Long Term Monitoring for Atrial Fibrillation in Cryptogenic Stroke

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Disclosures

Medtronic Honorarium

Objectives

01 Stroke Epidemiology

02 Diagnosis of Cryptogenic Stroke (CS)

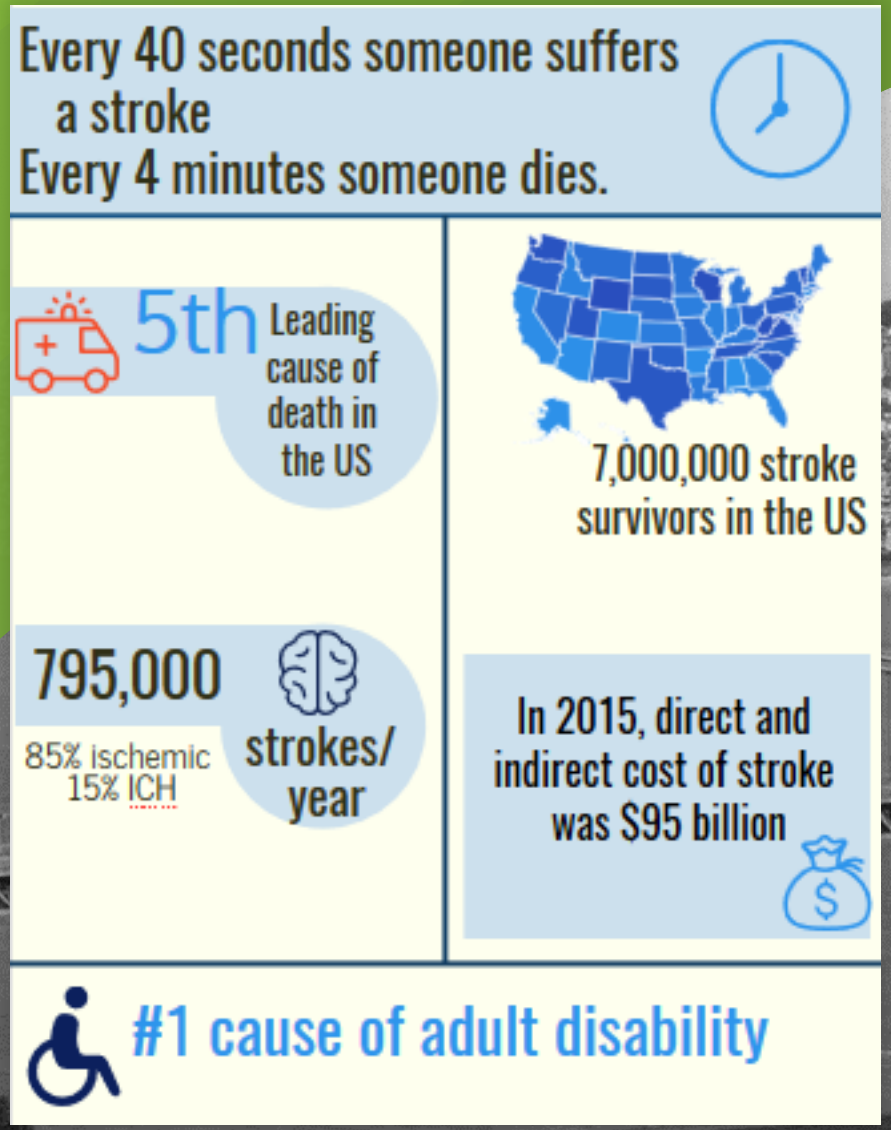
03 What about PFO's?

