TOP 3: EMBRACE

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Divulgation de conflits d'intérêts potentiels

Société des sciences vasculaires du Québec (SSVQ)

7e COLLOQUE NEUROVASCULAIRE

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Original Article

Atrial Fibrillation in Patients with Cryptogenic Stroke

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- Investigator initiated, open label, multi-center trial
- 16 stroke centers in the CSC (CSN funded)
- 572 patients with a recent cryptogenic stroke or TIA

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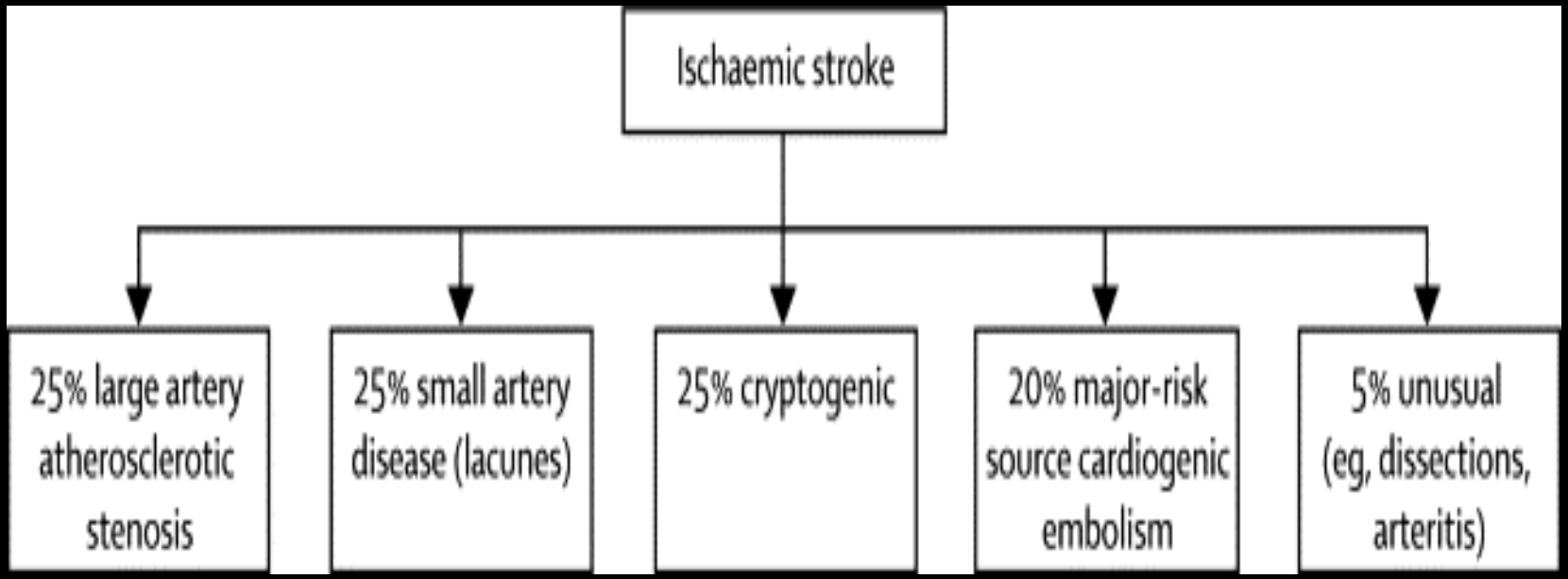


