all episodes of SCAF and recorded electrograms that were adjudicated by experts. We examined the temporal relationship between SCAF >6 minutes in duration and stroke or systemic embolism. Of 51 patients who experienced stroke or systemic embolism during follow-up, 26 (51%) had SCAF. In 18 patients (35%), SCAF was detected before stroke or systemic embolism. However, only 4 patients (8%) had SCAF detected within 30 days before stroke or systemic embolism, and only 1 of these 4 patients was experiencing SCAF at the time of the stroke. In the 14 patients with SCAF detected >30 days before stroke or systemic embolism, the most recent episode occurred at a median interval of 339 days (25th to 75th percentile, 211–619) earlier. Eight patients (16%) had SCAF detected only after their stroke, despite continuous monitoring for a median duration of 228 days (25th to 75th percentile, 202–719) before their event.

Conclusions—Although SCAF is associated with an increased risk of stroke and embolism, very few patients had SCAF in the month before their event.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00256152.

(*Circulation*. 2014;129:2094-2099.)

Temporal relationship of atrial tachyarrhythmias, cerebrovascular events, and systemic emboli based on stored device data: A subgroup analysis of TRENDS

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*From *Ohio State University Medical Center, Ross Heart Hospital, Columbus, Ohio, †Hackensack University Medical Center, Hackensack, New Jersey, ‡Libin Cardiovascular Institute of Alberta, Calgary, Alberta, Canada, and ¶Lankenau Institute for Medical Research, Philadelphia, PA; §Medtronic Inc., Minneapolis, Minnesota.*

BACKGROUND The temporal relationship between atrial tachyarrhythmias (atrial tachycardia [AT] and atrial fibrillation [AF]) and cerebrovascular events/systemic emboli (CVE/SE) is unknown.

OBJECTIVE The purpose of this study was to evaluate this relationship using stored AT/AF diagnostic data from implanted devices in patients with and those without AF.

METHODS The TRENDS study enrolled 2,486 patients with an indication for an implantable device, at least one stroke risk factor, and available device data. The current study includes the subgroup of 40 (1.6%) patients enrolled in TRENDS who experienced CVE/SE.

RESULTS AT/AF was detected *prior* to CVE/SE in 20 (50%) of 40 patients. Other than average and maximum daily AT/AF burden and duration of device monitoring prior to CVE/SE, no statistically significant differences were found between patients with and those without AT/AF prior to CVE/SE. For the 20 patients with AT/AF detected prior to CVE/SE, 9 (45%) did not have any AT/AF in the 30 days prior to CVE/SE. Therefore, 29 (73%) of 40 patients with CVE/SE had zero AT/AF burden within 30 days prior to CVE/SE. Fourteen (70%) of the 20 patients with AT/AF detected prior to CVE/SE were not in AT/AF at diagnosis of CVE/SE. The last episode of AT/AF in these 14 patients was 168 ± 199 days (range 3–642 days) before CVE/SE.

CONCLUSION The majority of CVE/SE in this population did not occur proximal to recent AT/AF episodes. These data imply that the mechanisms of CVE/SE in patients with implantable devices may importantly involve mechanisms other than cardioembolism due to atrial tachyarrhythmias.

KEYWORDS Atrial fibrillation; Atrial tachyarrhythmia; Implantable cardiac device; Stroke

ABBREVIATIONS **AF** = atrial fibrillation; **AT** = atrial tachycardia; **CVE** = cerebrovascular event; **SE** = systemic embolus; **TIA** = transient ischemic attack

(Heart Rhythm 2011;8:1416–1423)

Asymptomatic AF / Need for OAC

- The lack of proximate temporal relationship between subclinical AF and embolic events

  suggests that OAC may not be systematically required for stroke prevention in asymptomatic patients.

Multicenter randomized study of anticoagulation guided by remote rhythm monitoring in patients with implantable cardioverter-defibrillator and CRT-D devices: Rationale, design, and clinical characteristics of the initially enrolled cohort: The IMPACT study

John Ip, MD,[a] Albert L. Waldo, MD,[b] Gregory Y. H. Lip, MD,[c] Peter M. Rothwell, MD, PhD,[d] David T. Martin, MD,[e] Malcolm M. Bersohn, MD, PhD,[f] Wassim K. Choucair, MD,[g] Joseph G. Akar, MD,[h] Mark S. Wathen, MD,[i] Pooyan Rohani, ME,[j] and Jonathan L. Halperin, MD[k] for the IMPACT Investigators *Lansing, MI; Cleveland, OH; Birmingham and Oxford, United Kingdom; Burlington, MA; Los Angeles, CA; Corpus Christi, TX; Maywood, IL; Nashville, TN; Lake Oswego, OR; and New York, NY*