04 Long Term Cardiac Monitoring (LTM) for CS Patients

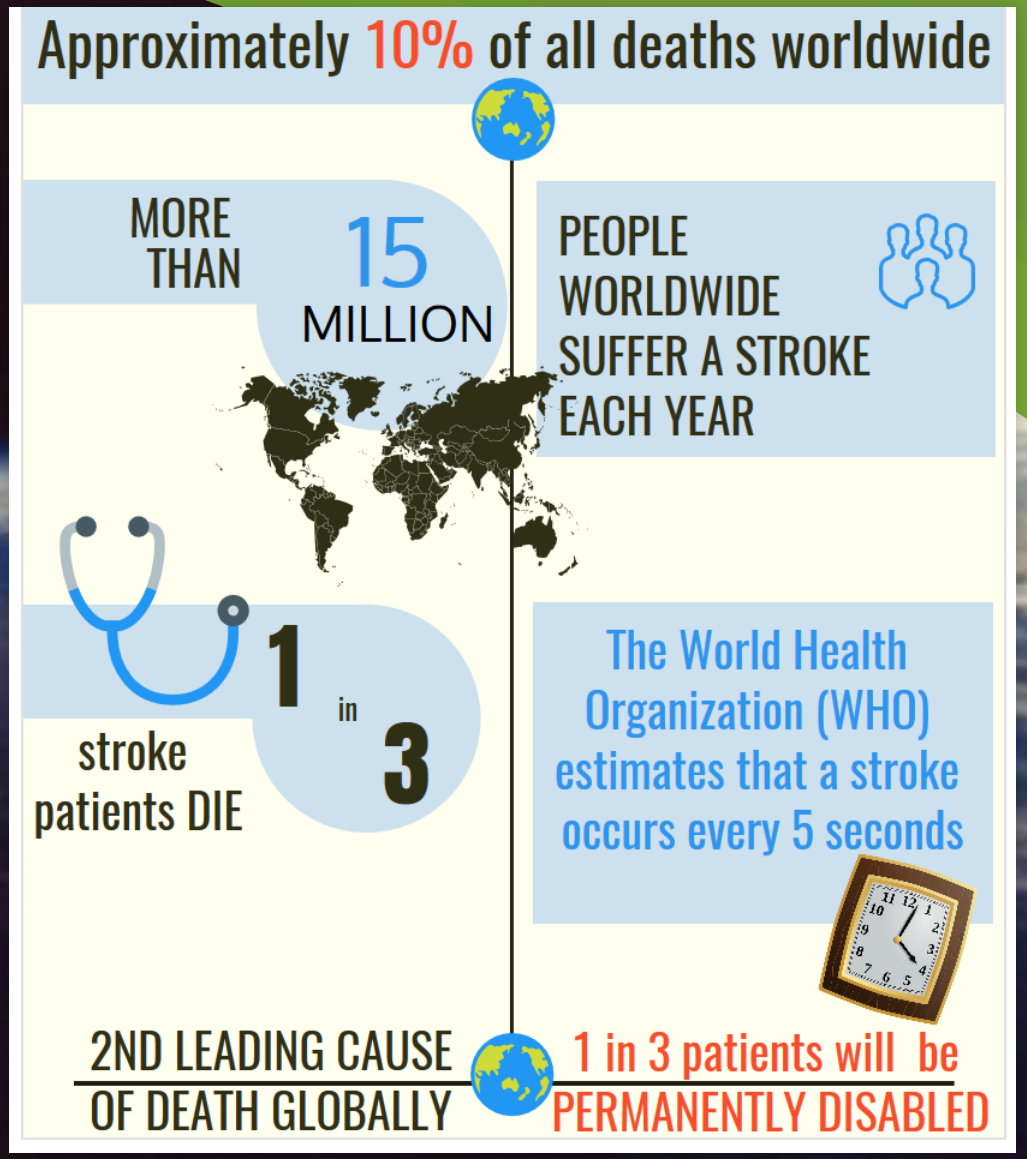
05 Case Example

06 Conclusion

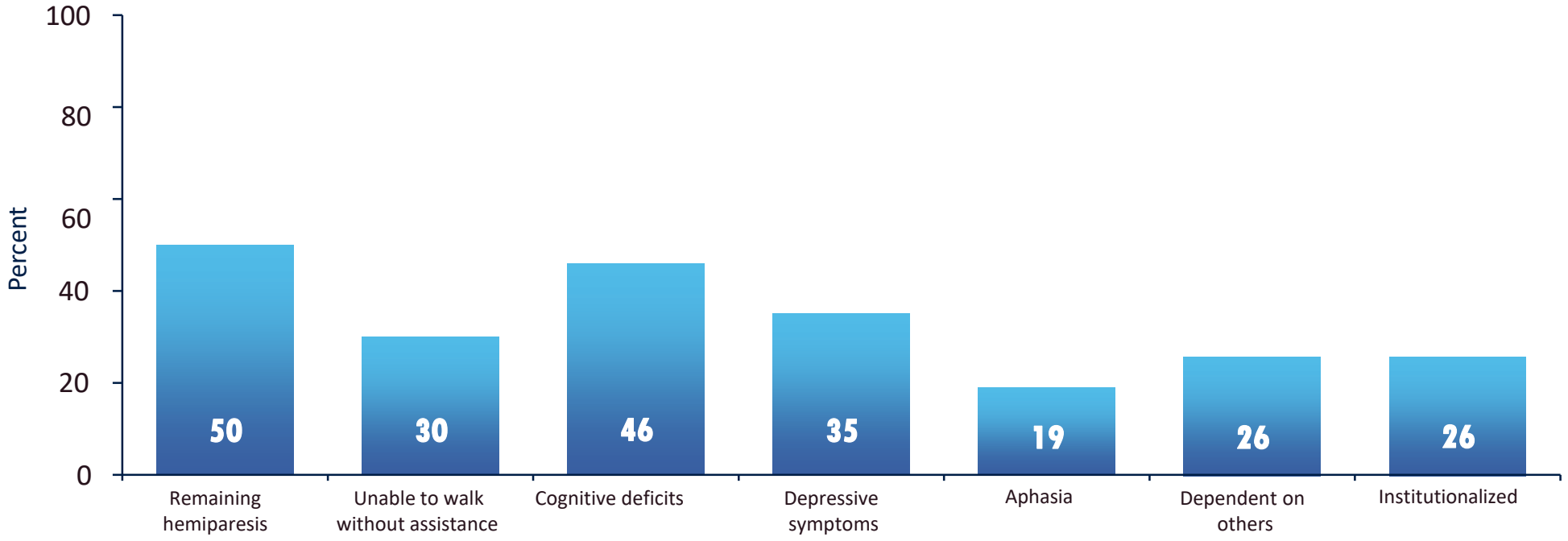
Statistics
United States



Statistics
World



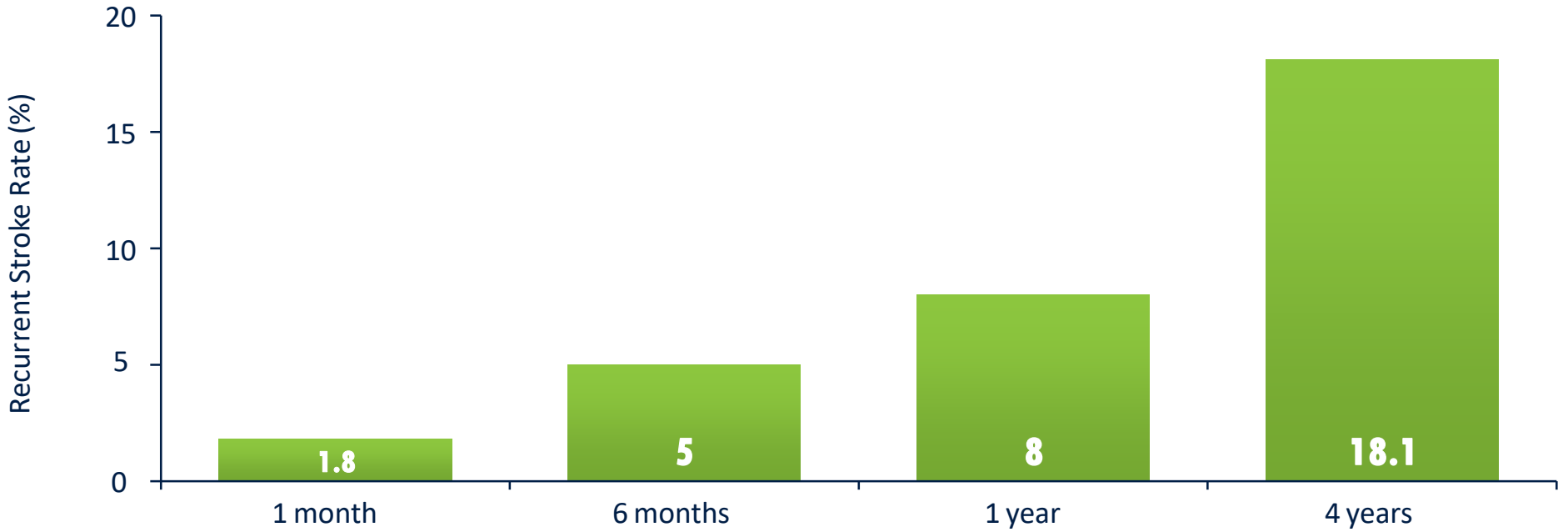
Disability Associated With Stroke



1. Go AS, et al. *Circulation.* 2013;127:e6-e245.

Recurrent Stroke

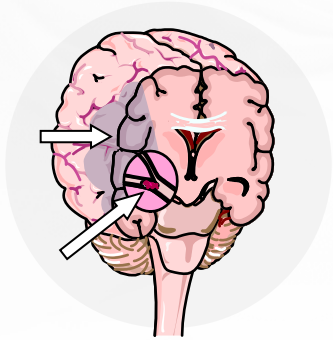
Recurrent Stroke Rate among Patients Discharged with a Primary Diagnosis of Stroke, South Carolina, 2002[1] (N = 10,399)



1. Feng W, et al. Neurology. 2010;74:588–593.

Stroke Subtypes

Focal Brain Dysfunction

Ischemic Stroke	Intracerebral Hemorrhage	Subarachnoid Hemorrhage
		
Clot occluding artery	Bleeding into brain	Bleeding around brain

Diffuse Brain Dysfunction

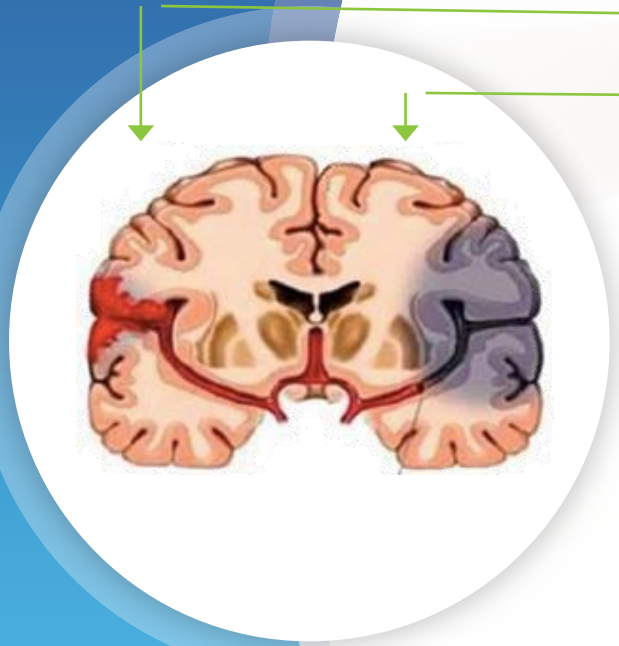
Ischemic Stroke:

Neurological dysfunction caused by focal cerebral, spinal, or retinal infarction.
Pathological, imaging, or other objective evidence in a defined vascular distribution.
85% of Strokes are Ischemic

Hemorrhagic Stroke:

Rupture of a blood vessel with bleeding into the brain parenchyma (ICH).
15% are Hemorrhagic