Cryptogenic stroke

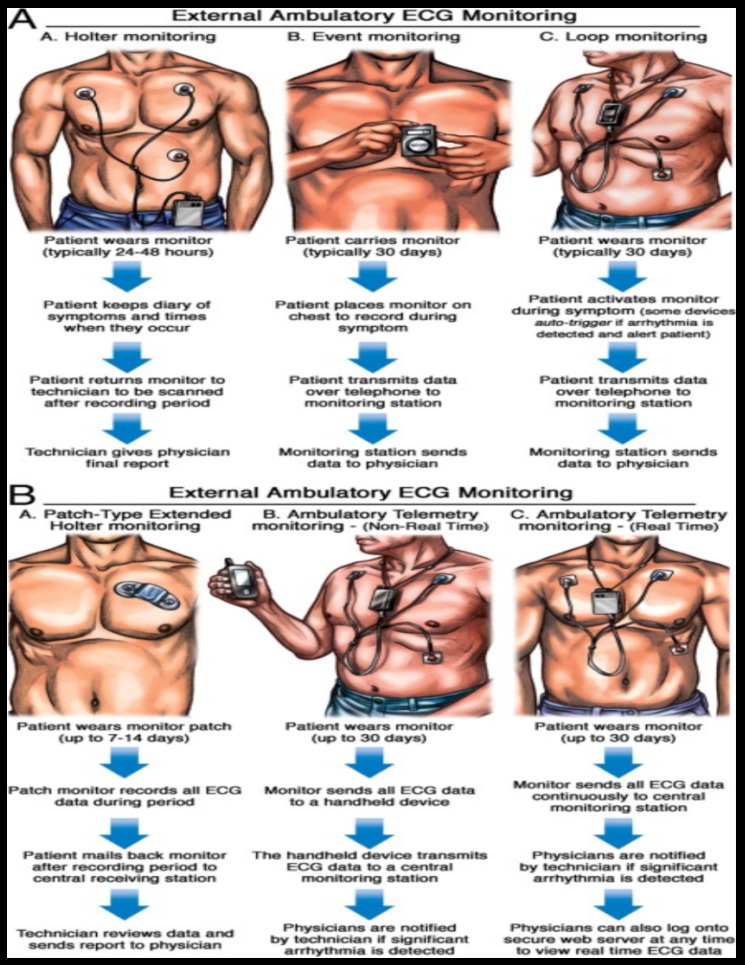
Stroke or TIA of Undetermined origin after standard workup (ECG, Holter≥24h, TTE, Brain and vascular imaging)