Interrupted at 75% of enrollees

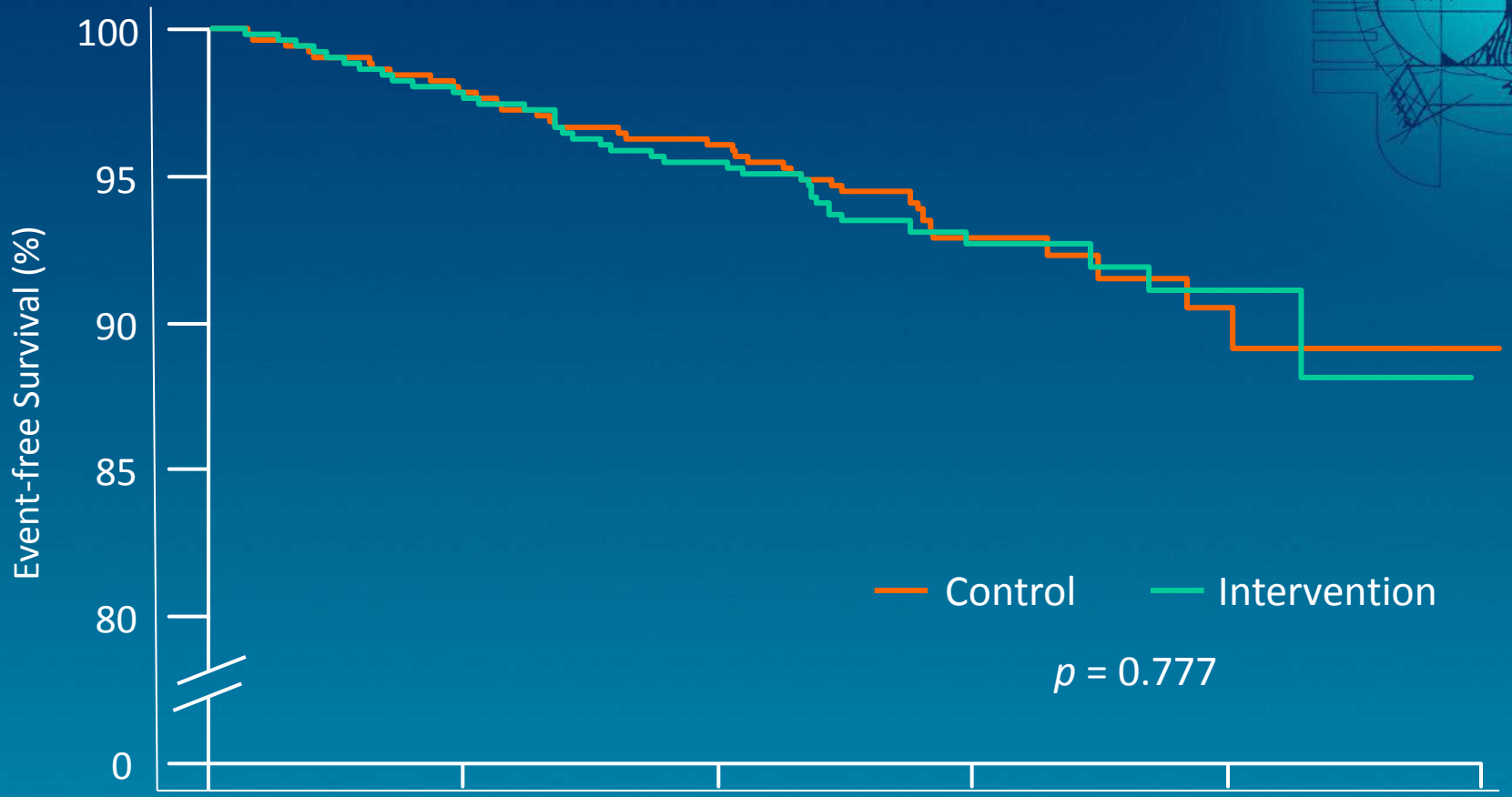
Atrial fibrillation and atrial flutter are common cardiac arrhythmias associated with an increased risk of stroke in patients with additional risk factors. Anticoagulation ameliorates stroke risk, but because these arrhythmias may occur intermittently without symptoms, initiation of prophylactic therapy is often delayed until electrocardiographic documentation is obtained. The IMPACT study is a multicenter, randomized trial of remote surveillance technology in patients with implanted dual-chamber cardiac resynchronization therapy defibrillator (CRT-D) devices designed to test the hypothesis that initiation and withdrawal of oral anticoagulant therapy guided by continuous ambulatory monitoring of the atrial electrogram improve clinical outcomes by reducing the combined rate of stroke, systemic embolism, and major bleeding compared with conventional clinical management. For those in the intervention group, early detection of atrial high-rate episodes (AHRE) generates an automatic alert to initiate anticoagulation based on patient-specific stroke risk stratification. Subsequently, freedom from AHRE for predefined periods prompts withdrawal of anticoagulation to avoid bleeding. Patients in the control arm are managed conventionally, the anticoagulation decision prompted by incidental detection of atrial fibrillation or atrial flutter during routine clinical follow-up. The results will help define the clinical utility of wireless remote cardiac rhythm surveillance and help establish the critical threshold of AHRE burden warranting anticoagulant therapy in patients at risk of stroke. In this report, we describe the study design and baseline demographic and clinical features of the initial cohort (227 patients). (Am Heart J 2009;158:364-370.e1.)