Stroke Etiologies

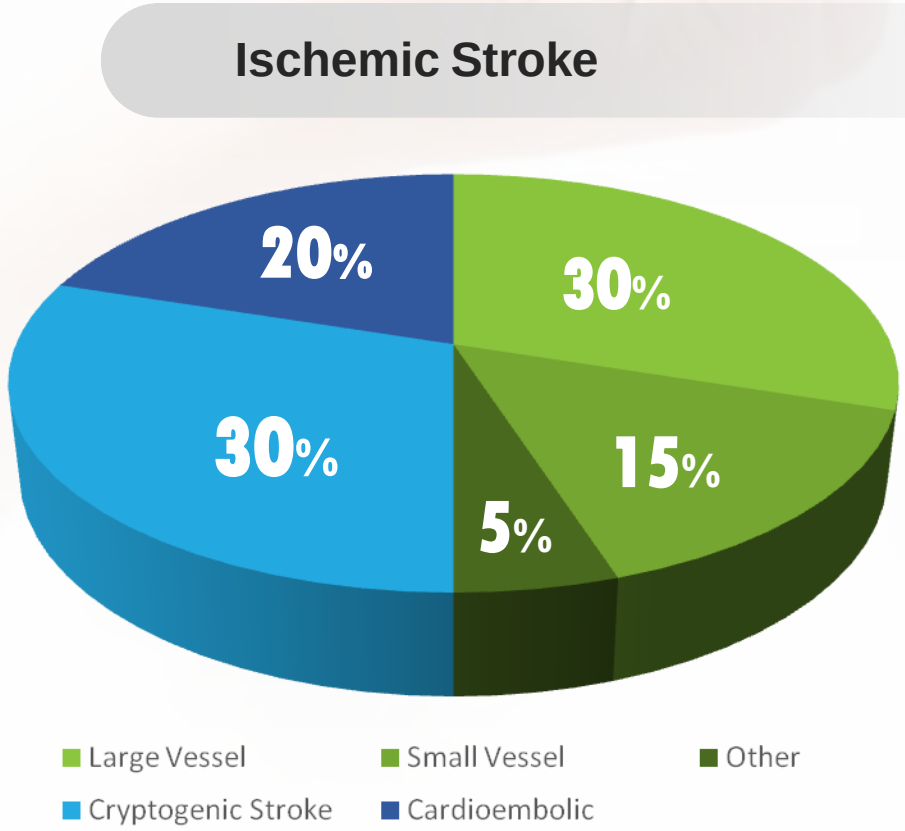


Etiology	%
Atherothrombotic Stenotic artery feeding area of infarction	**25-30**
Cardioembolic A thrombus or other material dislodges from the heart or aortic arch	**20**
Lacunar/Small Vessel Small; deep infarct	**15-20**
Other/Uncommon	**5-10**
Cryptogenic Unknown cause or ≥2 plausible causes	**25-30**

Adams HP Jr, et al, *Stroke*, **1993;24;35-41.** [33]
Foulkes MA, et al, *Stroke*, **1988;19;547-554.** [34]

Cryptogenic Stroke

- 678,000 ischemic strokes/year in the US[1]
- ~200,000 cryptogenic strokes yearly[1]



[1] Mozzafarian D, et al. *Circulation*. 2015;131:e29-e322.
[2] Kernan WN, et al. *Stroke*. 2014;45:2160-2236.
[3] Sacco RL, et al. *Ann Neurol*. 1989;25:382-390.
[4] Petty GW, et al. *Stroke*. 1999;30:2513-2516.
[5] Kolominsky-Rabas PL, et al. *Stroke*. 2001;32:2735-2740.
[6] Schulz UG, et al. *Stroke*. 2003;34:2050-2059.
[7] Schneider AT, et al. *Stroke*. 2004;35:1552-1556.
[8] Lee BI, et al. *Cerebrovasc Dis*. 2001;12:145-151.
[9] Sanna T, et al. *N Engl J Med*. 2014;370:2478-2486.

Definitions Of Cryptogenic Stroke

CLASSIFICATION SCHEME	REQUIRED WORK-UP
TOAST[1]	Not Specified
Causative Classification of Stroke (CCS)[2]	Brain CT/MR, 12-lead ECG, precordial echocardiogram, extra/intravascular imaging
Embolic strokes of undetermined source[3]	Brain CT/MR, 12-lead ECG, precordial echocardiogram, extra/intravascular imaging, cardiac monitoring for ≥ 24 hours
ASCO(D) phenotyping[4]	Does not include a cryptogenic stroke category

Adams HP, et al. *Stroke*. 1993;24:35-41.
Causative Classification System for Ischemic Stroke (CCS). Available at: https://ccs.mgh.harvard.edu/ccs_intro.php. Accessed April 15, 2015.
Hart RG, et al. *Lancet Neurol*. 2014;13:429-438.
Amarenco P, et al. *Cerebrovasc Dis*. 2013;36:1-5.

ESUS

Embolic Stroke of Undetermined Source

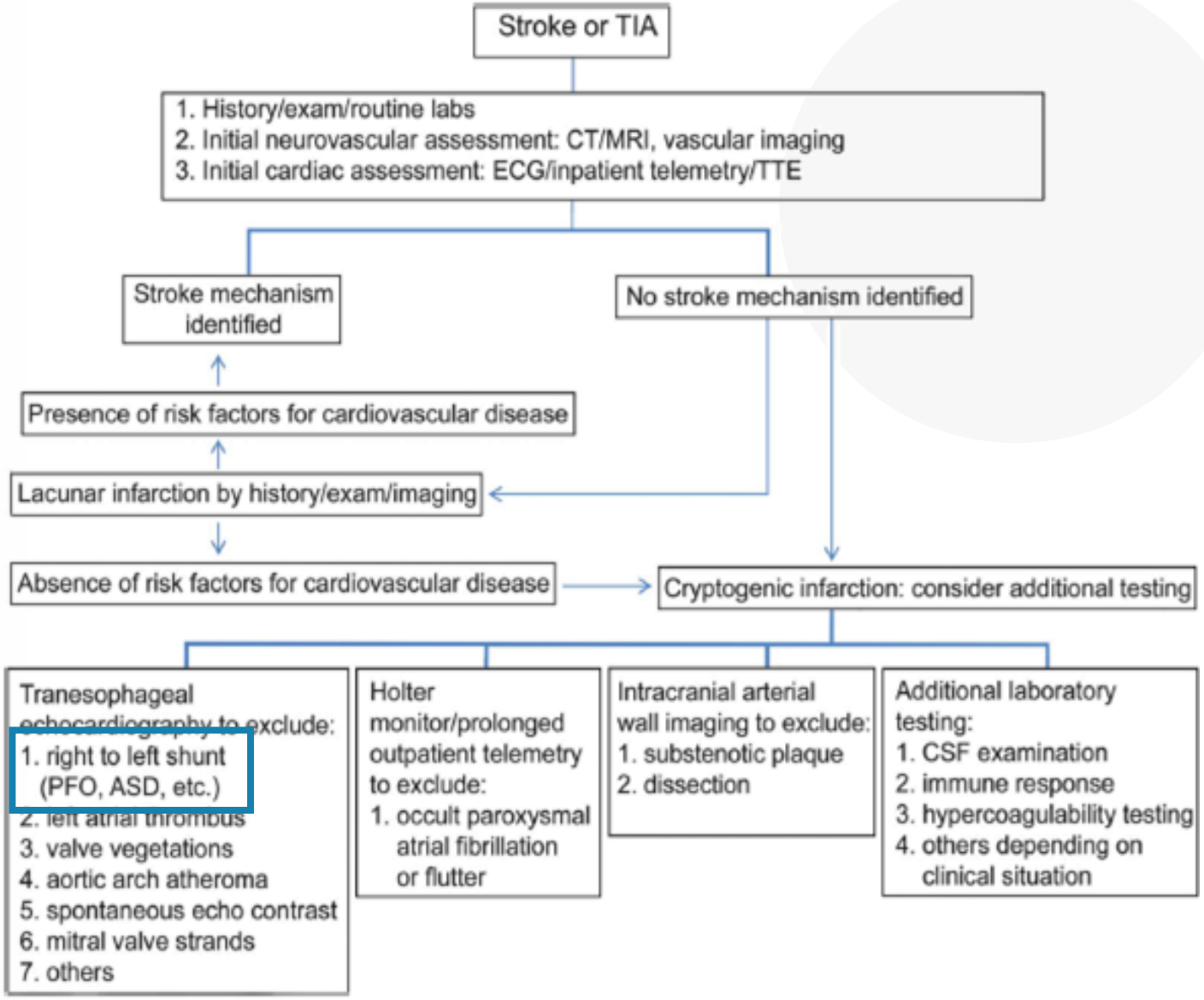
Definition:

Non-lacunar brain infarct without proximal arterial stenosis or cardioembolic sources implies that a full standard evaluation was done, whereas traditional definitions of cryptogenic stroke did not require a full evaluation.