-embolic strokes of undetermined source

-significant number may be due to PAF

-up to now anticoagulation is not indicated

Lancet Neurology, Volume 13, Issue 4, 2014, 429 - 438



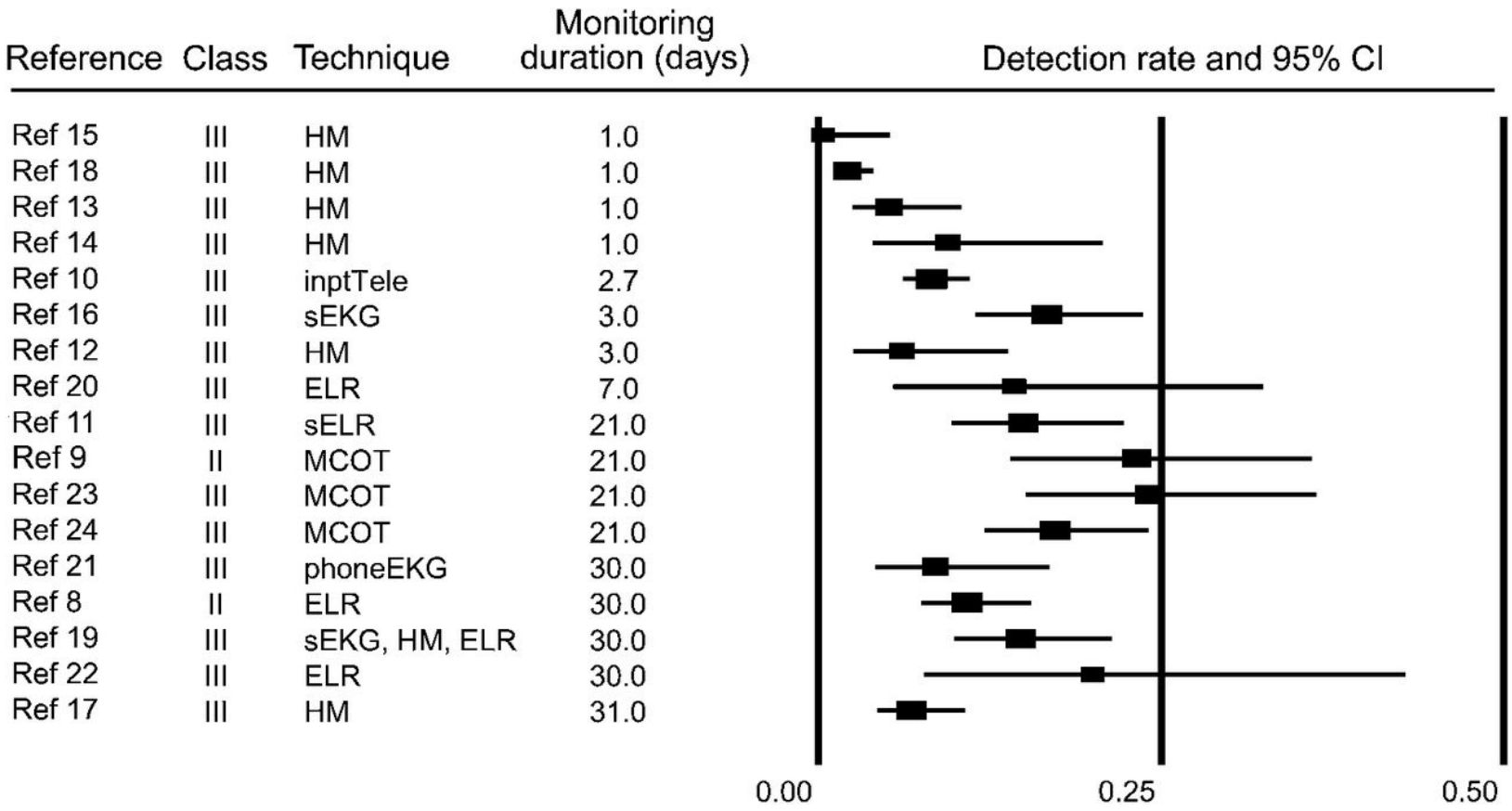
Clinical Question

For patients with cryptogenic stroke, how often does the use of various technologies, identify previously undetected NVAF?

- Two Class II[8,9] and 15 Class III[10–24] studies were identified that address this question.

Evidence-based guideline update: Prevention of stroke in nonvalvular atrial fibrillation: AAN
Culebras A et al. Neurology 2014;82:716-724

Figure 1 Proportion of patients with ischemic stroke identified with nonvalvular atrial fibrillation, by study (sorted by monitoring duration.)



Culebras A et al. Neurology 2014;82:716-724

A. Practice Recommendations

1. Clinicians might obtain cardiac rhythm studies for prolonged periods (e.g., for 1 or more weeks) instead of shorter periods (e.g., 24 hours) in patients with cryptogenic stroke , to increase the yield of identification of patients with occult NVAF (Level C).

Culebras A et al. Neurology feb 2014;82:716-724

EMBRACE: Trial Design

- Ambulatory Patients >55
  - stroke or TIA of undetermined origin
  - less than 6 months ago
  - randomly assigned to ambulatory ECG monitoring with a 30 day event triggered loop recorder versus 1 additional round of 24 h Holter monitoring and regular follow up.

