

### Silent AF and cryptogenic stroke

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# NO CONFLICT OF INTEREST TO DECLARE

## **Case Presentation**

55 y.o. AF Siccessful electric cardioversion

Three months later, during routine visit...completely asymptomatic





### **EHRA score of AF-related symptoms**

Classification of AF-related symptoms (EHRA score)			
EHRA class	Explanation		
EHRAI	'No symptoms'		
EHRA II	'Mild symptoms'; normal daily activity not affected		
EHRA III	'Severe symptoms', normal daily activity affected		
EHRA IV	'Disabling symptoms'; normal daily activity discontinued		

AF = atrial fibrillation; EHRA = European Heart Rhythm Association



www.escardio.org/guidelines

European Heart Journal (2010) 31, 2369-2429

## Silent AF: Key statements

- 1. There is a poor correlation of symptoms with AF, especially after rhythm control therapy is started, which makes subjective evaluation of the effect of any therapy unreliable
- 2. There are two main potential reasons for accurate arrhythmia monitoring :
  - In rhythm control trials when freedom from AF is the outcome parameter
  - In clinical practice to determine the efficacy of rhythm control therapy
- 3. Owing to the unpredictable nature of recurrences, AF is significantly underdetected by intermittent monitoring systems

### **Cardioversion: Poor Correlation with Symptoms**

- 356 persistent AF pts. one week after successful cardioversion: Comparison of perceived rhythm with rhythm on ECG
- Only 38 pts. in AF felt they were in AF
- Agreement between perceived heart rhythm and ECG is no more than poor to fair after successful cardioversion

	Perceived heart rhythm			
Rhythm on ECG	SR (n = 160)	AF (n = 59)	Unsure (n = 137)	
SR (n = 222)	130*	21	71	
AF (n=134)	30	38‡	66	

Nergardh A. Heart 2006; 92: 1244-1247

### Asymptomatic AF: Clinical Correlates, Management, and Outcomes in the EORP-AF Pilot General Registry

Am J Med. 2014 Dec 19. pii: S0002-9343(14)01207-8.

- Objective
- Atrial fibrillation is often asymptomatic, but outcomes require further characterization. The study
  objective was to investigate the clinical presentation, management, and outcomes in asymptomatic and
  symptomatic patients with atrial fibrillation who were prospectively enrolled in the EurObservational
  Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry.
- Methods
- A total of 3119 patients were enrolled, and 1237 (39.7%) were asymptomatic (European Heart Rhythm Association [EHRA] score I). Among symptomatic patients, 963 (51.2%) had mild symptoms (EHRA score II) and 919 (48.8%) had severe or disabling symptoms (EHRA III-IV). Permanent atrial fibrillation was 3-fold more common in asymptomatic patients than in symptomatic patients.

Asymptomatic atrial fibrillation is common in daily cardiology practice and is associated with elderly age, more co-morbidities, and high thromboembolic risks. A higher 1-year mortality was found in asymptomatic patients compared with symptomatic patients.

Subclinical atrial tachyarrhythmias (AT) can be detected by various cardiac monitoring methods

- External surface monitoring
  - Standard 12-lead electrocardiogram,
  - Ambulatory Holter monitors,
  - Event monitors
- Cardiac implantable electronic devices
  - Implantable cardiac monitors,
  - Dual-chamber pacemakers,
  - Dual chamber implantable cardioverter-defibrillators,
  - Cardiac resynchronization therapy [CRT] devices), many of which enable remote monitoring.

## Monitoring Continuum



#### Insertable Cardiac Monitor

Smart Phone-Based Monitoring Technology

a. Holter Monitor (By Misscurry (Template:Entwicklung) CC-BY-SA-3.0-2.5-2.0-1.0); b. Braemar (CardioNet); c. Zio Patch (iRhythm Technologies); d. Reveal LINQ (Reproduced with permission from Medtronic, Inc.), SJM Confirm (St. Jude Medical); e. AliveCor.

#### Stepwise Screening of Atrial Fibrillation in a 75-Year-Old PopulationClinical Perspective

by Johan Engdahl, Lisbeth Andersson, Maria Mirskaya, and Mårten Rosenqvist

### Fishing for AF

Circulation Volume 127(8):930-937 February 26, 2013



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Study design and flow of participants.





#### Study flow with regard to ECG diagnostics.



Among 403 persons with  $\geq 2$  risk factors for stroke, who completed the handheld ECG event recording, 30 (7.4%) were diagnosed with paroxysmal AF. Thus 75/848 (9%) of the screened population were candidates for new oral anticoagulation treatment, of those 57 actually started oral anticoagulation treatment.

Conclusions—Stepwise risk factor–stratified AF screening in a 75-yearold population yields a large share of candidates for oral anticoagulation treatment on AF indication



Engdahl J et al. Circulation. 2013;127:930-937



VBWG

### AF: The more you look, the more you find

Estimated correlation between follow-up technique and AF recurrence following catheter ablation



\*During 3-month follow-up <sup>†</sup>As the theoretical gold standard Tele = transtelephonic

Arya A et al. Pacing Clin Electrophysiol. 2007;30:458-62.