Criteria:

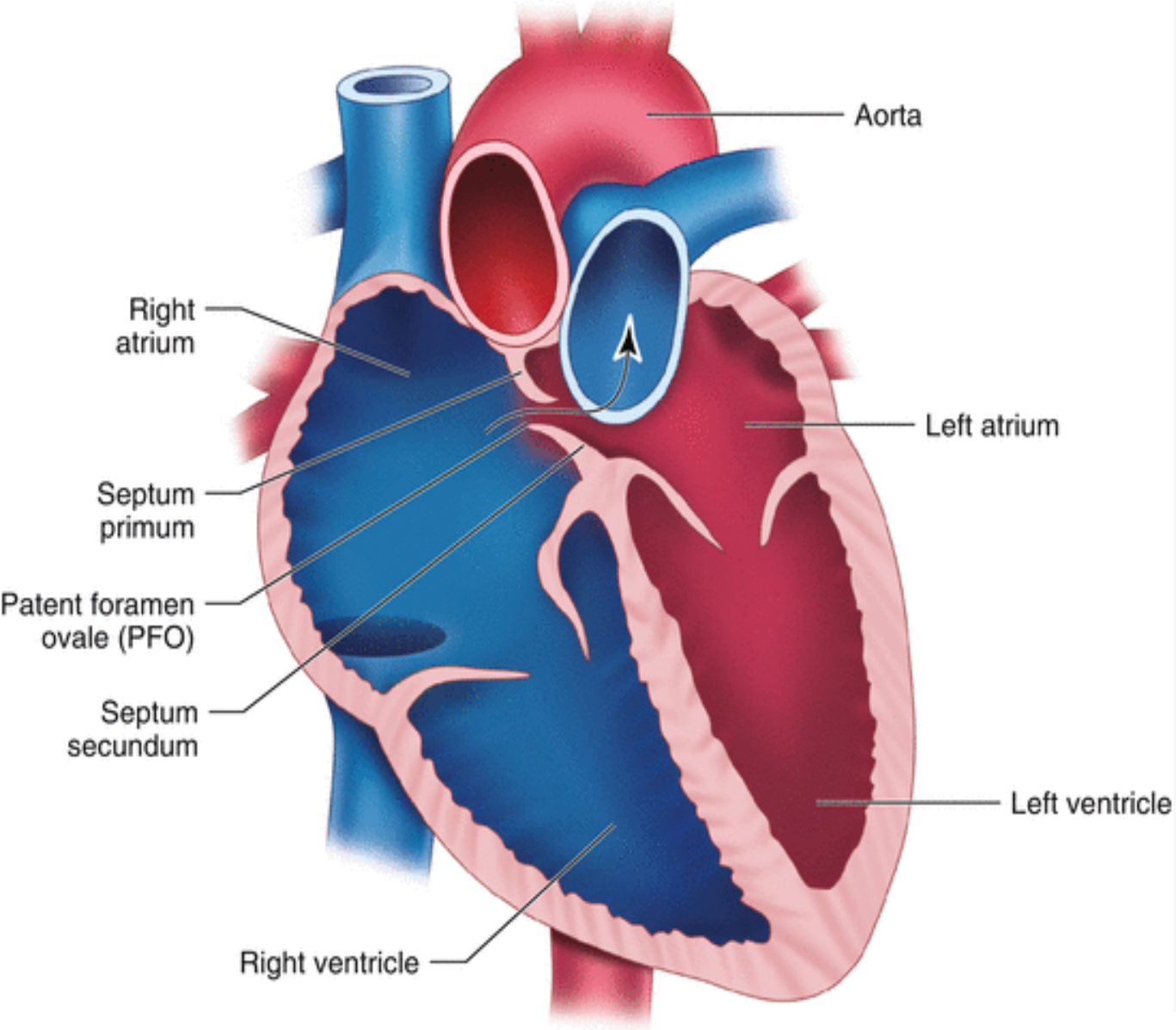
- Identified CT or MRI, not lacunar (subcortical infarct in the distribution of the small, penetrating cerebral arteries whose largest dimension is ≤1.5 cm on CT or ≤2.0 cm on MRI DWI)
- Absence of extracranial or intracranial atherosclerosis causing ≥50 percent luminal stenosis of the artery supplying the area of ischemia
- No major-risk cardioembolic source of embolism (ie, no permanent or paroxysmal atrial fibrillation, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumors, mitral stenosis, recent (within four weeks) myocardial infarction, left ventricular ejection fraction <30 percent, valvular vegetations, or infective endocarditis)
- No other specific cause of stroke identified (eg, arteritis, dissection, migraine, vasospasm, drug abuse)
- ESUS represents a subset of cryptogenic stroke and emphasizes the likelihood that most strokes of unexplained etiology are probably embolic from an unestablished source

Suggested approach for further evaluation of cryptogenic stroke



ASD = atrial septal defect; PFO = patent foramen ovale; TTE = transthoracic echocardiography.

Shadi Yaghi, and Mitchell S.V. Elkind Neurol Clin Pract 2014;4:386-393



- Connection between the left and right atria at the fossa ovale in fetal circulation remains open.
- 20-25% of the adult population
- Implicated in etiology of cryptogenic stroke
- 40% of adults with cryptogenic stroke
- Prevalence: greater in those <30 years old and less in those >80 years old.
- Decades of observational data up to 2012 suggested benefit of PFO closure in secondary stroke prevention of cryptogenic stroke compared with medical therapy arm but these observational studies were likely biased by patient selection, differential ascertainment of recurrent events and publication bias.

Study	Patients	Intervention	Comparison	Outcome	Conclusions
Furlan et al. (2012)[40] CLOSURE I trial	PFO with recent (<6 months) cryptogenic stroke or TIA (18–60 years old)	PFO closure with the STARFlex Septal Closure System®, clopidogrel for 6 months & aspirin indefinitely (n=447)	Warfarin or aspirin or both (n=462)	A composite of stroke/TIA, death	Lower rate of composite end point in closure group (5.5% vs. 6.8%) but statistically not significant (2-year mean follow-up)
Meier et al. (2013)[41] PC trial	PFO with cryptogenic stroke, TIA, or a peripheral thromboembolic event (<60 years old)	PFO closure with AMPLATZER PFO Occluder®, ticlopidine/clopidogrel for 1–6 months & aspirin for ≥5 months (n=204)	Antiplatelet therapy or oral anticoagulation (n=210)	A composite of death, nonfatal stroke, TIA, or peripheral embolism	Lower rate of composite end point in closure group (3.4% vs. 5.2%) but statistically not significant (4-year mean follow-up)
Mas et al. (2017)[4] CLOSE trial	PFO with recent (<6 months) stroke attributed to PFO, and atrial septal aneurysm or large interatrial shunt (16–60 years old)	PFO closure, DAPT for 3 months followed by antiplatelet therapy indefinitely (n=238)	Antiplatelet therapy only arm (n=235) & oral anticoagulation arm (n=187)	Occurrence of fatal or nonfatal stroke	Significantly lower stroke risk in closure group compared to antiplatelet arm (0% vs. 6%) but an increased risk of atrial fibrillation after closure (4.6% vs. 0.9%). Stroke rate 1.5% in anticoagulation group vs. 3.8% in the matched antiplatelet-only subcohort (5-year mean follow-up)
Saver et al. (2017)[5] RESPECT trial	PFO with cryptogenic ischemic stroke (<270 days) (18–60 years old)	PFO closure with the AMPLATZER PFO Occluder®, DAPT for 1 month followed by aspirin only for 5 months, then antithrombotic use per treating physician (n=499)	Any antiplatelet therapy or oral anticoagulation (n=481)	A composite of recurrent nonfatal or fatal ischemic stroke, or early death after randomization	Significantly lower rate of recurrent ischemic strokes (3.6% vs. 5.8%) but higher venous thromboembolism in the closure arm (3.4% vs. 0.8%) (5.9-year median follow-up)
Søndergaard et al. (2017)[6] Gore REDUCE Clinical Study	PFO with cryptogenic stroke (<180 days), 81% with moderate/large interatrial shunts (18–59 years old)	PFO closure with the Helex Septal Occluder® or the Cardioform Septal Occluder®, 300 mg clopidogrel load then antiplatelet monotherapy (n=441)	Any antiplatelet monotherapy (n=223)	Co-primary end points: (1) Clinical ischemic stroke, (2) composite of clinical ischemic stroke or silent brain infarction detected on imaging	Significantly lower clinical ischemic stroke (1.4% vs. 5.4%) but higher rates of device complications (1.4%) and atrial fibrillation (6.6% vs. 0.4%) in the closure arm (3.2-year median follow-up)

PFO Trials

LIMITATIONS:

Trials **did not require prolonged cardiac monitoring** to rule out AF as a stroke etiology to consider inclusion into the ‘cryptogenic stroke’ category.

Cryptogenic population was not selective enough. ESUS subset of cryptogenic stroke is radiographically selective and requires thorough diagnostic testing to ensure truly no underlying explanation for stroke. The ESUS definition does not exclude presence of PFO, and so limiting inclusion to ESUS would assess the most appropriate patient population.