- Primary outcome:
  - Detection of ≥1 episode of AF lasting ≥30 sec

Secondary Outcomes

- Atrial fibrillation or flutter ≥30 seconds, Other Non-sustained irregular atrial rhythms, Composite endpoint

- Proportion of patients prescribed oral anticoagulation, at 90-day follow-up

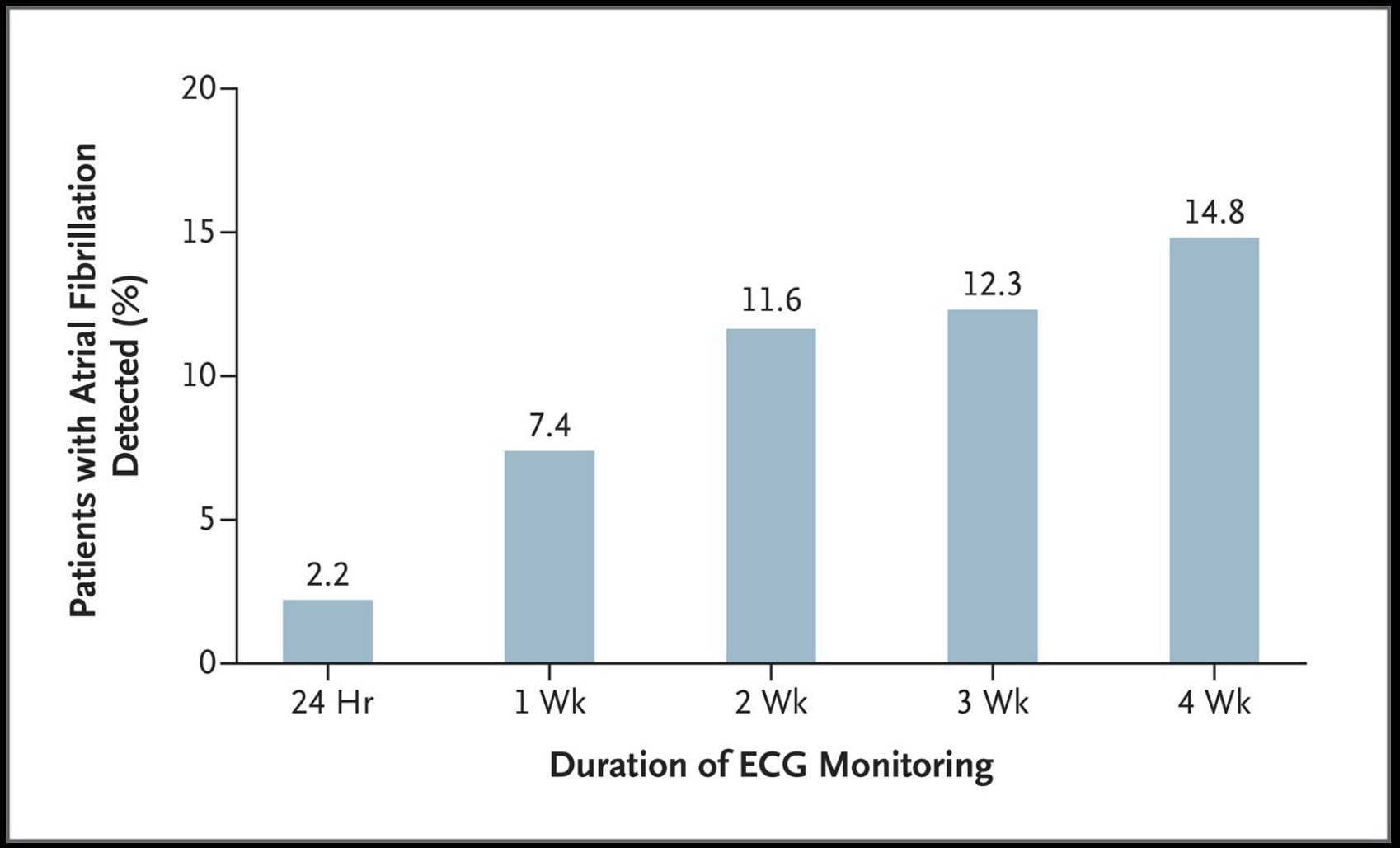
- Patient adherence with 30-day monitoring

- 1 and 2-year rates of recurrent ischemic stroke/TIA, death, hemorrhagic stroke, major adverse bleeding events, detection of atrial fibrillation outside of the study protocol

