Cryptogenic Stroke: Understanding the Definition and Excluding Treatable Causes

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Heart.org/Quality

Speaker

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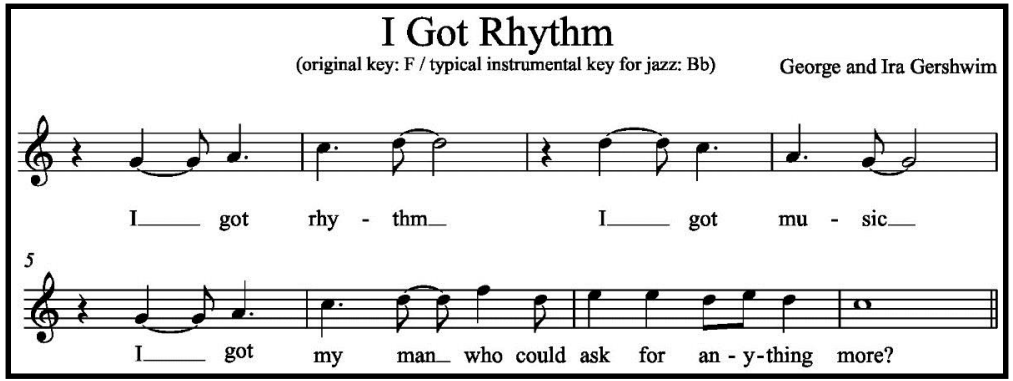
Disclosure

- Clinical trials consultant to Medtronic (Steering Committee VICTORY AF, REACT AF; Co-PI Stroke AF)
- DSMB member for Novo-Nordisk DeVOTE trial, Penumbra Separator 3D trial
- Chair, Stroke Clinical Workgroup AHA GWTG-Stroke

Overview

- What or when is a stroke cryptogenic ?
- Discuss the nature of the stroke workup
- Review the current data on occult causes of stroke
- Review the role of occult AF in cryptogenic stroke



Sec of Defense Donald Rumsfeld Briefing the Press on Cryptogenic Stroke

- "Reports that say that something hasn't happened are always interesting to me, because as we know, there are **known knowns**; there are things we know we know. (e.g., lacunar stroke)

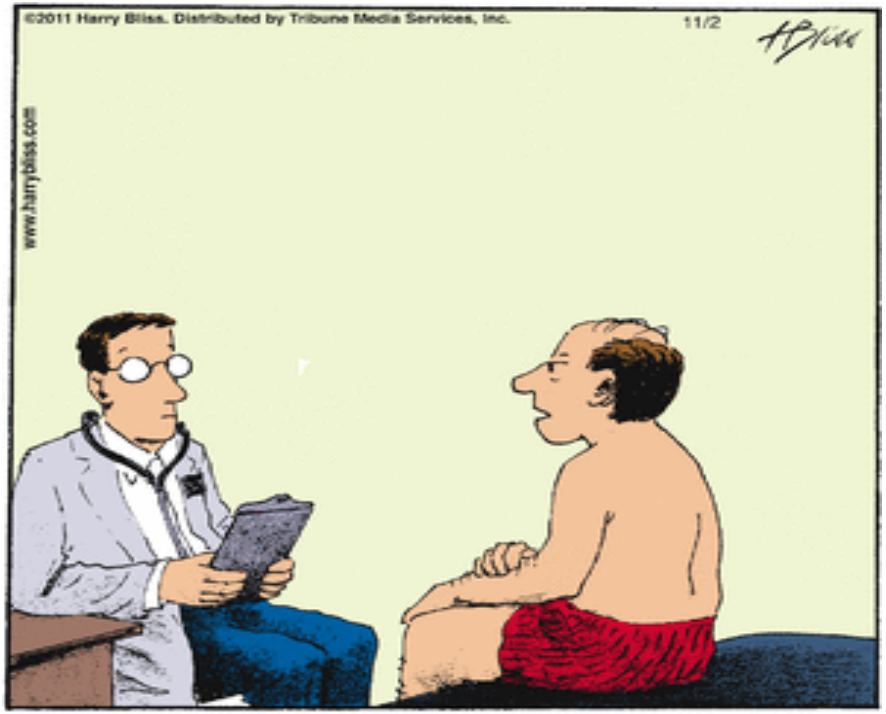
- We also know there are **known unknowns**; that is to say we know there are some things we do not know. (e.g., cryptogenic stroke)

- But there are also **unknown unknowns** – the ones we don't know we don't know. And if one looks throughout the history of our country and other free countries, it is the latter category that tend to be the difficult ones" (e.g., how often is a lacunar stroke cardioembolic?)

Defense.gov News Transcript: DoD News Briefing – Secretary Rumsfeld United States Department of Defense (defense.gov)

What is a Cryptogenic Stroke?

Depends on Who You Ask and How Hard You Look

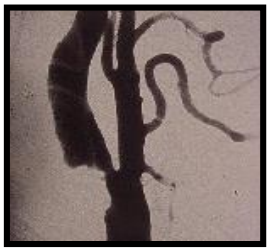


"Doc, enough with the 'English' — just give it to me in plain academic medical terminology!"

Cerebrovascular Disease: Stroke Subtypes

Ischemic Stroke (85%)

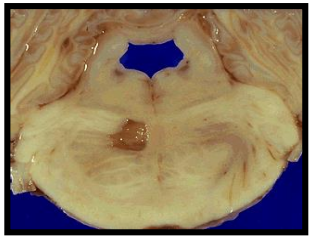
Atherothrombotic Cerebrovascular Disease (20%)



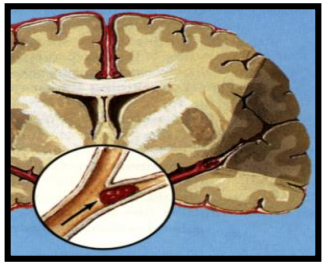
Cryptogenic (30%)

?

Lacunar (25%)
(small vessel disease)

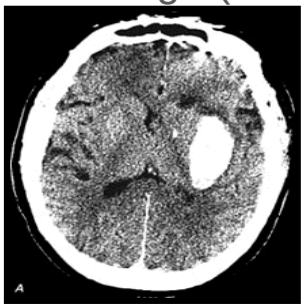


Cardioembolic (20%)

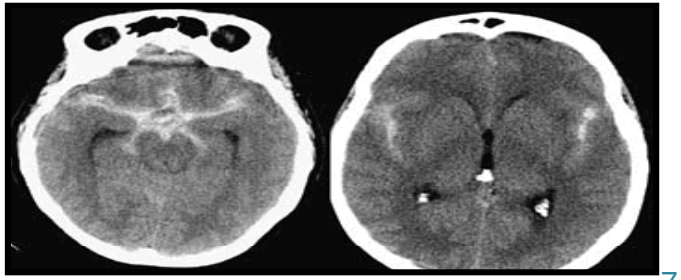


Hemorrhagic Stroke (15%)

Intracerebral Hemorrhage (70%)



Subarachnoid Hemorrhage (30%)



Stroke Classification Systems: TOAST

- Large Artery Atherosclerosis*
- Cardioembolism* (high and medium risk sources)
- Small Vessel Occlusion*
- Stroke of Other Determined Etiology*
- Stroke of Undetermined Etiology
  - 2 or more causes identified
  - Negative Evaluation
  - Incomplete Evaluation

*possible or probable depending on ancillary tests
Amerenco et al. Cerebrovac Dis 2009

Stroke Classification Systems: Oxford Community Stroke Project (OCSP)

- Total Anterior Circulation (TAC)
- Partial Anterior Circulation (PAC)
- Lacunar (LAC)
- Posterior Circulation (POC)

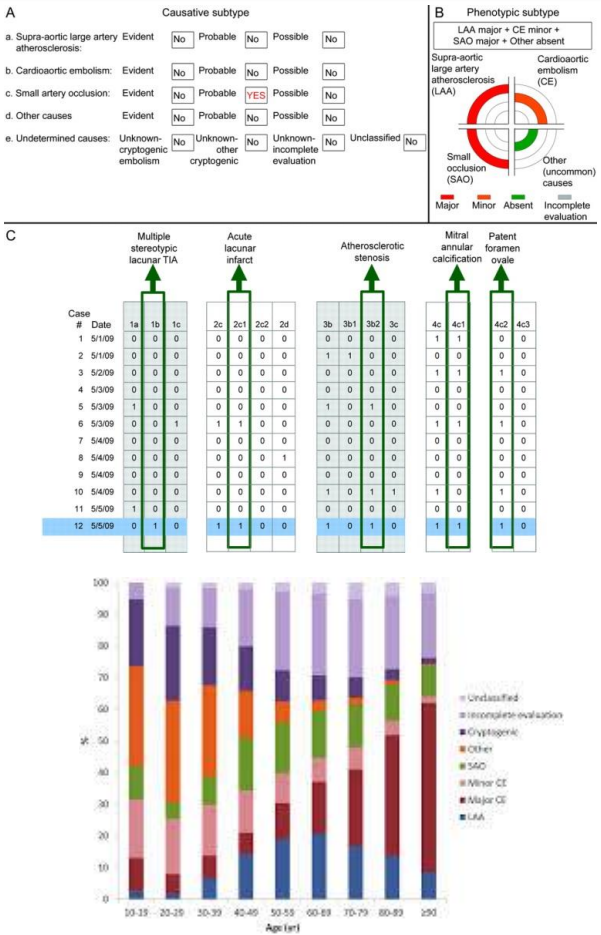
Stroke Type is amended as a final letter

  - I for infarct
  - S for syndrome prior to imaging or if indeterminate

Stroke Classification Systems: Causative Classification of Stroke

Table Causative stroke subtypes according to the Causative Classification of Stroke System (CCS)[a]