All primary outcomes from the clinical trials included recurrent strokes of all causes and not just cryptogenic stroke.

What have we learned ?

TABLE 1. UNIQUE LESSONS LEARNED FROM INDIVIDUAL TRIALS

RESPECT (long term)	• Long-term follow-up is critical with low event rates to prove a treatment effect. US-based trials have a problem with retention in long-term trials. • Atrial septal aneurysm and large shunts predict a greater treatment effect. • Greater treatment effect for PFO closure was also suggested when compared with antiplatelet therapy, not anticoagulation treatment. • Deep venous thrombosis and pulmonary embolism were more frequent in the device arm but appeared related to a history of deep vein thrombosis and the medical arm having 20% of patients treated with anticoagulation, which was allowed. • Patients had a higher burden of cardiovascular risk factors and a significant proportion of recurrent strokes had a defined mechanism, especially when patients crossed the 60 years of age threshold.
REDUCE	• Overall successful primary outcomes, the clear benefit in reducing recurrent strokes, and the good safety profile will likely lead to approval of the Cardioform Septal Occluder. • The number needed to treat at only 2 years was approximately 28. • Despite its conformable nature, atrial fibrillation was still more frequent in the device arm. • Brain imaging detected additional recurrent strokes not detected clinically.
CLOSE	• The dramatic results appeared linked to study design with inclusion of only patients with atrial septal aneurysm or large shunts, patients with a low burden of traditional vascular risk factors, comparison of PFO closure plus antiplatelet therapy to antiplatelet therapy only, and excellent trial conduct with minimal missing data. • A trend showed reduced recurrent stroke rates in patients treated with anticoagulants versus antiplatelet agents. • Atrial fibrillation was more common in the device arm at 4.6%. • There is a suggestion that treatment benefit is a class effect.

Wiktor, Carrol. Practical Neurology January 2018.

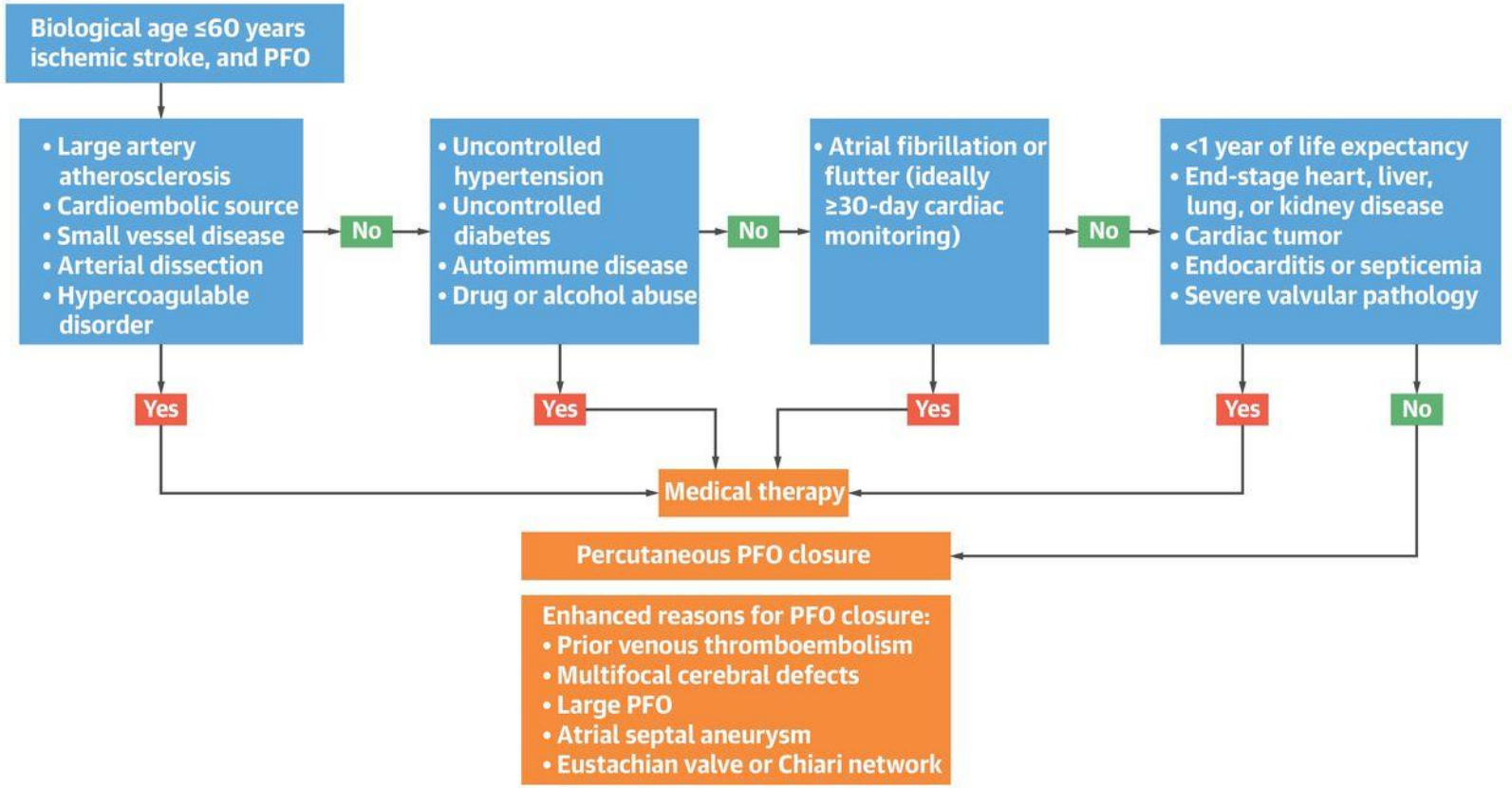
PFO Guidelines

Guideline	Year	Recommendation
European Society of Cardiology[27]	2010	In the case of documented systemic embolism probably caused by paradoxical embolism, isolated device closure of ASD/PFO should be considered (*Class IIa; Level of Evidence C*)
American College of Chest Physicians (ACCP)[25]	2012	In patients with cryptogenic stroke and PFO or atrial septal aneurysm, who experience recurrent events despite aspirin therapy, we suggest treatment with VKA therapy (target INR 2.5; range 2.0–3.0) and consideration of device closure over aspirin therapy (Grade 2C) In patients with cryptogenic stroke and PFO, with evidence of DVT, we recommend VKA therapy for 3 months (target INR 2.5; range 2.0–3.0) (Grade 1B) and consideration of device closure over no VKA therapy or aspirin therapy (Grade 2C)
National Institute for Health and Care Excellence (NICE)[28]	2013	Evidence on the safety of percutaneous closure of patent foramen ovale to prevent recurrent cerebral embolic events shows serious but infrequent complications. Evidence on its efficacy is adequate. Therefore this procedure may be used with normal arrangements for clinical governance, consent, and audit.
American Heart Association/ American Stroke Association (AHA/ASA)[24]	2014	For patients with a cryptogenic ischaemic 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*). In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT (*Class IIb; Level of Evidence C*).
American Academy of Neurology (AAN)[23]	2016	Clinicians should not routinely offer percutaneous PFO closure to patients with cryptogenic ischaemic stroke outside of a research setting (Level R). For recurrent strokes despite adequate medical therapy with no other mechanism identified, clinicians may offer the AMPLATZER PFO Occluder if it is available (Level C)

DVT, deep vein thrombosis; INR, international normalized ratio; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

Ahmad Y, et al. Patent foramen ovale closure vs. medical therapy for cryptogenic stroke: a meta-analysis of randomized controlled trials. Eur Heart J. 2018;39(18):1638–49

CENTRAL ILLUSTRATION: Evidence-Based Algorithm for PFO Closure in Ischemic Stroke Patients for Highest Clinical Yield, Based on Randomized Trials



Mojadidi, M.K. et al. J Am Coll Cardiol. 2018;71(9):1035-43.