#### FIGURE 1 Mechanisms of Stroke in Atrial Fibrillation



Cardioembolic sources, almost exclusively represented by left atrial appendage thrombi, account for >90% of embolic events. Noncardioembolic origin, more often embolic material dislodged from thoracic and or carotid plaques, account for the remaining 10% of events. Graphics source: National Institutes of Health/National Heart, Lung, and Blood Institute.

### Cryptogenic Stroke

- 1 in 4 ischemic strokes are of undetermined cause ('cryptogenic')
- Some 'cryptogenic' strokes may be due to undiagnosed paroxysmal AF



## **Cryptogenic Stroke**

- 25% of all ischemic strokes are considered cryptogenic, despite intensive workup.<sup>a</sup>
- There is the potential that undiagnosed AF is associated with cryptogenic stroke.
- Up to 90% of paroxysmal AF (PAF) episodes may be asymptomatic.<sup>b</sup>
- Risk of stroke annually is equal for PAF and permanent AF.<sup>c</sup>
- Detection of AF in cryptogenic stroke patients changes treatment.
  - Guidelines state change from antiplatelet to oral anticoagulant.

a. Adams HP Jr, et al. Stroke. 1993;24:35-41<sup>[3]</sup>; b. Page RL, et al. Circulation. 1994;89:224-227<sup>[4]</sup>;
 c. Hart RG, et al. Coll Cardiol. 2000;35:183-187.<sup>[5]</sup>

CRYptogenic STroke and underlying AtriaL Fibrillation (CRYSTAL AF): Long-Term Follow-Up Results

Rod S. Passman, MD, MSCE, Johannes Brachmann, MD, Ph.D. Carlos Morillo, MD, Tommaso Sanna, MD, Richard Bernstein, MD, Ph.D., Vincenzo Di Lazzaro, MD, Hans-Christoph Diener, MD, Ph.D., Marilyn Rymer, MD, Frank Beckers, Ph.D, Tyson Rogers, M.S., Paul Ziegler, M.S. for the Crystal AF Investigators

## **CRYSTAL-AF: Primary Objective**

 Assess whether a long-term cardiac monitoring strategy with an insertable cardiac monitor (ICM) is superior to standard monitoring for the detection of AF in patients with cryptogenic stroke



## Conclusions

- AF detection in cryptogenic stroke patients increases over time with monitoring, with an estimated rate of AF detection of 30% in the ICM versus 3% in the control arm at 36 months
- For those patients with detected AF in the ICM arm, the duration was more than 6 minutes on one or more days in > 94% of patients
- Physicians took action when AF was found with 89% of patients being prescribed OAC
- Majority of first AF episodes (75%) were asymptomatic
- At 36 months, more than 250 tests were required in order to find 5 patients with AF in the control arm
- The time to first AF detection was beyond the time-frame of typical external monitors
- Long-term continuous monitoring should be performed in patients with cryptogenic stroke
   CRYSTAL AF



Prolonged Ambulatory Cardiac Monitoring Improves the Detection and Treatment of Atrial Fibrillation in Patients with Cryptogenic Stroke:

### Primary Results from the EMBRACE Multicenter Randomized Trial

David J. Gladstone MD, PhD, FRCPC University of Toronto, Canada on behalf of the EMBRACE Study Steering Committee

N Engl J Med 2014;370:2467–77.



AF	Detection	Retween-Group	Comparison
AF	Detection	Derween-Group	companson

	Repeat Holter (n=285)	30-day Monitor (n=287)	p-value	Absolute Detection Difference (95% CI)	NNS
Primary Outcome					
AF ≥30 seconds (within 90 days)	3%	16%	<0.001	13% (9%-18%)	8
AF ≥30 sec (study monitors only)	2%	15%	<0.001	13% (9%-18%)	8
Secondary Outcomes					
AF ≥2.5 min	2%	10%	<0.001	8% (4%-12%)	13
Any AF	4%	20%	<0.001	16% (10%-21%)	6

## Conclusions

- 1 in 6 patients aged ≥55 years with 'cryptogenic' stroke or TIA has paroxysmal AF
  - 1 in 5 patients over age 75 years
- 1 or 2 Holter monitors post-stroke/TIA is insufficient to exclude paroxysmal AF
- Prolonged continuous monitoring for a target of 30 days
  - is feasible
  - significantly more effective for paroxysmal AF detection
  - has an incremental yield over 30 days
  - resulted in a significant increase in anticoagulant use

### Electrocardiographic Monitoring for Detecting Atrial Fibrillation After Ischemic Stroke or Transient Ischemic Attack Systematic Review and Meta-Analysis

Charles Dussault, MD; Hadi Toeg, MD, MSc; Meena Nathan, MD; Zhi Jian Wang, MD; Jean-Francois Roux, MD; Eric Secensky, MD