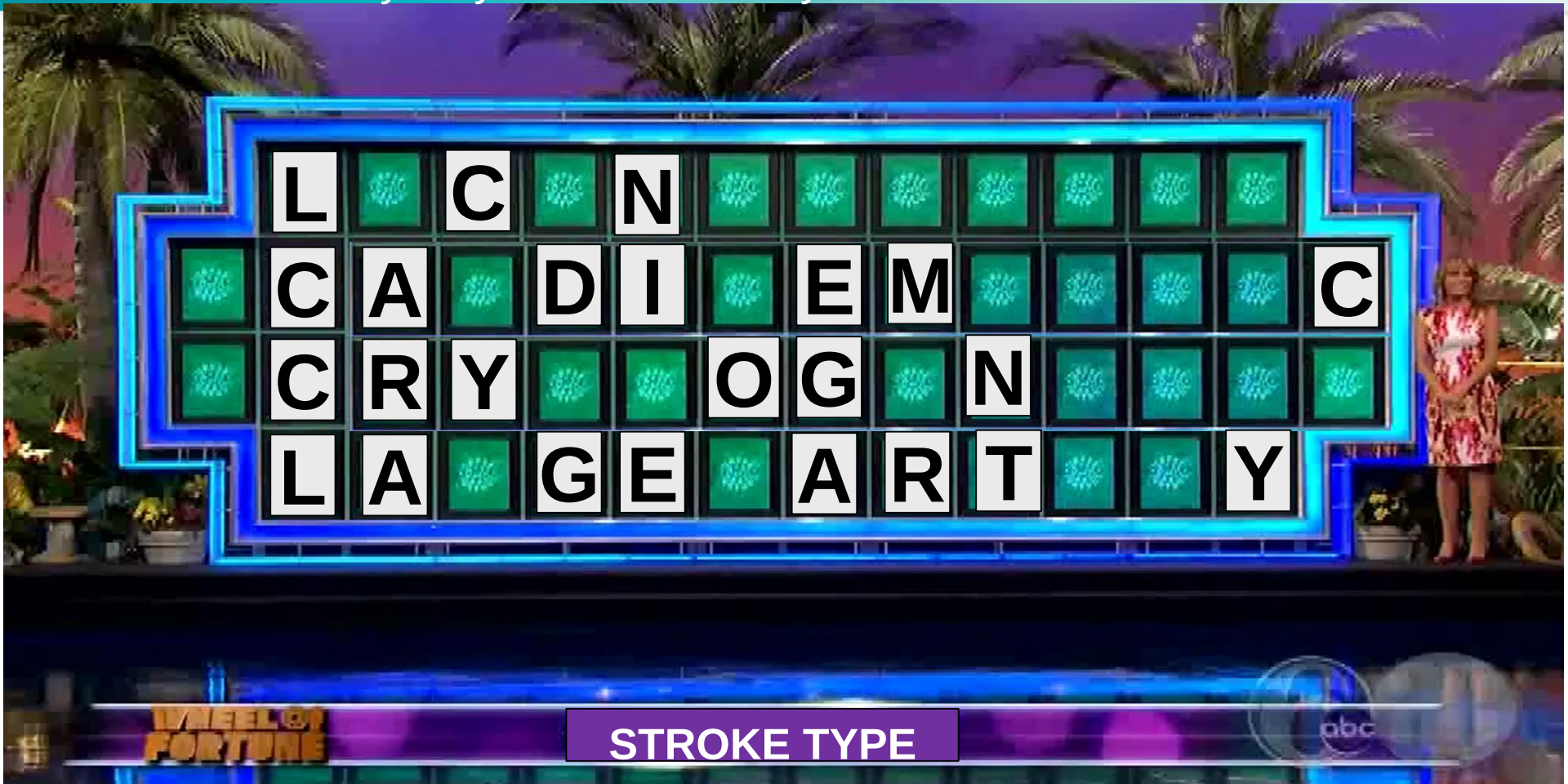
5 Subtype CCS	8 Subtype CCS	16 Subtype CCS
Supra-aortic large-artery atherosclerosis	Supra-aortic large-artery atherosclerosis	Supra-aortic large-artery atherosclerosis
		Evident, probable, possible
Cardioaortic embolism	Cardioaortic embolism	Cardioaortic embolism
		Evident, probable, possible
Small-artery occlusion	Small-artery occlusion	Small-artery occlusion
		Evident, probable, possible
Other uncommon causes	Other uncommon causes	Other uncommon causes
		Evident, probable, possible
Undetermined	Undetermined	Undetermined
	Unknown-cryptogenic embolism	Unknown-cryptogenic embolism
	Unknown-other cryptogenic	Unknown-other cryptogenic
	Unclassified	Unclassified
	Incomplete evaluation	Incomplete evaluation



E.M. Arsava et al. Neurology 2010;75:1277-1284

Stroke Diagnosis: Can I Buy a Vowel?

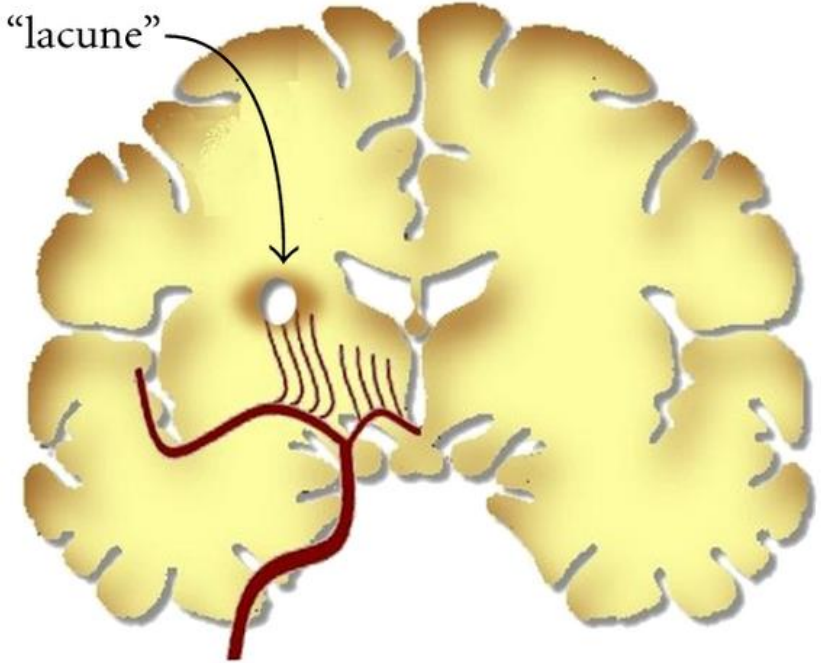
How much certainty do you need before you answer?

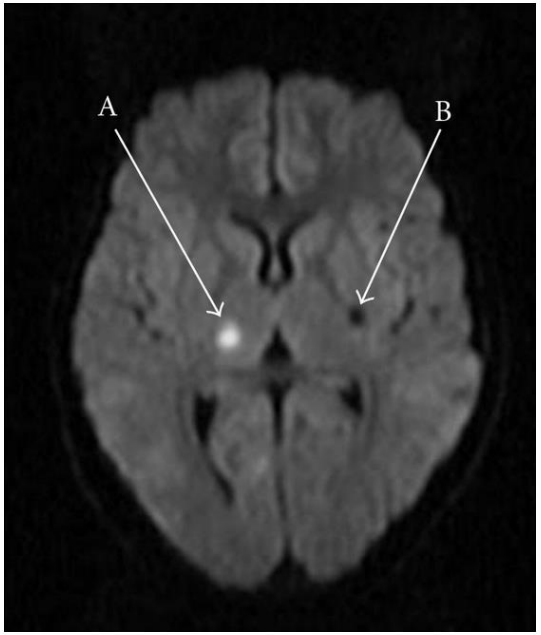


Common things are Common
AF is increasingly common with aging

- AF prevalence increases with age
- AF increases the stroke risk
- Several risk scores are available to determine the likelihood of stroke and help select the most appropriate antithrombotic
- Once a patient has had an ischemic stroke and AF is detected, all guidelines recommend use of an anticoagulant if safe

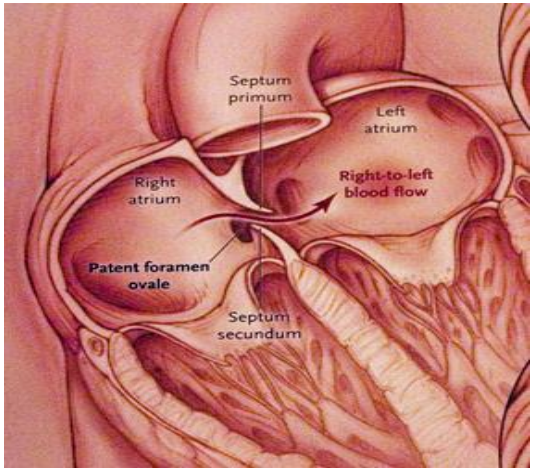
In a Patient with AF and Prior Lacunes, is this a Cryptogenic Stroke?

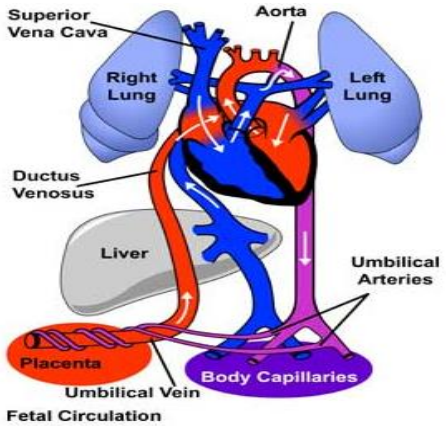


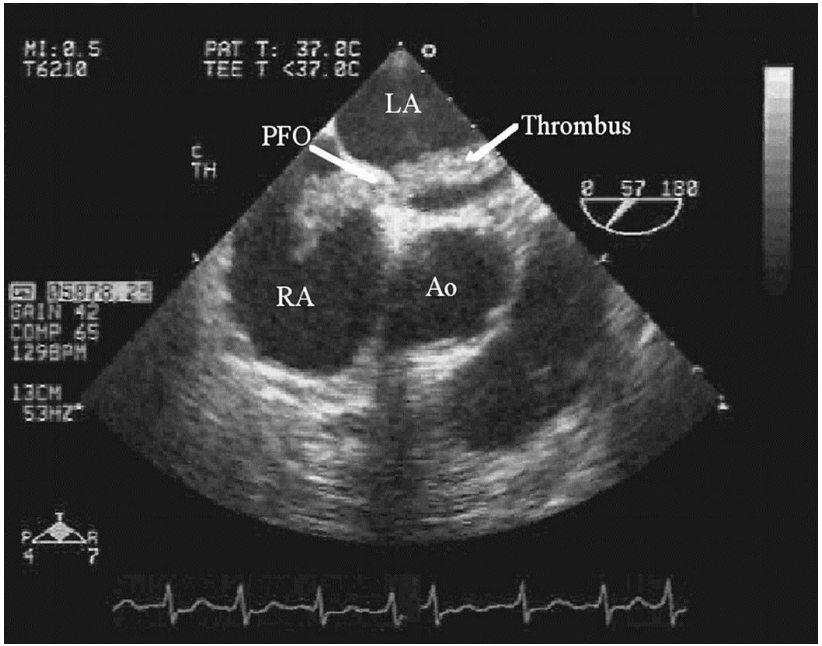


An illustration of coronal cross section of the brain showing a small cavity termed a "lacune" within the subcortical white matter and in the territory of perforating arteries. (A) acute DWI SVI, (B) chronic lacune on DWI MRI

Is Stroke in a Young Patient with a PFO Cryptogenic?