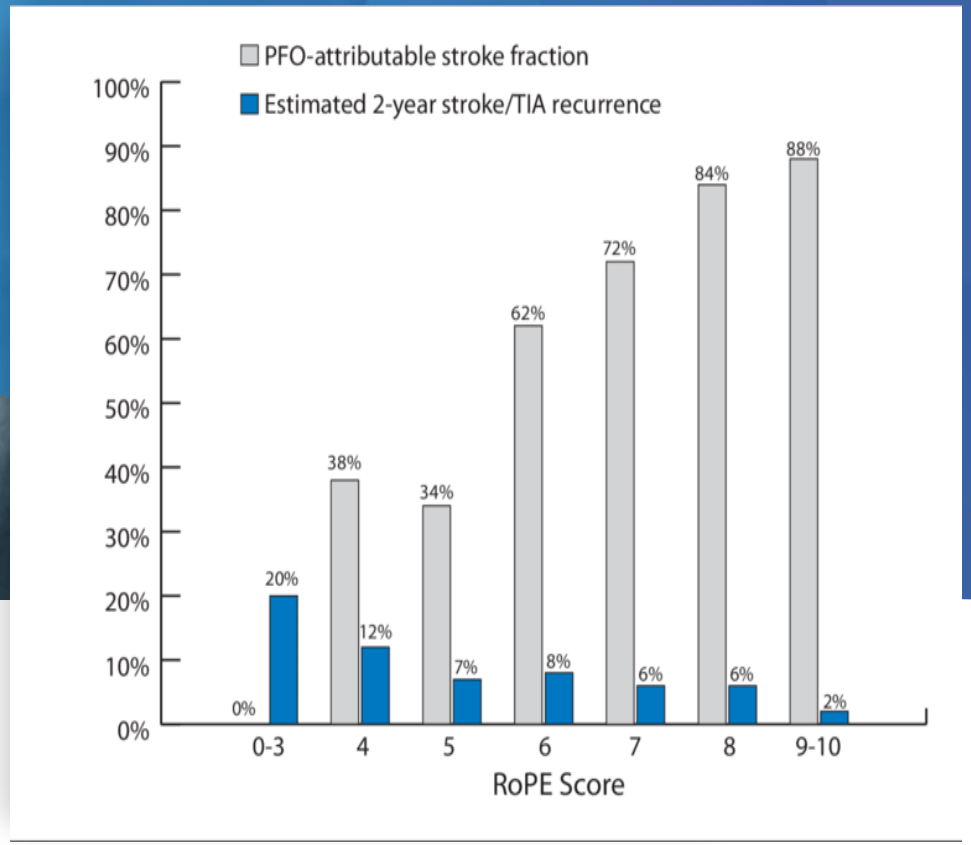
RoPE SCORE

(Risk of Paradoxical Embolism)

Table 4 RoPE score calculator

Characteristic	Points	RoPE score
No history of hypertension	1	
No history of diabetes	1	
No history of stroke or TIA	1	
Nonsmoker	1	
Cortical infarct on imaging	1	
Age, y		
18–29	5	
30–39	4	
40–49	3	
50–59	2	
60–69	1	
≥70	0	
Total score (sum of individual points)		
Maximum score (a patient <30 y with no hypertension, no diabetes, no history of stroke or TIA, nonsmoker, and cortical infarct)		10
Minimum score (a patient ≥70 y with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct)		0

Abbreviation: RoPE = Risk of Paradoxical Embolism.



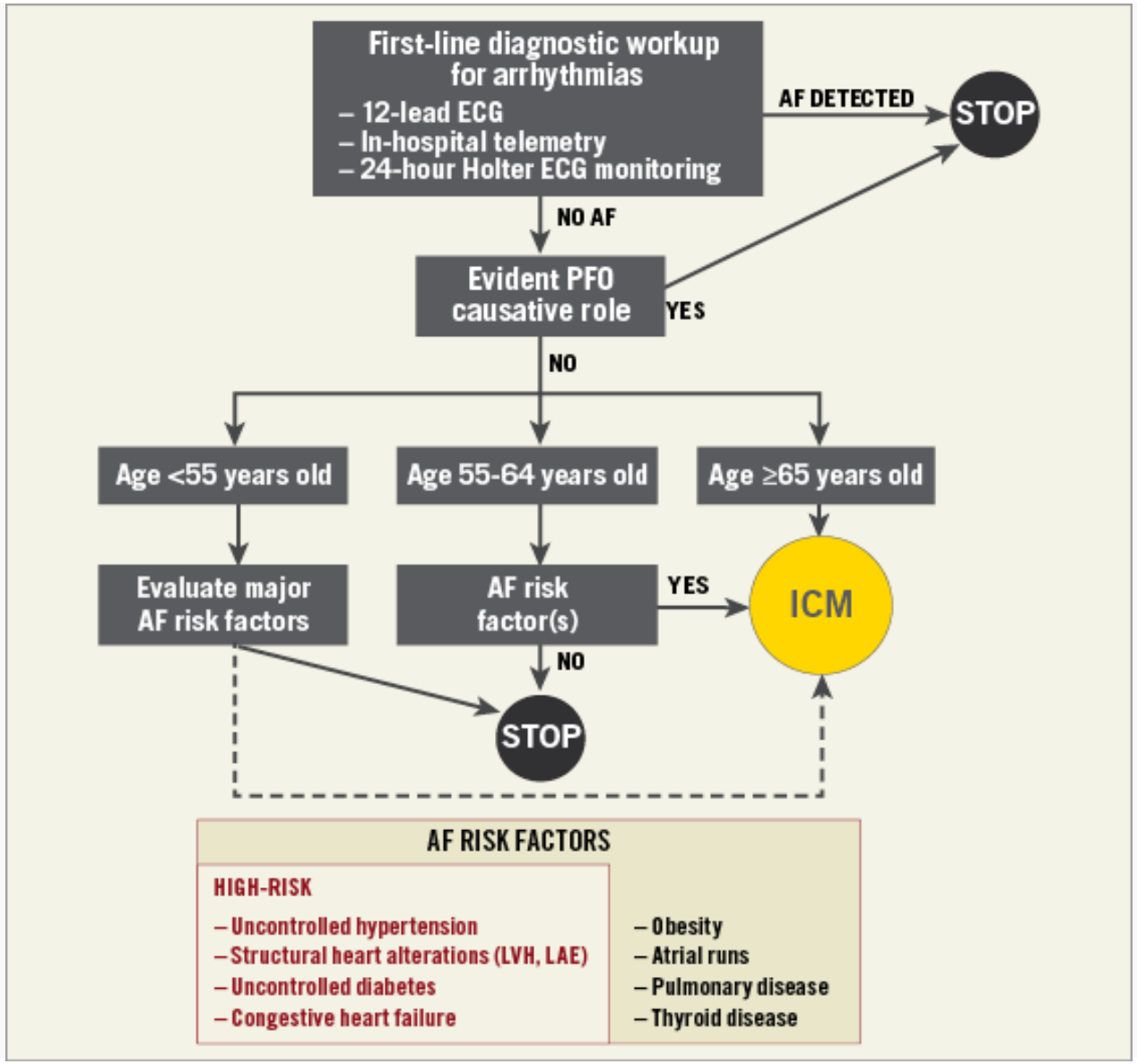
[1] Kent DM, Ruthazer R, Weimar C, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. *Neurology*. 2013;81(7):619-25.

European Position Paper on Management of PFO

- Risk of recurrence: low based on observational/randomized studies.
- Recurrent stroke risk on medical therapy of 4.6% over 3.8 years of follow-up.
- NNT to prevent 1 stroke:
  - All patients: 37 (95% [CI], 26-68)
  - Patients with high-risk PFO: 21 (95% CI, 16-61)
- ASA, moderate-to-severe shunt, atrial septal hypermobility: strongly associated with causal role of PFO.
- ASA: convey a higher risk of recurrence
- RoPE score: should only be used as part of comprehensive evaluation.
- Interdisciplinary collaboration (interventional cardiologist, neurologist) and active collaboration with patient are key.

European Position Paper on the Management of Patients With Patent Foramen Ovale. General Approach and Left Circulation Thromboembolism. Eur Heart J 2018;Oct 25

European Position Paper on Management of PFO



PFO Case Examples

Case 1	Case 2	Case 3
30 yo female with no PMH, L MCA stroke. 2decho with + bubble, TEE with large PFO + ASA.	55 yo male with multifocal strokes, HTN, DM, HLD 2decho w/o moderate sized PFO. TEE w/ moderate sized PFO without high risk features.	70 yo female with HTN/HLD, R PCA stroke, small-moderate PFO, no high risk features.
High Risk PFO: large, ASA High RoPE Score No risk factors	<55-64 years old Moderate risk PFO Traditional risk factors	>65yo No high risk PFO features Traditional risk factors
30 days of monitoring was negative, PFO closed.	Refer for ILR. If no AFIB > 6 months, closure considered, patient deferred.	Refer for ILR. Reasonable to discuss closure if 6-12 months no AFIB.