- Background—Atrial fibrillation (AF) is a major cause of stroke. Although standard investigations after an event include electrocardiographic monitoring, the optimal duration to detect AF is unclear. We performed a systematic review and meta-analysis to determine whether the duration of electrocardiographic monitoring after an ischemic event is related to the detection of AF.
- Methods and Results—Prospective studies that reported the proportion of new AF diagnosed using electrocardiographic monitoring for >12 hours in patients with recent stroke or transient ischemic attack were analyzed. Studies were excluded if the stroke was hemorrhagic or AF was previously diagnosed. A total of 31 articles met inclusion criteria. Longer duration of monitoring was associated with an increased detection of AF when examining monitoring time as a continuous variable (P<0.001 for metaregression analysis). When dichotomizing studies based on monitoring duration, studies with monitoring lasting  $\leq$ 72 hours detected AF in 5.1%, whereas monitoring lasting  $\geq$ 7 days detected AF in 15%. The proportion of new diagnosis increased to 29.15% with extended monitoring for 3 months. Significant heterogeneity within studies was detected for both groups ( $\leq$ 72 hours, F=91.3%;  $\geq$ 7 days, F=75.8). When assessing the odds of AF detection in the 3 randomized controlled trial, there was a 7.26 increased odds of AF with long-term monitoring (95% confidence intervals [3.99–12.83]; P value <0.001).
- Conclusions—Longer duration of electrocardiographic monitoring after cryptogenic stroke is associated with a greater detection of AF. Future investigation is needed to determine the optimal duration of long-term monitoring. (Circ Arrhythm Electrophysiol. 2015;8:263-269. DOI: 10.1161/CIRCEP.114.002521.)







Figure 2 Methods for screening silent AF in patients with pharmacological rhythm control strategy and after pulmonary vein (PV) isolation.

## Screening and investigations

- Regular pulse palpation was routinely recommended for identifying silent AF in patients older than 65 years of age by 43.8% of the responders

- Most responders (71.8%) recommended routine screening for silent AF in patients with previous stroke or TIA

- Other categories of patients that routinely underwent screening were patients with :

- Arterial hypertension (45.9% of the responders)
- Diabetes mellitus (40.6%)
- Heart failure and low EF (50%)
- Valvular heart disease (37.5%)
- Post-MI (21.9%)
- No screening 15.6%

Europace (2013) **15**, 1223–1225 doi:10.1093/europace/eut227 But what is the clinical and prognostic significance of silent AF after cytogenetic stroke?

- Asymptomatic AF is associated with increased mortality (doubled compared with controls); the mortality is even higher than that observed in symptomatic AF (9.4% versus 4.2% at 1 year, in the EORP-AF Pilot General Registry)
- At present, the literature is lacking in data on this issue; the only information we have is indirect and comes from patients treated with implantable electronic devices (pacemaker, implantable cardioverter-defibrillator, or CRT device) for an arrhythmic problem.
- In these patients, detection of silent AF by the device is associated with an increased risk of thrombo-embolic events, with a hazard ratio ranging from 2.2 to 9.4.

# What length of silent AF episodes or what amount of silent AF burden convey a substantial risk?

MOST (Mode Selection Trial)	5 Minutes
<b>ASSERT trial (</b> Asymptomatic AF and Stroke Evaluation in Pacemaker Patients and the AF Reduction Atrial Pacing Trial)	6 Minutes
SOS-AF (Stroke Prevention Strategies Based on AF Information From Implanted Devices) Project	1 hour
Home Monitor CRT trial	3.8 hours
TRENDS trial	5.5 hours
Italian AT500 Registry	24 hours

*Circulation.* 2003;107:1614–1619. *N Engl J Med.* 2012;366:120–129 *Eur Heart J.* 2014;35:508–516 *Europace.* 2012;14:230–237 *Circ Arrhythm Electrophysiol.* 2009;2:474–480 *J Am Coll Cardiol.*2005;46:1913–1920

# Is silent AF the direct cause of the stroke or just a marker of an increased risk?

- In the majority of patients (73% to 94%), no AF was found on device recordings in the 30 days before the thrombo-embolic event. Moreover, when AF was detected, this happened >30 days before thrombo-embolic events in 29% to 50% of cases and after thromboembolic events in 3% to 16% of cases.
- These results indicate that a proximate temporal relationship between asymptomatic AF and stroke occurrence does not exist and suggest that silent AF is not the direct cause of the stroke in the majority of cases of device-detected AF.

## Conclusion

- Prolonged electrocardiographic monitoring, especially the use of an implantable loop recorder, enables silent AF to be detected in a high proportion of patients with cytogenetic stroke (≤30%) and should be encouraged and preferred to conventional short-term monitoring.
- Although the prognosis of asymptomatic AF seems to be the same as—or even worse than—that of symptomatic AF, further trials are needed to establish the length and burden of silent AF episodes that convey a greater risk of stroke.
- Finally, despite the lack of randomized trials on the benefit of oral anticoagulation therapy, it is reasonable to prescribe this therapy for patients with cryptogenic stroke and silent AF, who are, by definition, at high risk of recurrent thrombo-embolic events.