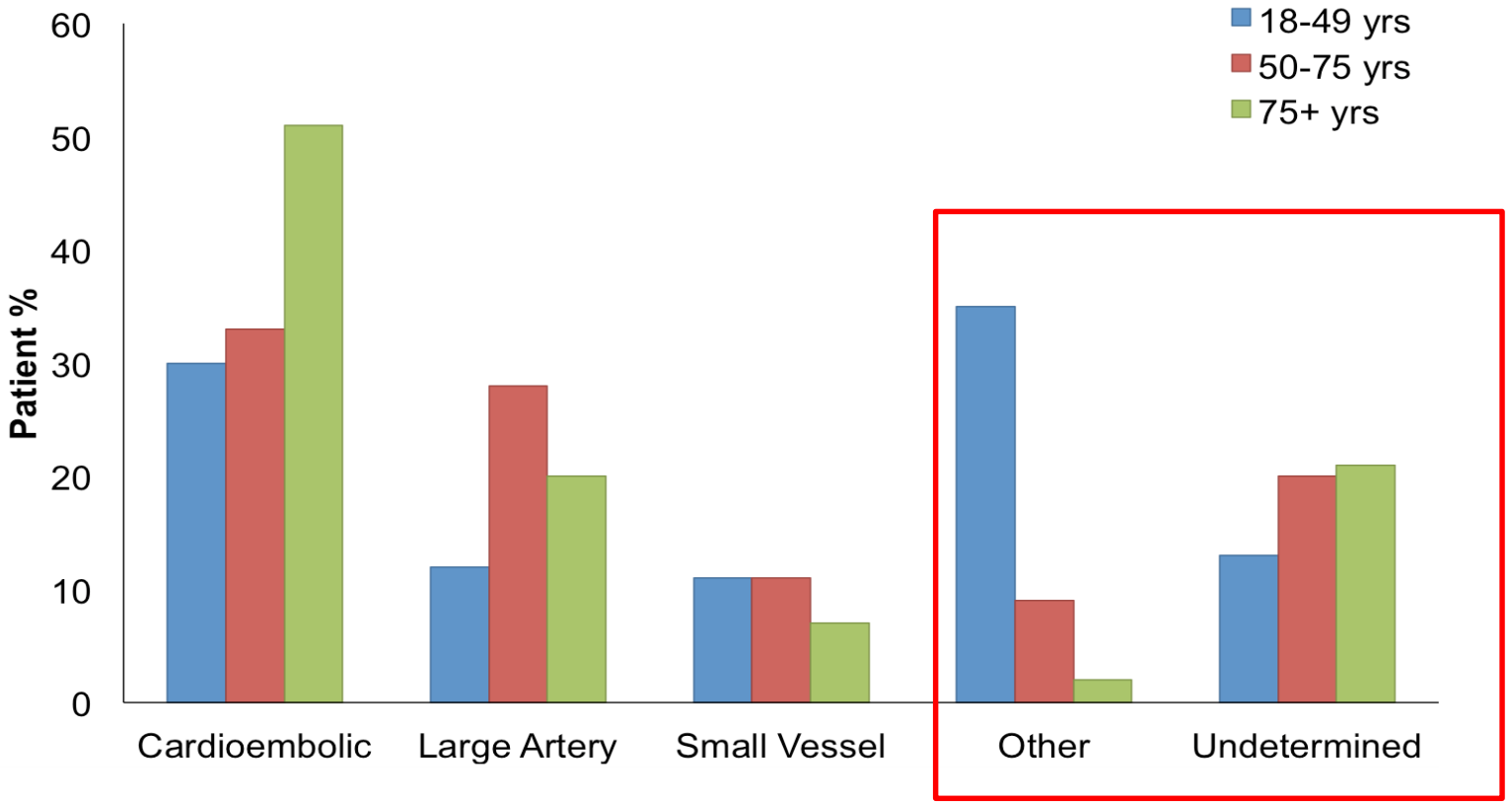






D.J. Beacock, j.euje.2005.03.010 171-174

Stroke Subtypes Differ Across All Age Groups at MGH



Razmara, ISC 2014

Rule #1: Just cause it's **hard to find**, doesn't mean it's not there.
Rule #2: Just cause you **found it**, doesn't mean it is the cause.
Rule #3: Just cause it isn't the **cause**, doesn't mean you ignore it.

The Impact on Positive Predictive Value (PPV) as Prevalence Changes, for a test with 99% Sensitivity and 95% Specificity

	Prevalence	**1%**	**10%**	**20%**
a	# in population	1,000	1,000	1,000
b	Diseased	10	100	200
c	Not diseased	990	900	800
d	True Positives on the test (b x 0.99)	10	99	198
e	False positives on the test (c x (1-0.95))	50	45	40
f	Total # positive on test (d + e)	60	144	238
	PPV (d / f)	**17%**	**69%**	**83%**

(Source: Dr. Chan Shah: Public health and preventive medicine in Canada. Elsevier, Canada, 2003)

Different strokes for different folks

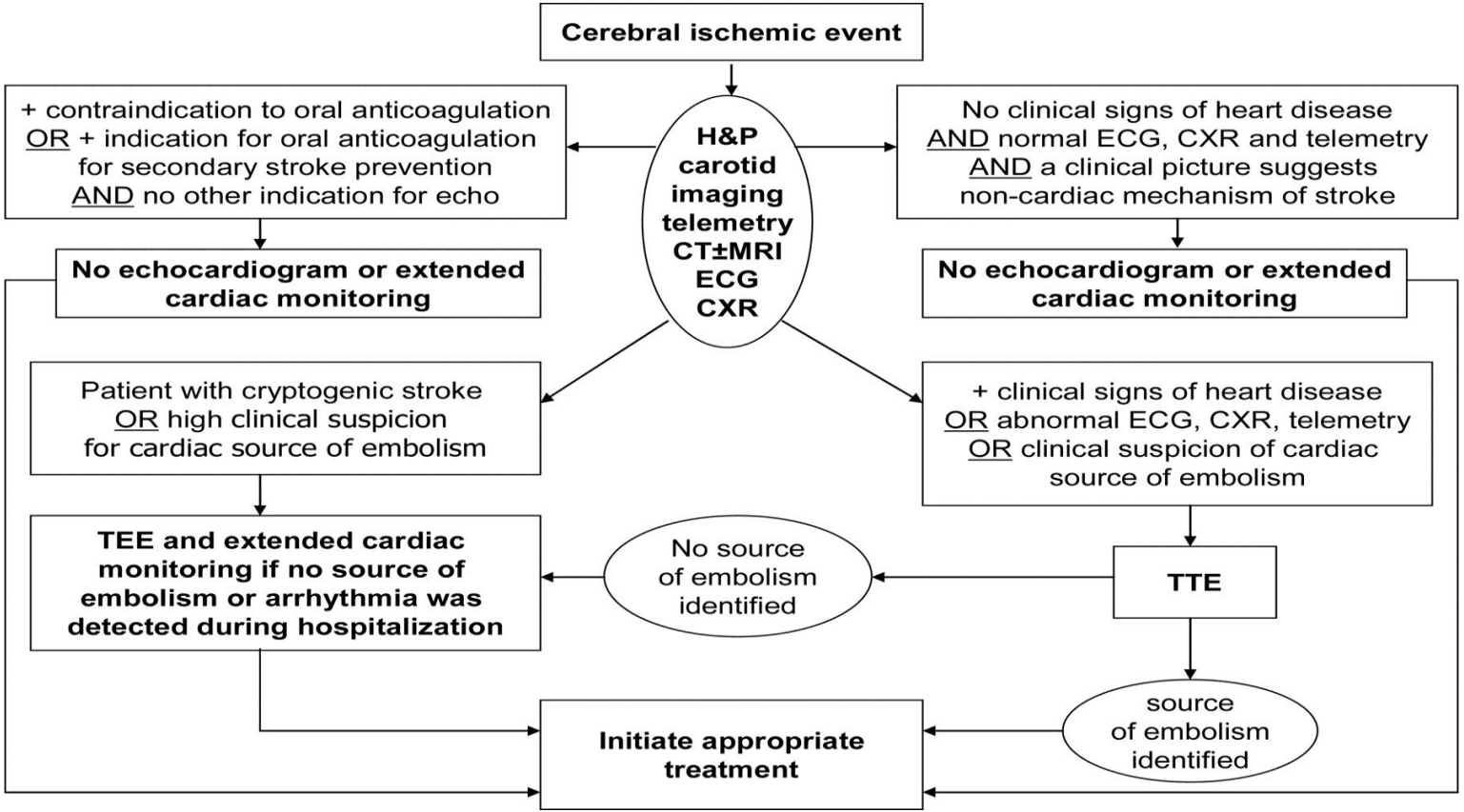
Stroke Workups 50% off sale!

Unusual Causes of Stroke: How often will you find one of these?

- Cardiac Disease
  - Infectious and non-bacterial thrombotic endocarditis
  - Rheumatic valvular heart disease
  - Cardiac tumors (e.g. atrial myxoma, papillary fibroelastoma)
  - Patent foramen ovale and congenital heart defects
- Hypercoagulable states
  - Inherited deficiencies of protein S, protein C, or antithrombin; factor V Leiden mutation, Prothrombin gene mutation
  - Acquired due to malignancy, pregnancy, hormonal exposure, nephrotic syndrome, antiphospholipid Ab, HIT, etc
- Cerebral artery dissection (spontaneous, FMD, EDS, Marfan's)
- Reversible cerebral vasoconstriction syndromes
- Moya-Moya Syndrome
- Sickle cell disease
- Various infectious, inflammatory, genetic or postpartum arteriopathies
- Migraine-induced Stroke
- Cortical Venous Sinus Thrombosis
- Illicit drug abuse (e.g. cocaine, amphetamines)

Yaeger, Singhal and Nogueira, NEJM 2012

Suggested algorithmic approach to the cardiac work-up of ischemic stroke or TIA



Jane G. Morris et al. Stroke. 2009;40:2893-2898

AHA Stroke Guidelines for Secondary Prevention Highlight the Importance of PAF

- Extracranial Vascular Imaging
  - It is important to evaluate the extracranial vasculature after the onset of acute cerebral ischemia (stroke or TIA) to aid in the determination of the mechanism of the stroke and thus potentially to prevent a recurrence
- Antiplatelet Therapy
  - Oral administration of aspirin (initial dose is 325 mg) within 24 to 48 hours after stroke onset is recommended for treatment of most patients.
- **Anticoagulation Therapy**
  - **Anticoagulation is recommended for high risk cardioembolic sources**
  - Young patients with cryptogenic TIA or stroke and PFO should be evaluated for lower extremity or pelvic venous thrombosis, which would be an indication for anticoagulation
- PFO
  - For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for DVT, available data do not support a benefit for PFO closure (Class III; Level of Evidence A).