Protocol: device

- Devices were purchased and manufacturer had no role in the study (Braemar)
  - Automatic recording of irregularity in the R-R interval over 30 beats
  - 30 minute memory capacity and could record max. 2.5 minutes per episode.
  - Dry –electrode belt around the chest (improve compliance)
  - Data transmitted by telephone for central interpretation
  - AF episodes adjudicated by a cardiologist and an internist
  - Results then sent to study sites and Rx left to the discretion of the MD

Incremental Yield of Prolonged ECG Monitoring for the Detection of Atrial Fibrillation in Patients with Cryptogenic Stroke or TIA.



Gladstone DJ et al. N Engl J Med 2014;370:2467-2477

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Baseline Characteristics of the Patients.

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Intervention Group (N=286)	Control Group (N=285)
Age		
Mean age — yr	72.5±8.5	73.2±8.8
≥75 yr — no. (%)	104 (36.4)	118 (41.4)
Female sex — no. (%)	132 (46.2)	125 (43.9)
Race — no. (%)†		
White	257 (89.9)	260 (91.2)
Asian	15 (5.2)	14 (4.9)
Black	6 (2.1)	2 (0.7)
Other	8 (2.8)	9 (3.2)
Modified Rankin scale score ≤2 — no. (%)‡	274 (95.8)	263 (92.3)
Medical history — no. (%)		
Hypertension	204 (71.3)	191 (67.0)
Diabetes	55 (19.2)	55 (19.3)
Hyperlipidemia	191 (66.8)	177 (62.1)
Smoking status		
Current smoker	19 (6.6)	24 (8.4)
Previous smoker	141 (49.3)	131 (46.0)
Previous ischemic stroke	45 (15.7)	36 (12.6)
>1 Previous stroke	12 (4.2)	12 (4.2)
Previous transient ischemic attack	42 (14.7)	46 (16.1)
Congestive heart failure	5 (1.7)	7 (2.5)
Myocardial infarction	48 (16.8)	42 (14.7)
Coronary angioplasty or stenting	24 (8.4)	23 (8.1)
Coronary bypass surgery	29 (10.1)	19 (6.7)
Cardiac-valve surgery	6 (2.1)	1 (0.4)
Type of index event — no. (%)		
Ischemic stroke	188 (65.7)	172 (60.4)
Transient ischemic attack	98 (34.3)	113 (39.6)
Oxfordshire classification[18] of the index event — no. (%)§		
Total anterior circulation syndrome	7 (2.4)	5 (1.8)
Partial anterior circulation syndrome	201 (70.3)	216 (75.8)
Posterior circulation syndrome	63 (22.0)	56 (19.6)
Lacunar syndrome	15 (5.2)	7 (2.5)
No. of days from index event to randomization	76.6±37.5	73.7±39.7

* Plus–minus values are means ±SD. There were no significant differences between the two study groups at the 0.05 significance level.
† Race was determined by the investigator.
‡ Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms and 6 indicating death; a score of 2 or less indicates that the patient is ambulatory and functionally independent in activities of daily living.
§ Data were missing for one patient in the control group.

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Detection of Atrial Fibrillation in the Two Monitoring Groups.

Table 2. Detection of Atrial Fibrillation in the Two Monitoring Groups.

Outcome	Intervention Group (N=286)	Control Group (N=285)	Absolute Difference (95% CI)	P Value	No. of Patients Needed to Screen (95% CI)*
	number/total number (percent)		*percentage points*		
Primary outcome: detection of atrial fibrillation with duration ≥30 sec within 90 days†	45/280 (16.1)	9/277 (3.2)	12.9 (8.0–17.6)	<0.001	8 (5.7–12.5)
Secondary outcomes‡					
Detection of atrial fibrillation with duration ≥30 sec	44/284 (15.5)	7/277 (2.5)	13.0 (8.4–17.6)	<0.001	8 (5.7–11.9)
Detection of atrial fibrillation with duration ≥2.5 min	28/284 (9.9)	7/277 (2.5)	7.4 (3.4–11.3)	<0.001	14 (8.8–29.4)
Detection of atrial fibrillation of any duration	56/284 (19.7)	13/277 (4.7)	15.0 (9.8–20.3)	<0.001	7 (4.9–10.2)

* The number of patients needed to screen was defined as the number of patients who would need to be screened in order to detect atrial fibrillation in one additional patient (with a 30-day monitoring strategy vs. repeat 24-hour Holter monitoring).