PFO: Summary

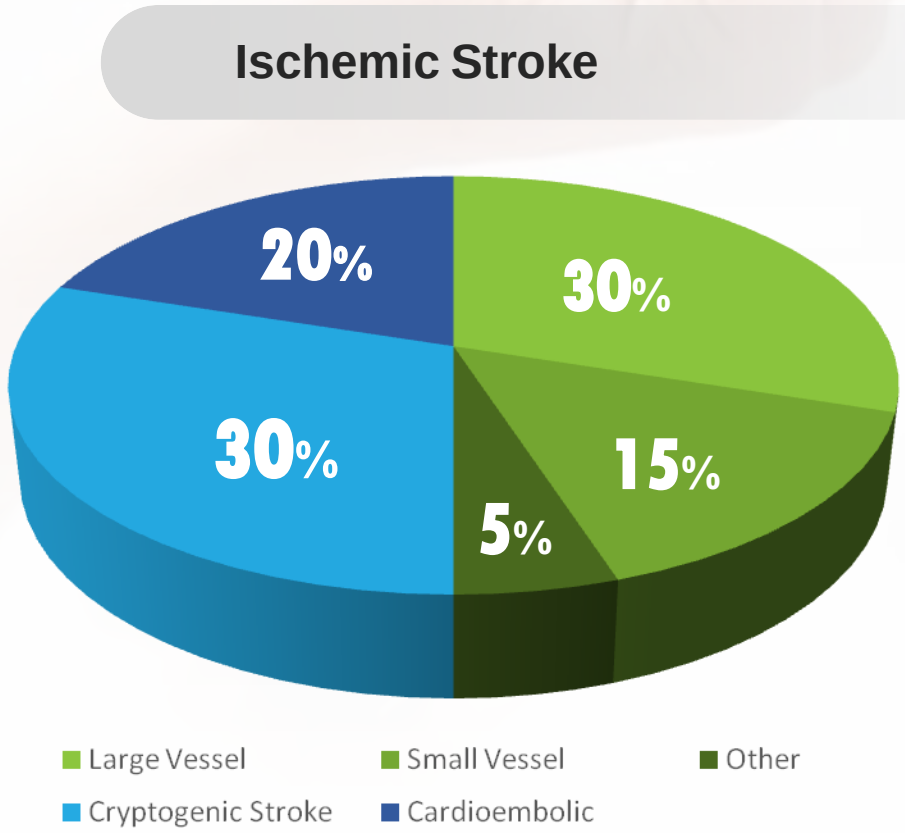
PFO closure is of moderate benefit compared to antiplatelet therapy alone in the prevention of recurrent ischemic stroke in adults up to 60 years of age.

Patient selection should be limited to patients who meet strict criteria and based on shared decision making with a cardiologist, neurologist, and patient.

LTM should be considered.

Cryptogenic Stroke

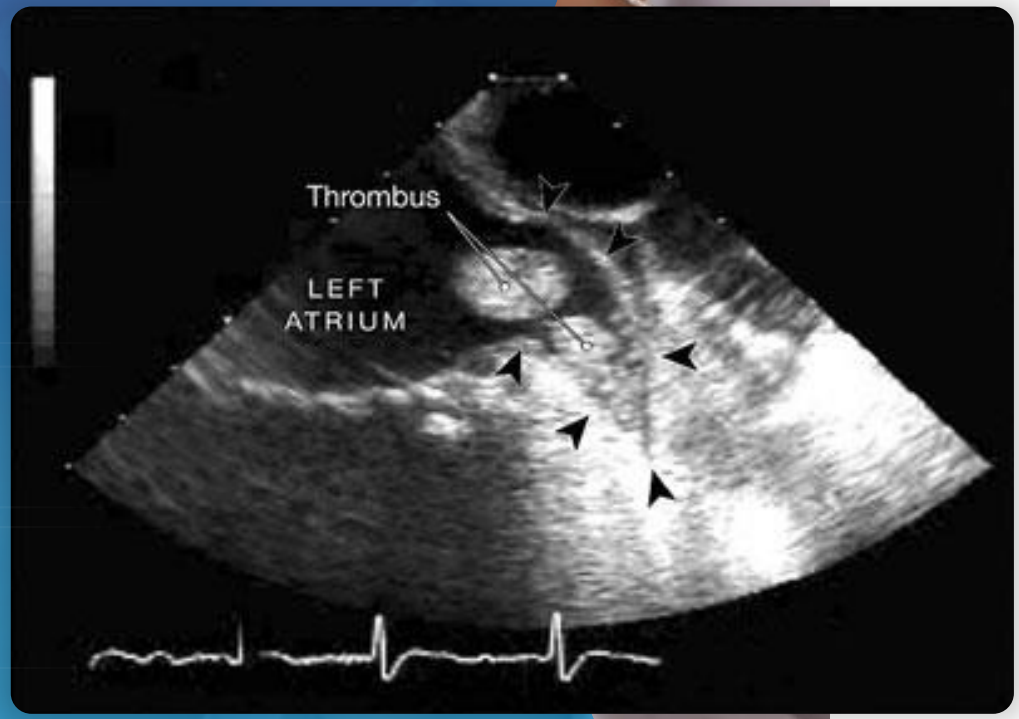
- 678,000 ischemic strokes every year in the US[1]
  - Leading cause of disability in the US and worldwide
- ~200,000 cryptogenic strokes yearly[1]
- Most cryptogenic stroke patients receive anti-platelet for secondary prevention[2]
- Long-term monitoring reveals AF in ~30% of cryptogenic stroke patients[3-9]
  - These patients benefit from anticoagulant therapy



[1] Mozzafarian D, et al. *Circulation*. 2015;131:e29-e322.
[2] Kernan WN, et al. *Stroke*. 2014;45:2160-2236.
[3] Sacco RL, et al. *Ann Neurol*. 1989;25:382-390.
[4] Petty GW, et al. *Stroke*. 1999;30:2513-2516.
[5] Kolominsky-Rabas PL, et al. *Stroke*. 2001;32:2735-2740.
[6] Schulz UG, et al. *Stroke*. 2003;34:2050-2059.
[7] Schneider AT, et al. *Stroke*. 2004;35:1552-1556.
[8] Lee BI, et al. *Cerebrovasc Dis*. 2001;12:145-151.
[9] Sanna T, et al. *N Engl J Med*. 2014;370:2478-2486.

Risk For Stroke In Patients With Atrial Fibrillation

- AF is the most common cause of embolic stroke[1]
- 15% of all strokes in the US can be attributed to AF[1]
- AF is associated with an increase in mortality, from 1.3-2 times[2]



1 Nattel. Lancet 2006;367:262-272
2.Page. N Engl J Med 2004;351:2408-16

Risk For Stroke In Patients With AF

5-FOLD

increase in ischemic stroke risk for AF patients.[1]

2X

more likely for AF-related ischemic stroke to be fatal as non-AF stroke.[2]

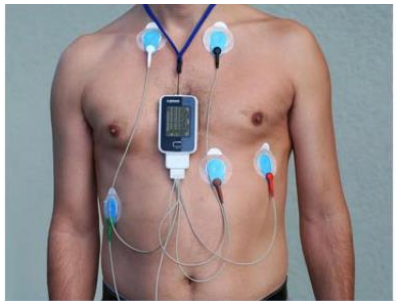
67%

decrease in stroke risk with oral anticoagulants.[3]

[1] Wolf PA, et al. *Arch Intern Med*. 1987;147:1561-1564.
[2] Lin HJ, et al. *Stroke*. 1996; 27:1760-1764.
[3] Stroke Prevention in Atrial Fibrillation Study. *Circulation*. 1991;84:527-539.

How Can We Find It??

Cardiac Monitoring



Conventional Monitoring Strategies

Holter Monitor

- 24-48 hours of monitoring
- External loop recorder
- Saves all cardiac rhythm data

Event Recorder

- Up to 30 days of monitoring
- Event-triggered loop recorder
- Saves events only
- 62% patient compliance[1]

Mobile Cardiac Telemetry

- Up to 30 days of monitoring
- Ambulatory event monitor
- Saves all cardiac rhythm data
- 53-90% patient compliance*[2-5]

* Dependent on type of MCT.

1. Vasamreddy CR, et al. *J Cardiovasc Electrophysiol*. 2006;17:134-139;
2. Gladstone DJ, et al. *N Engl J Med*. 2014;370:2467-2477;
3. Rosenberg MA, et al. *Pacing Clin Electrophysiol.* 2013;36:328-333;
4. Kamel H, et al. *Stroke.* 2013;44:528-530.
5. Shinbane JS, et al. Heart Rhythm Society 2013 34th Annual Scientific Sessions, Volume 10, Issue 5S, 2013.