Kernan. Stroke 2014

Detection of Occult AF

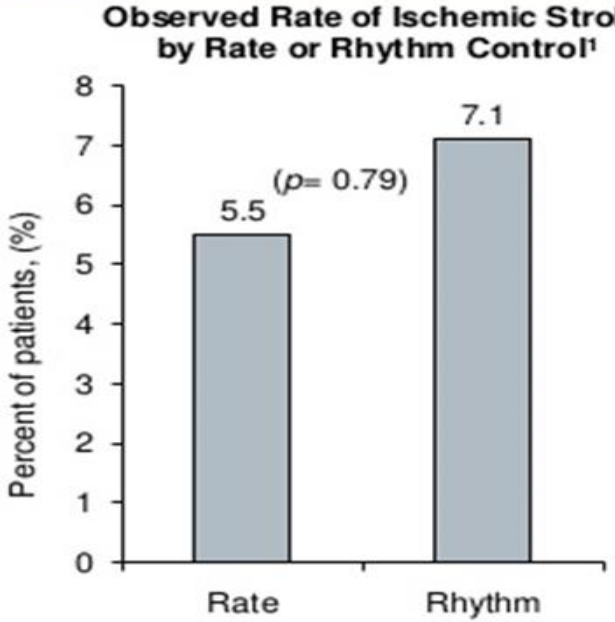
- Approximately 10% of patients with acute ischemic stroke or TIA will have new AF detected during their hospital admission
- In stroke or TIA patients with an indication for a pacemaker, interrogation of the device identified a 28% incidence of occult AF during 1 year
- A similar rate of occult AF has been reported among high-risk, non-stroke patients with implantable cardiac rhythm devices
- Occult AF detected during pacemaker interrogation in stroke-free patients or mixed populations is associated with increased risk for stroke

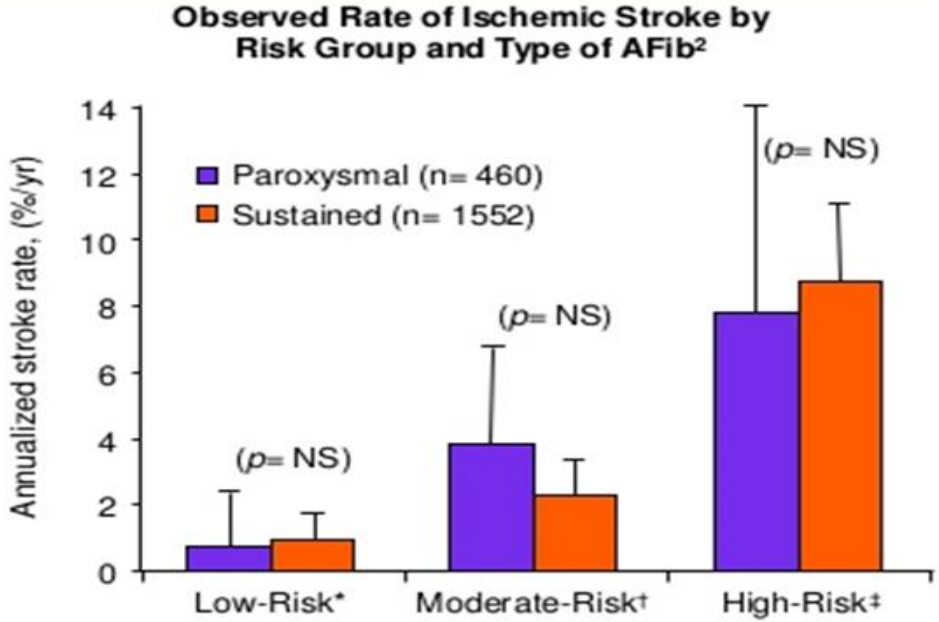
Detecting AF after IS or TIA: Systematic Review and Meta-Analysis

- Prospective studies (n=31) reporting proportion of new AF diagnosed using ECG-monitoring for >12 hr in patients with recent stroke or TIA were analyzed
- Longer duration of monitoring was associated with an increased detection of AF when examining monitoring time as a continuous variable ($p<0.001$ for meta-regression analysis) or as ≤ 72 hours vs. ≥ 7 days vs. 3 months (5.1% vs. 15% vs. 29%)
- Significant heterogeneity within studies was detected for both groups (≤72 hr: $I^2 = 91\%$; ≥7 d: $I^2 = 75\%$)
- When assessing the odds of AF detection in the 3 randomized controlled trial, there was a 7.26 increased odds of AF detection with long-term monitoring (95% CI [3.99-12.83]; $p<0.001$)

Dussault. Circ Arrhythm Electrophysiol. 2015 Jan 31.

“AF by any other name is still AF”

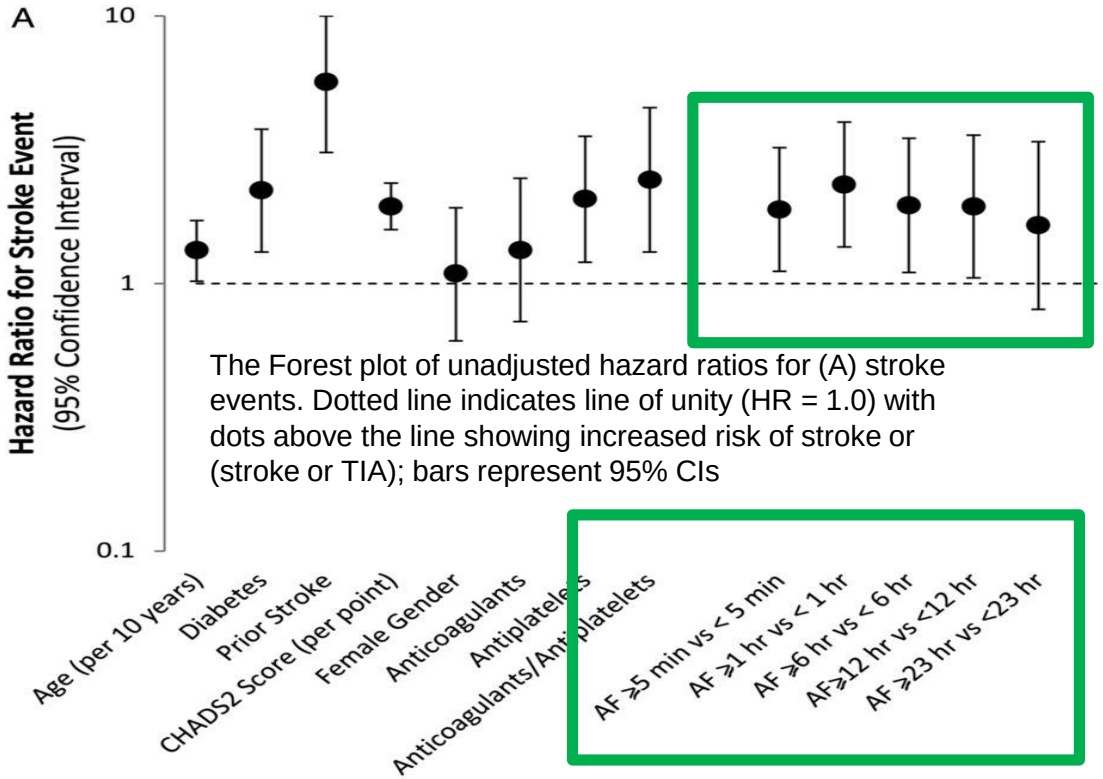




*No moderate or high-risk features.
†Hypertension (systolic BP > 160 mm Hg or diastolic BP > 90 mm Hg) and age ≤ 75 years; diabetes (definition not indicated), and no high-risk features.
‡Age > 75 years and hypertension or female, prior stroke or TIA.

1. Wyse DG et al. *N Engl J Med*. 2002;347:1825-1833.
2. Adapted with permission from Hart RG et al. *J Am Coll Cardiol*. 2000;35:183-187.

AF Burden and Stroke Risk: A Meta-Analysis
Risk of stroke is increased regardless of duration



The Forest plot of unadjusted hazard ratios for (A) stroke events. Dotted line indicates line of unity (HR = 1.0) with dots above the line showing increased risk of stroke or (stroke or TIA); bars represent 95% CIs

Device-detected atrial fibrillation and risk for stroke: an analysis of >10 000 patients from the SOS AF project (Stroke preventiOn Strategies based on Atrial Fibrillation information from implanted devices

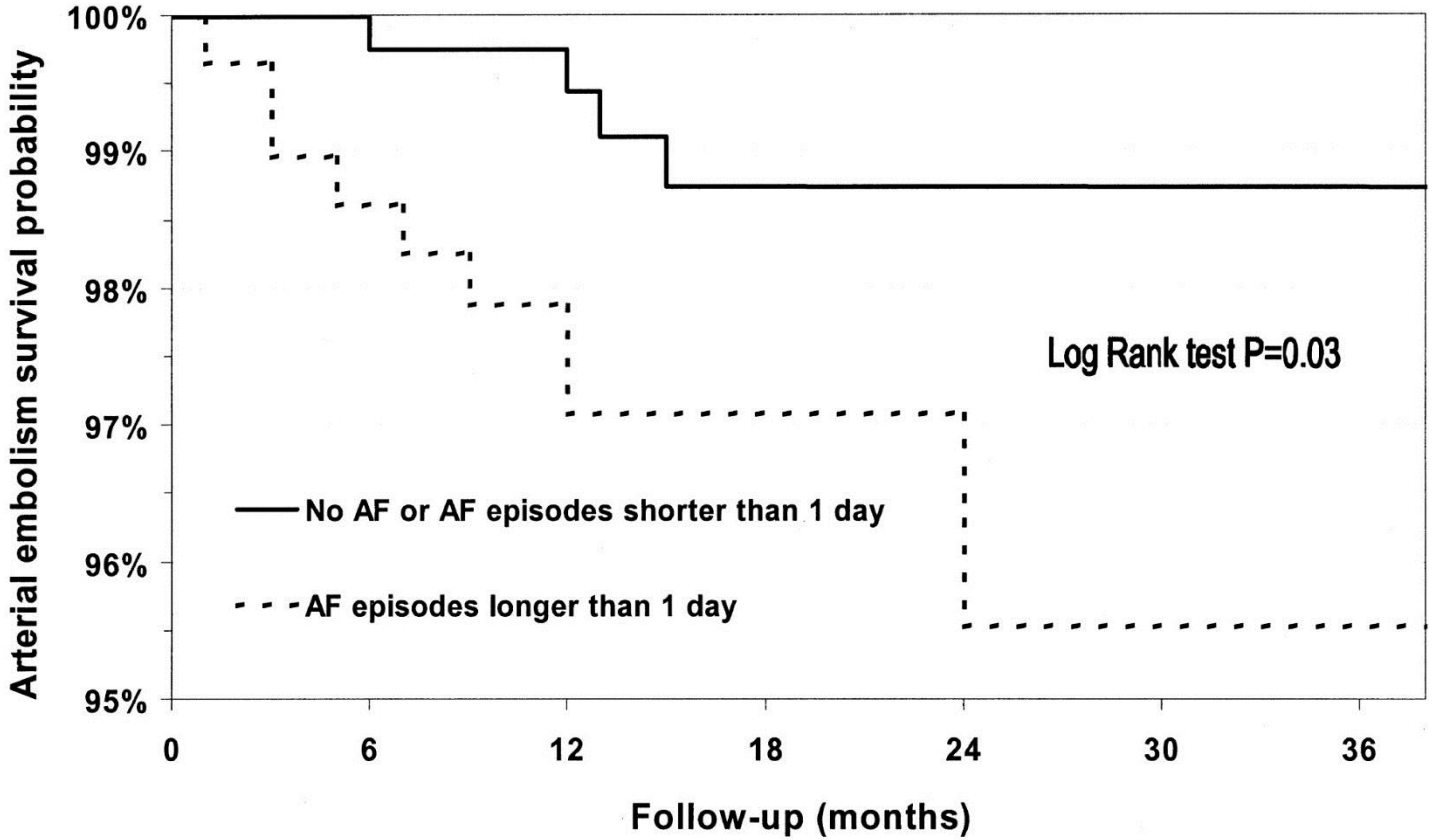
Giuseppe Boriani et al. Eur Heart J 2013;eurheartj.eht491