IMPACT -Study Overview

Hypothesis:	**Initiation of OAC early after detection of AF and withdrawal of OAC when AF abates might reduce thromboembolism and hemorrhage in patients with ICD and CRT-D devices**
Design:	Multicenter, single-blinded, randomization stratified by $CHADS_2$ category and device type
Treatment Groups:	Intervention: Remote monitoring for AT with pre-defined anticoagulation plan based on AT burden and $CHADS_2$ Control: In-office identification of AT with OAC directed by treating physician
Primary Endpoint:	First stroke, systemic embolism, or major bleed
Secondary Endpoints:	All-cause mortality, stroke rate, AT burden
Number of Patients:	2,718 from 104 sites (North America, Europe, & Australia)
Scheduled Visits:	At least every 6 months until last subject completes 3 year visit

Primary Outcome Events

(Stroke, systemic embolism or major bleed)

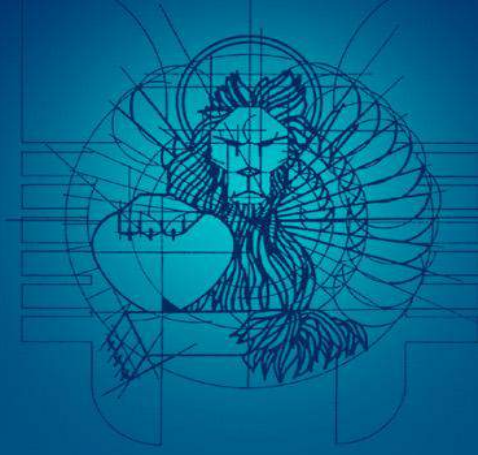


N, Events						
Control	1361, 0	928, 27	543, 43	228, 57	75, 60	2, 61
Intervention	1357, 0	906, 28	538, 49	214, 59	66, 62	3, 63

Conclusions (1)

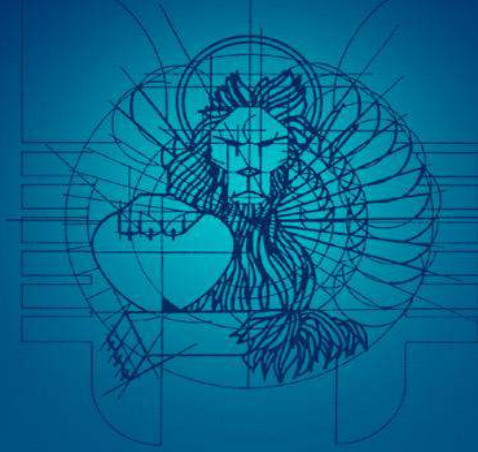
- Asymptomatic or silent AF is a common finding in different clinical settings when prolonged ECG monitoring is performed.

Conclusions (2)



- Patients with silent AF seem to have the same prognosis than patients with symptomatic AF.
- However, the length of silent AF episodes and the burden of the arrhythmia that convey a greater risk of stroke are still uncertain and need to be clarified by further large prospective studies.

Conclusions (3)



- In the majority of patients with device-detected AF, there is no proximate temporal relationship between asymptomatic AF and stroke occurrence.

  This suggests that silent AF is not the direct cause of the stroke, but rather represents only a marker of increased thromboembolism.

Conclusions (4)

- Future studies have to establish if and when patients with asymptomatic AF really benefit from oral anticoagulant therapy.