† The primary analysis included all the patients who underwent randomization for whom outcome data were available (i.e., patients who underwent any amount of cardiac monitoring or 90-day follow-up in whom the status of atrial fibrillation could be determined). In the primary analysis, atrial fibrillation was detected either clinically or by means of study monitoring.

‡ The secondary analyses included all the patients who underwent randomization and any amount of cardiac monitoring. The detection of atrial fibrillation in the secondary analyses was by means of the study monitors.

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Anticoagulant Therapy in the Two Monitoring Groups.

Table 3. Anticoagulant Therapy in the Two Monitoring Groups.*

Therapy	Intervention Group (N=286)	Control Group (N=285)	Absolute Difference (95% CI)	P Value
	no./total no. (%)		*percentage points*	
Baseline				
Anticoagulant therapy before the index stroke or TIA	3/286 (1.0)	2/285 (0.7)	—	—
Anticoagulant therapy at randomization after the index stroke or TIA	16/286 (5.6)	19/285 (6.7)	—	—
After study monitoring				
Therapy at 90 days after randomization				
Anticoagulant therapy	52/280 (18.6)	31/279 (11.1)	7.5 (1.6 to 13.3)	0.01
Antiplatelet therapy only	223/280 (79.6)	246/279 (88.2)	−8.6 (−14.6 to −2.5)	0.006
Therapy at randomization changed by 90 days				
From antiplatelet therapy to anticoagulant therapy	38/280 (13.6)	13/279 (4.7)	8.9 (4.2 to 13.6)	<0.001
From anticoagulant therapy to antiplatelet therapy	3/280 (1.1)	2/279 (0.7)	0.4 (−1.2 to 1.9)	0.66

* Anticoagulant therapy was defined as the use of any oral anticoagulant (warfarin, dabigatran, rivaroxaban, or apixaban). Antiplatelet therapy was defined as the use of any antiplatelet medication (aspirin, clopidogrel, aspirin–extended-release dipyridamole, dipyridamole, or other antiplatelet agent) and no oral anticoagulant therapy.

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Study Overview

- patients with cryptogenic stroke randomly assigned to undergo intensive ECG monitoring for 30 days had a higher incidence of detected atrial fibrillation (16%) than those assigned to receive standard 24-hour monitoring (3%).

- nearly doubled the rate of anticoagulant treatment, as compared with the standard practice of short-duration ECG monitoring

Comparing EMBRACE with Crystal-AF

	EMBRACE	Crystal-AF
Monitor type	External	Implanted
Rate of detection	16.1% (90days)	8.9% (6 m)
Hazard ratio	5	6.4
Mean patient age	73	61.5
Time to randomisation/Time to discover AF	75d / 75% in 2weeks	38d / median 41d
mRS	<2	<2
AF episodes > 2.5 minutes duration	2/3	Average time in AF 4 min.
Rate of anticoagulation vs non-monitorred	double	double

What we have learned

- Paroxysmal AF evades detection and requires at least several weeks of continuous monitoring.
  - Current techniques are grossly inferior and standard practices may have to change consequently

At least two questions may remain

1. Cryptogenic stroke:

   Even after long-term follow-up (up to 3 years in CRYSTAL AF), less than one third of the patients had evidence of atrial fibrillation.

2. May need more evidence to guide therapy for subclinical atrial fibrillation.

Thank you for your attention