Yield of MCOT after Cryptogenic Stroke in Patients with Extensive Cardiac Imaging may be Lower

- Detection of paroxysmal atrial fibrillation (AF) after cryptogenic stroke (CS) or transient ischemic attack ranges from 5% to 24%, but yield of 30 dMCOT in CS patients who undergo **extensive cardiac imaging** before monitoring is unknown
- In 85 patients studied from 2009-2014, 89.4% underwent TTE, 68.2% TEE, and 38.8% cMRI
- 4/85 (4.7%, 95% CI: 1.5% to 11.9%) patients had AF by 14-30 d MCOT
- There were no univariate predictors of AF.
- The diagnostic yield of cardiac rhythm monitoring for up to 30 days in CS patients may be lower than previously reported.
- This may be because of the routine use of cardiac imaging to identify a likely source of embolism, resulting in a lower incidence of occult AF in patients who are labeled as "cryptogenic."
- Longer monitoring may be needed to detect this dysrhythmia in high-risk patients who have already undergone extensive cardiac imaging.

Kalani et al. J Stroke Cerebrovasc Dis. 2015 Sep;24(9):2069-73.

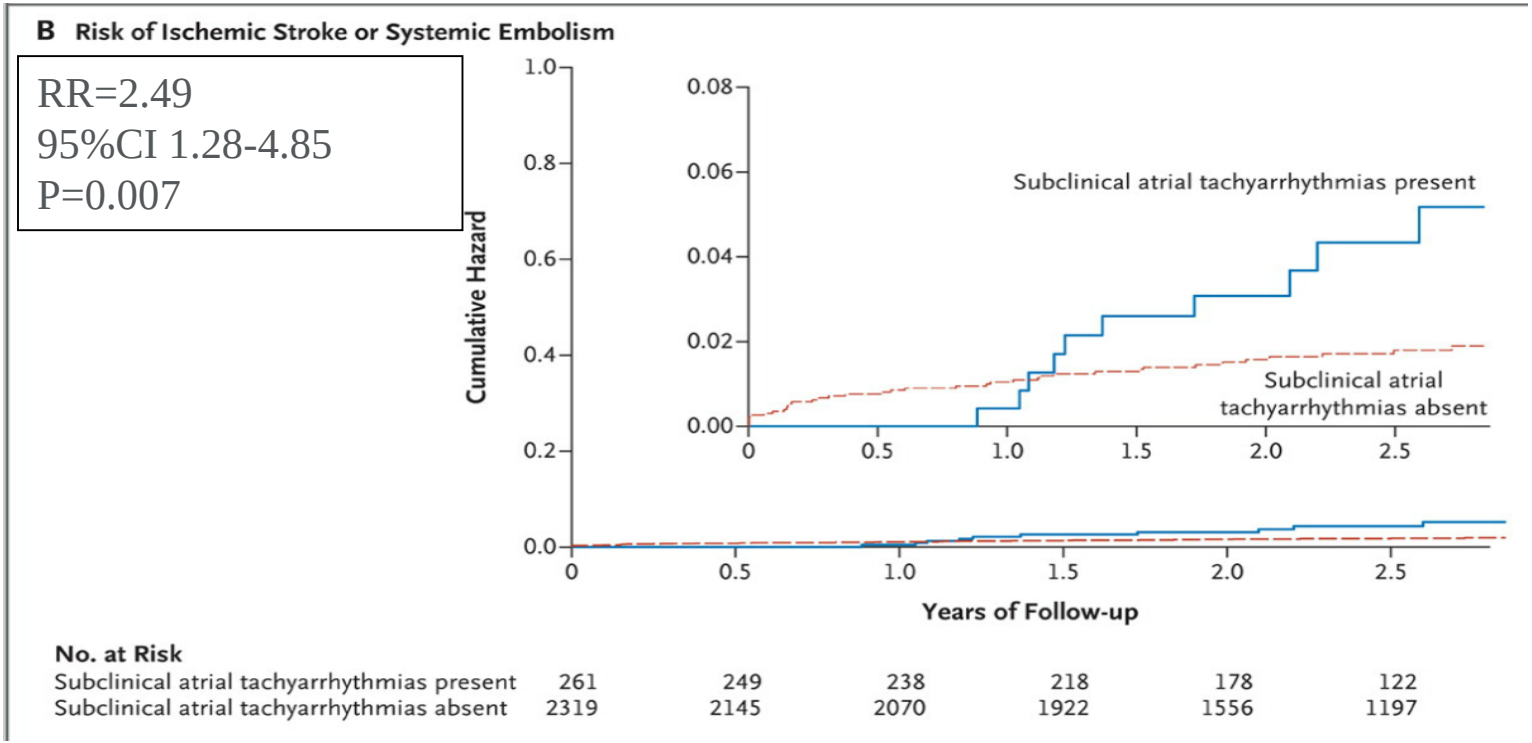
How Much AF Do You Need To Have A Stroke – 24 Hours?



Capucci A: JACC 2005;46:1913

ASSERT: 6 Minutes of PCM/ICD-detected AT increased risk of stroke or arterial embolism

Subclinical AT was associated with an increased risk of clinical AF (HR 5.56)



Healey; NEJM 2012; 366:120 - 129

ASSERT: Stroke Risk increases with CHADS and Burden

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 and the 3-Month Visit.

$CHADS_2$ 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)

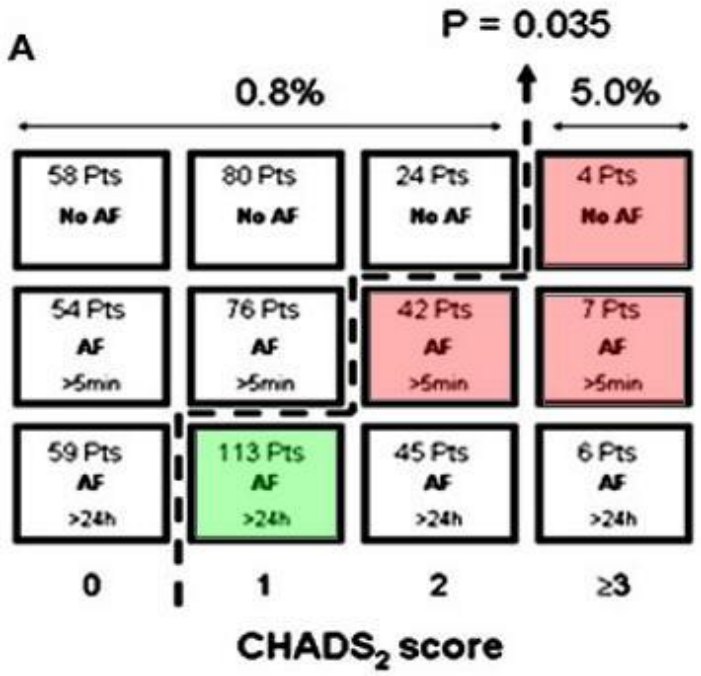
* The P value for trend is 0.35.

When 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.

AF: Burden Matters

- Analysis of 568 patients with a pacemaker and a history of AF, with patients broken into three groups
- **"In patients with recurrent AF episodes, risk stratification for thromboembolic events can be improved by combining $CHADS_2$score with AF presence/ duration."**

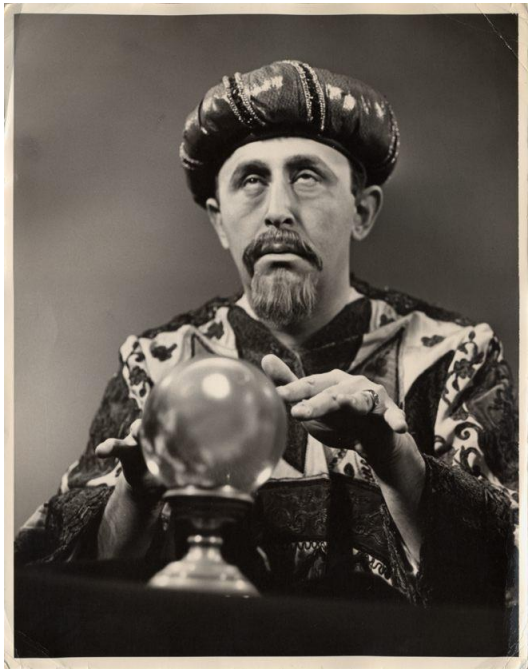
Risk of Thromboembolic Events by AF duration and $CHADS_2$



Botto G. et al.; J Cardiovasc Electrophysiol, Vol 20, p 241, March 2009

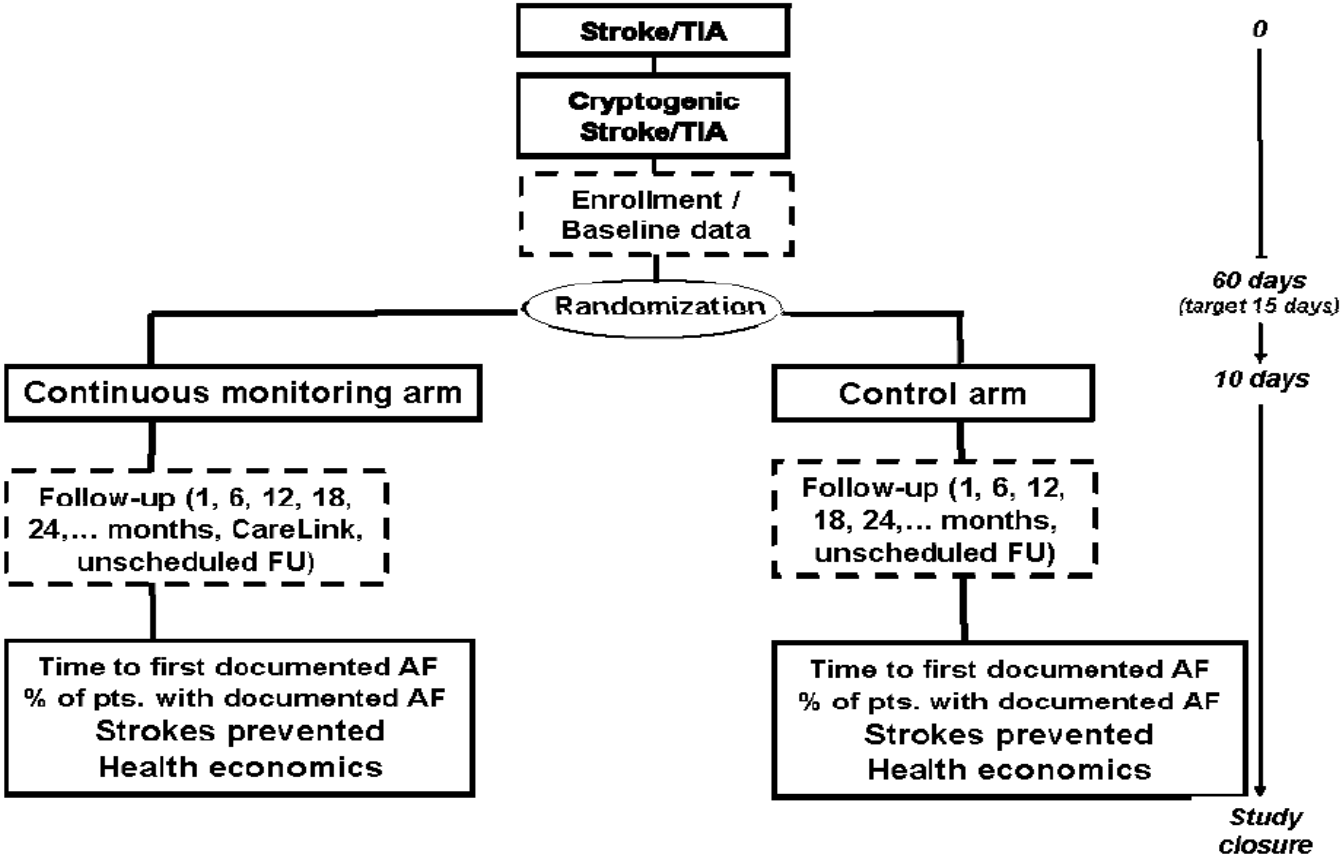
CRYSTAL AF
CRYptogenic STroke And underLying AF trial

- A randomized, controlled study of 441 patients to assess whether long-term monitoring with an insertable cardiac monitor (ICM) is more effective than conventional follow-up (control) for detecting atrial fibrillation in patients with cryptogenic stroke.
- Patients 40 years of age or older with no evidence of atrial fibrillation during at least 24 hours of ECG monitoring underwent randomization within 90 days after the index event.
- The primary end point was the time to first detection of atrial fibrillation (lasting >30 seconds) within 6 months. Among the secondary end points was the time to first detection of atrial fibrillation within 12 months.
- Data were analyzed as intention-to-treat



Sanna T ; NEJM 2014;370;2478

CRYSTAL AF
CRYptogenic STroke And underLying AF trial



Sanna T ; NEJM 2014;370;2478

CRYSTAL-AF: Baseline Characteristics

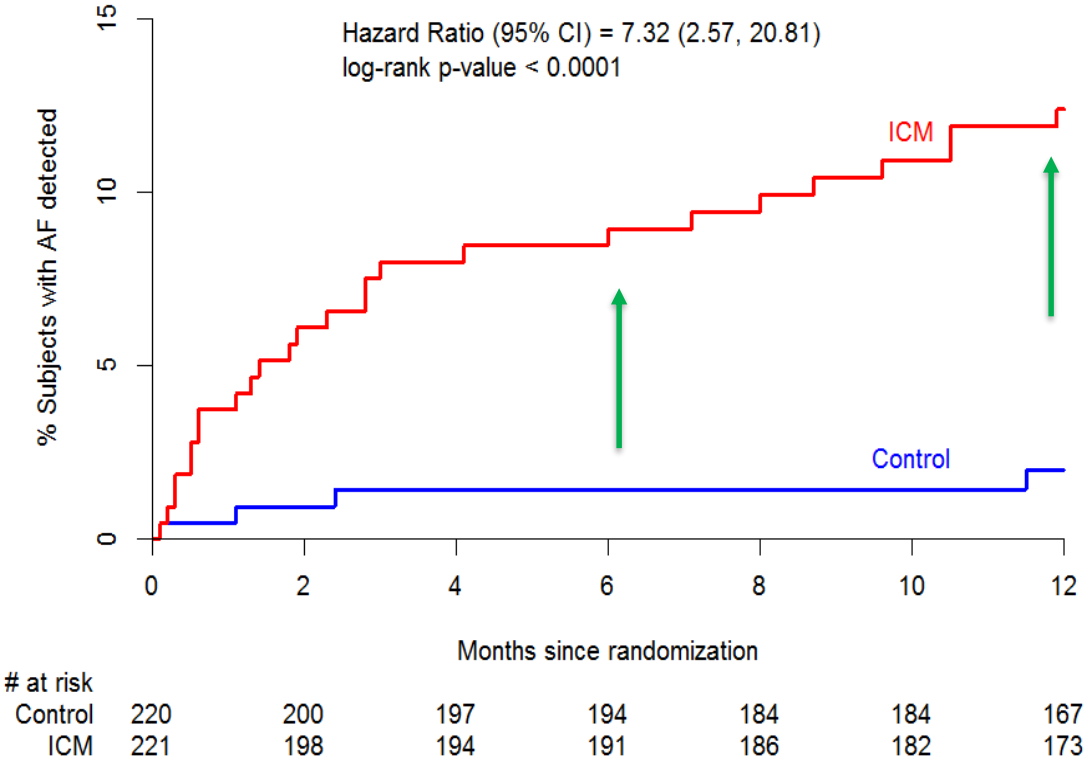
	ICM (LINQ)	Control
Age	61.6 ± 11.4 years	61.4 ± 11.3 years
Gender - Male	64.3%	62.7%
Index Event – Stroke	90.5%	91.4%
Index Event – TIA	21 (9.5%)	19 (8.6%)
PFO	24%	21%
Modified Rankin Score 0-2	83%	85%
NIH stroke scale	1.6 ± 2.7	1.9 ± 3.8
CHADS2 score 2-3	73%	78%
Time between index event and randomization	36.6 ± 28.2 days	39.6 ± 26.9 days
Time between randomization and device insertion	8.7 ± 27.6 days	n/a

Sanna T ; NEJM 2014;370;2478

Crystal AF: Detection Rates at 6 and 12 months

Primary Endpoint:
Detection of AF at
6 mo (8.9% vs. 1.4%)
HR: 6.43 (1.90, 21.74)
p = 0.0006

Secondary Endpoint:
Detection of AF at
12 mo (12.4% vs. 2.0%)
HR: 7.32 (2.57, 20.81)
p < 0.0001

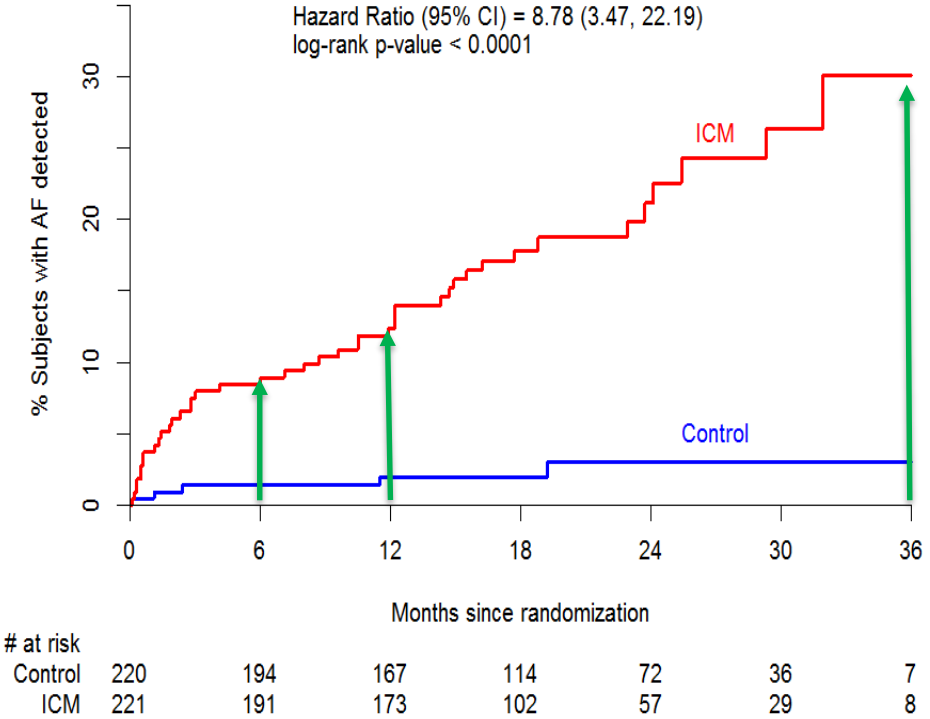


Sanna T ; NEJM 2014;370;2478

Crystal AF: Detection Rates Rise Continuously

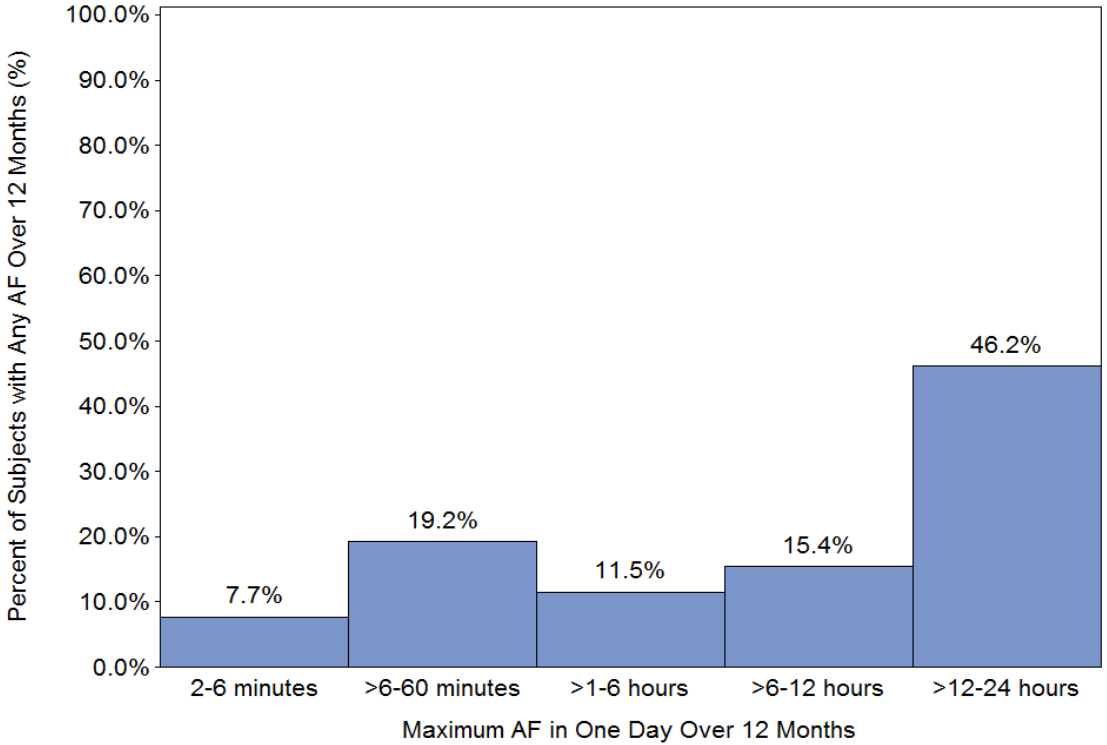
Primary Endpoint:
Detection of AF at
6 mo (8.9% vs. 1.4%)
HR: 6.43 (1.90, 21.74)
p = 0.0006

Secondary Endpoints:
Detection of AF at
12 mo (12.4% vs. 2.0%)
HR: 7.32 (2.57, 20.81)
p < 0.0001; at **36 mo**
HR 8.78 (3.47, 22.19)



Sanna T ; NEJM 2014;370;2478

CRYSTAL AF: AF Duration in ICM Arm
50% of all Patients had duration <12 hr, 25% <1 hr



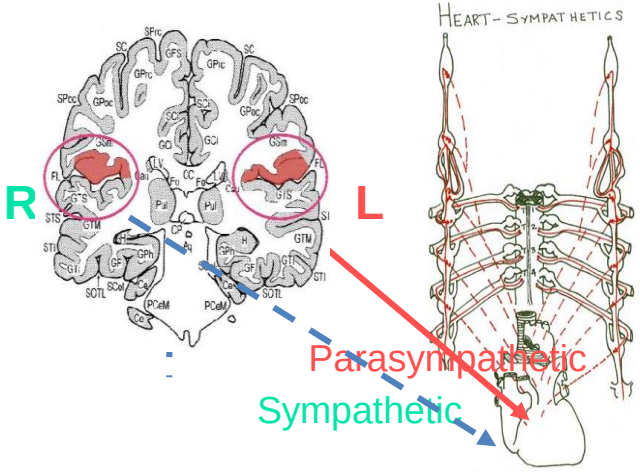
Passman R, ACC 2014

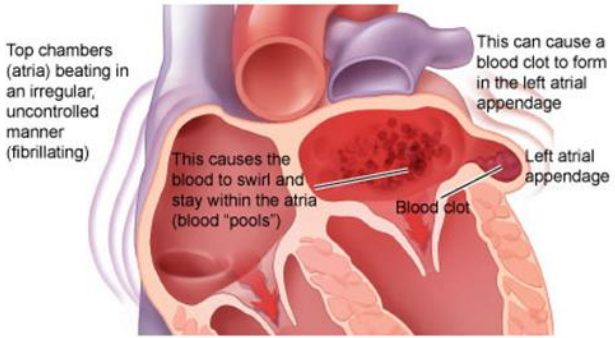
Independent Predictors of AF in the Cryptogenic Stroke Population

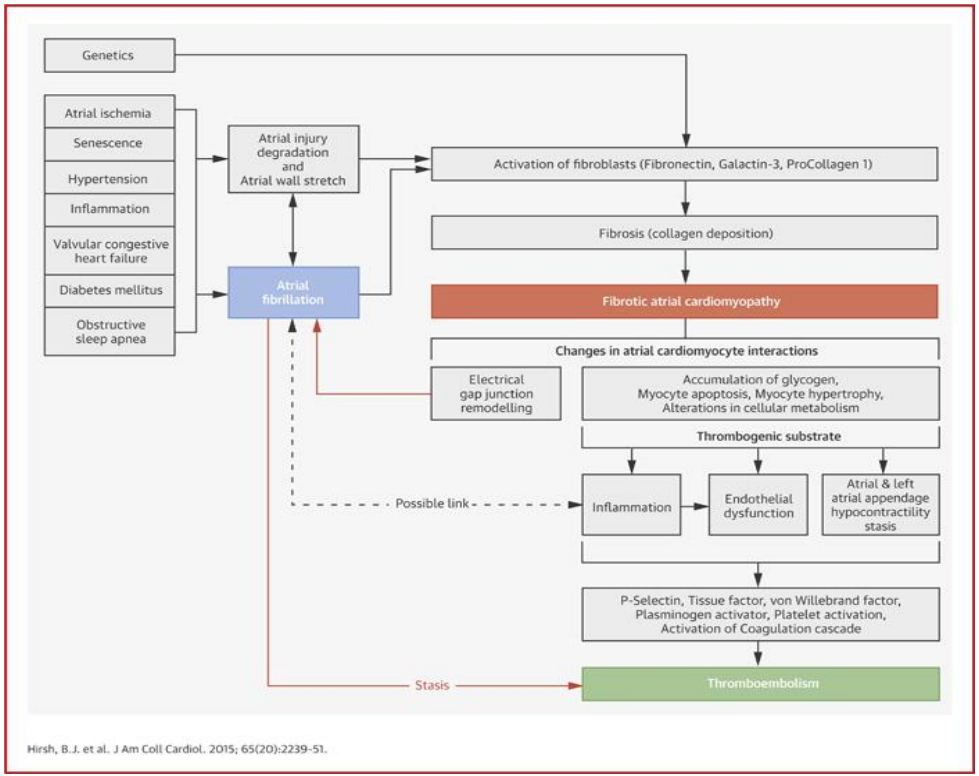
Variable	HR (95% CI)	p-value
Age (per 10 years)	1.91 (1.31, 2.80)	0.0009
PR interval (per 10 ms)		
On PR-lengthening medication	1.17 (1.02, 1.35)	0.02
Off PR-lengthening medication	1.58 (1.32, 1.90)	<0.0001

Assar M, Passman R:; ESC 2014

Mechanisms of AT/AF and Stroke: Mechanical Effects, Altered Expression, Stroke-Induced?

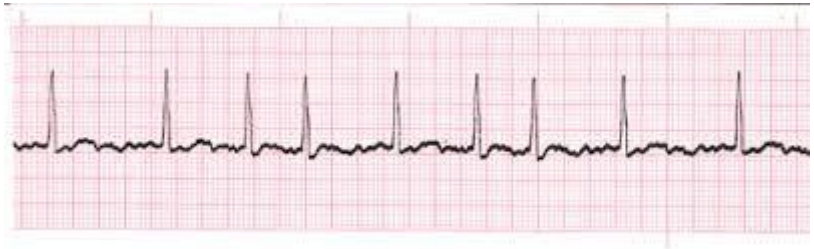


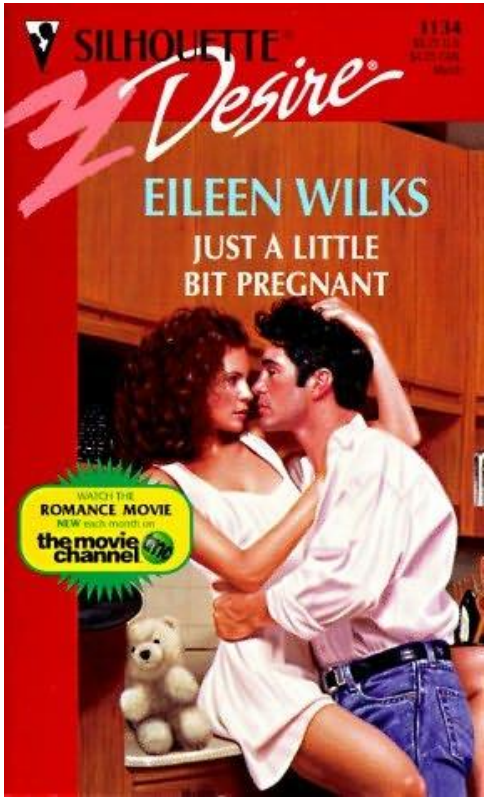




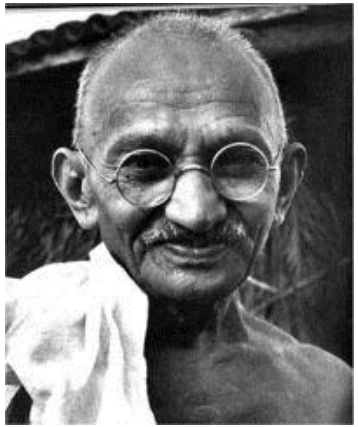
Can you have “just a little AF” and if so, what do you do about it?

- Signal vs. noise?
- Cause or effect? Does it matter?
- Treat everyone with anticoagulation?
- Is ablation sufficient?
- How much AF is enough to justify lifelong anticoagulation?

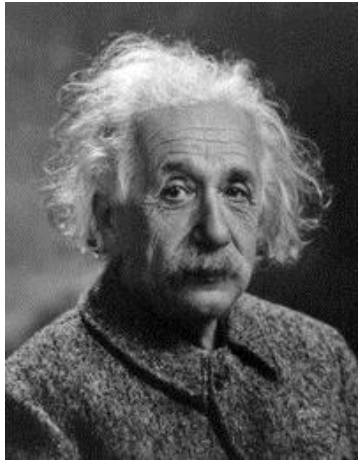




Thank You for Your Attention



"It is unwise to be too sure of one's own wisdom. It is healthy to be reminded that the strongest might weaken and the wisest might err"
– Mahatma Gandhi



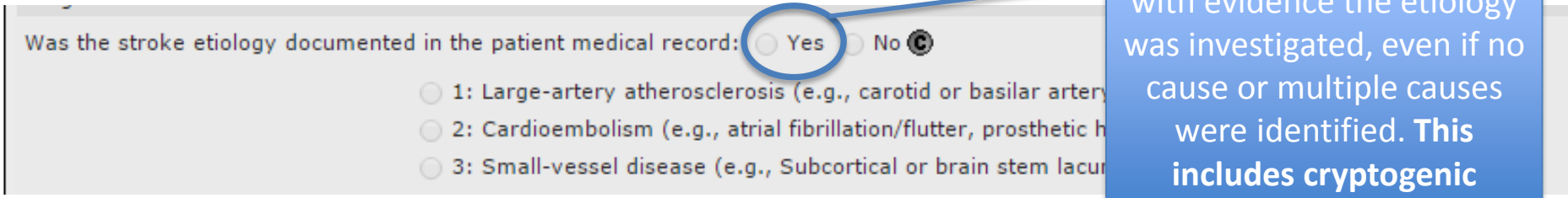
"A true genius admits that he knows nothing"
– Albert Einstein

Patient Management Tool Updates

Coding Instructions

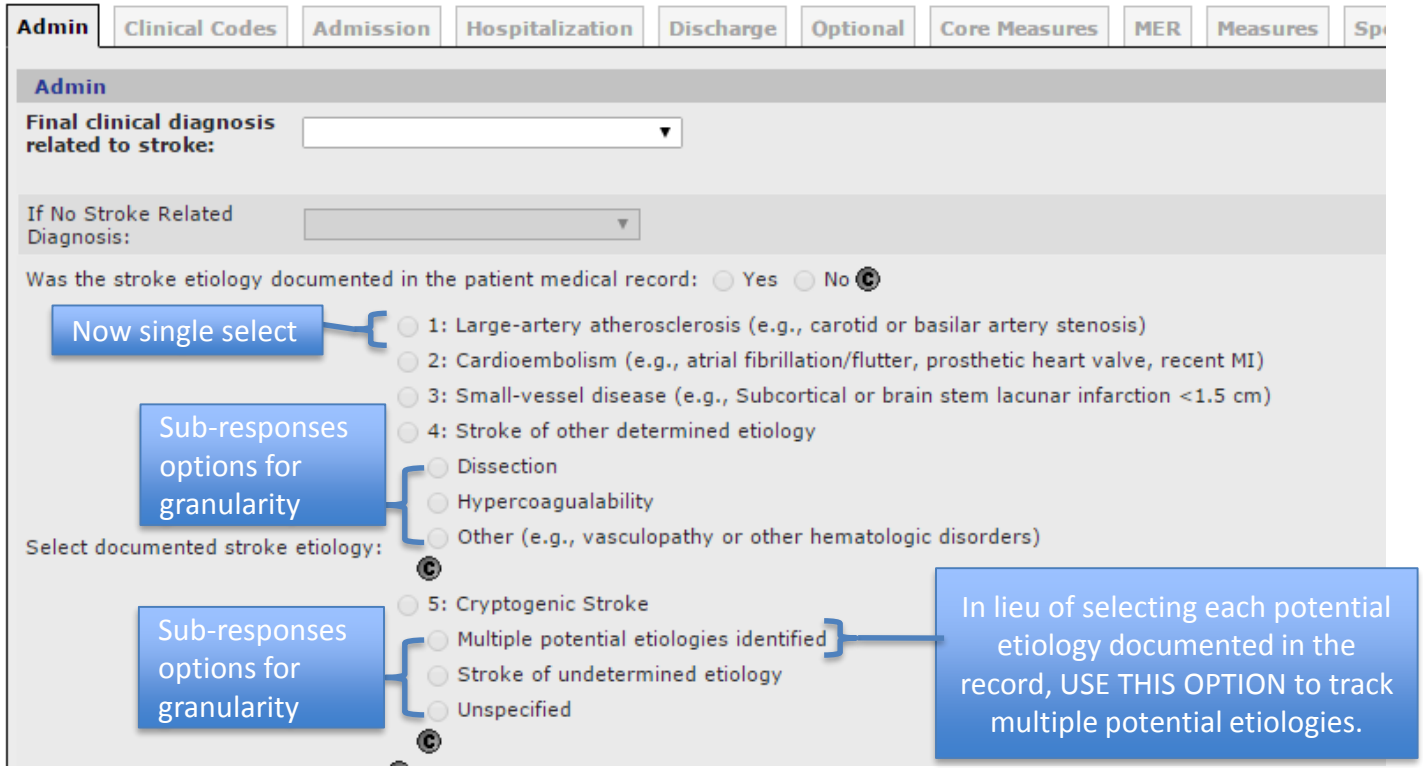
Was the stroke etiology documented in the patient medical?

Yes: There is clear documentation by a physician, nurse practitioner or physician's assistant in the patient medical record indicating that a potential underlying cause(s) of ischemic stroke was identified. This option should be selected when there is evidence in the medical record that the stroke etiology was investigated, even if no cause was identified despite the investigation or if multiple potential causes were identified.



Select "Yes" in patients with evidence the etiology was investigated, even if no cause or multiple causes were identified. **This includes cryptogenic stroke.**

Select documented stroke etiology

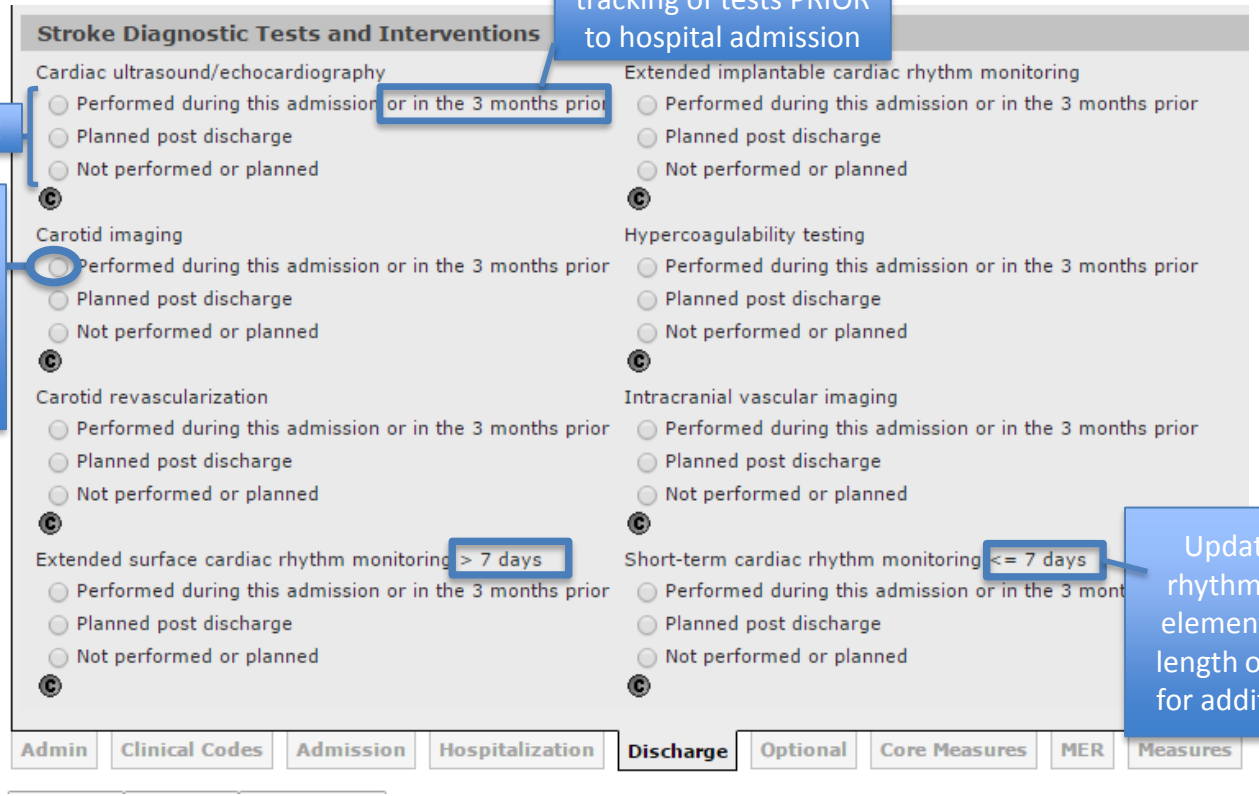


Select Documented Stroke Etiology- Cryptogenic

5: Cryptogenic stroke: A potential cause of stroke was not identified following thorough diagnostic evaluation: This includes a diagnosis of *undetermined cause* following diagnostic evaluation. Select this option only if testing to determine stroke etiology has been performed and does not confirm a likely cause or when multiple potential etiologies are identified. For most strokes, this includes cardiac ultrasound, extracranial arterial vessel imaging (carotid artery ultrasound, CTA or MRA). Patients with an *undetermined cause of stroke (cryptogenic stroke)* often have one or more risk factors of uncertain significance such as patent foramen ovale (PFO), heart failure with preserved ejection fraction, mitral annulus calcification, atrial or ventricular arrhythmias other than atrial fibrillation or flutter. The role of these risk factors in the cause of stroke is uncertain. Also select one of the below options to report additional information regarding the cause or potential causes:

- **Multiple potential etiologies identified:** Select this option when following diagnostic evaluation, a single etiology is uncertain between two or more possible causes.
- **Stroke of undetermined etiology:** Select this option when a potential etiology was not identified or documented following diagnostic evaluation.
- **Unspecified**: Select this option when there is no documentation of the results of the diagnostic evaluation.

Stroke Diagnostic Test and Interventions



Timing of Stroke Diagnostic Tests and Interventions

Performed during this admission or in the 3 months prior: The diagnostic test or intervention was performed during this episode of care or within three months prior to this admission. Select this option when a test was performed during admission and a repeat test is planned post discharge.

Planned post discharge: There is documentation in the patient medical record that the test or intervention was not done during the admission but is planned following hospital discharge. This may be indicated by a specific appointment time for the procedure, or by reference to the plan after discharge, such as "Cardiac monitoring for 28 days will be arranged post discharge", or "Patient will be referred for carotid endarterectomy after review of CT at 4 weeks post stroke to evaluate swelling and hemorrhagic transformation". If a TTE was performed during admission, but a repeat TTE or TEE is planned post discharge, do not select this option.

Not performed or planned: There is no documentation in the patient medical record that the test or interventions was performed during this episode of care or planned post-discharge.