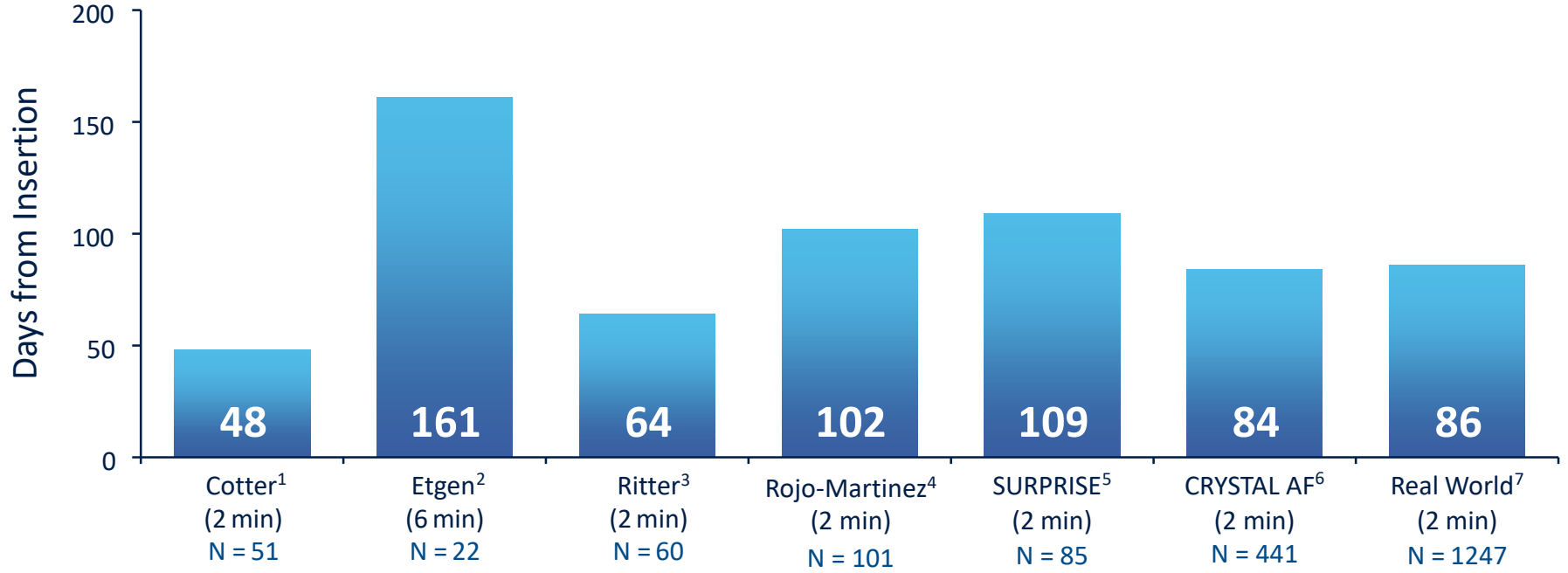
Insertable Cardiac Monitors (ICM)

Multiple studies have assessed the ability of ICMs to detect AF in patients with cryptogenic stroke

- Cotter study
- **CRYSTAL AF**
- SURPRISE
- Ritter study
- Etgen study
- Rojo-Martinez study

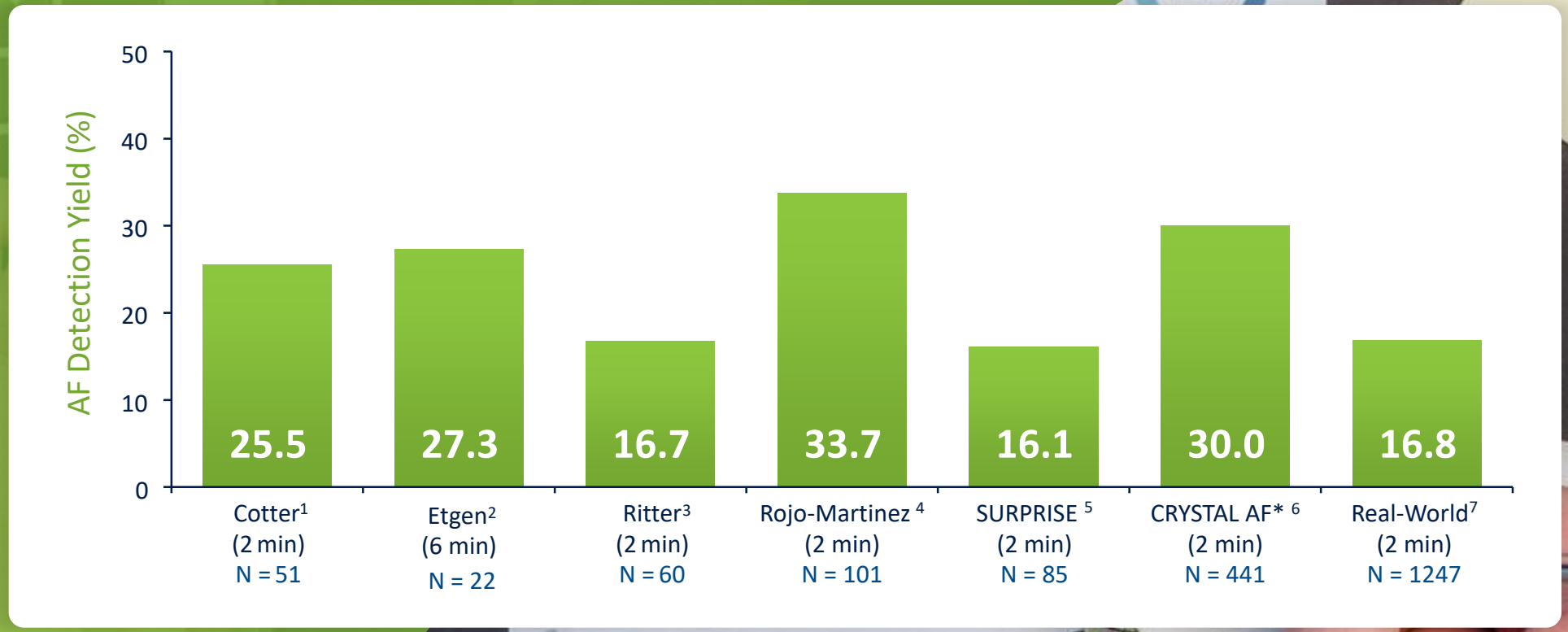
Summary:

Days To Detection of AF in Clinical Studies Of ICMs[1-7]



1. Cotter PE, et al. *Neurology*. 2013;80:
2. Etgen T, et al. *Stroke*. 2013;44:2007-
3. Ritter MA, et al. *Stroke*. 2013;44:144
4. Rojo-Martinez E, et al. *Rev Neurol*. 2
5. Christensen LM, et al. *Eur J Neurol*. 2
6. Sanna T, et al. *N Engl J Med*. 2014;3
7. Rogers J et al, American Academy of http://www.abstractsonline.com/pp

Summary:
AF Detection Yield in Clinical Studies of ICMs[1-7]



1. 1. Cotter PE, et al. Neurology. 2013;
2. Etgen T, et al. Stroke. 2013;44:2007-
3. Ritter MA, et al. Stroke. 2013;44:144
4. Rojo-Martinez E, et al. Rev Neurol. 2
5. Christensen LM, et al. Eur J Neurol. 2
6. Sanna T, et al. N Engl J Med. 2014;37
7. Rogers J et al, American Academy of http://www.abstractsonline.com/pp

The NEW ENGLAND JOURNAL of MEDICINE

Original Article

Cryptogenic Stroke and Underlying Atrial Fibrillation

Tommaso Sanna, M.D., Hans-Christoph Diener, MD, Ph.D.,
Rod S. Passman, M.D., M.S.C.E., Vincenzo Di Lazzaro, MD,
Richard A. Bernstein, MD, Ph.D., Carlos A. Morillo, M.D.,
Marilyn Mollman Rymer, M.D., VincentThijs, MD, Ph.D.,
Tyson Rogers, M.S., Frank Beckers, Ph.D., Kate Lindborg, Ph.D.,
andjohannes Brachmann, M.D., For the CRYSTAL AF lnvestigators‘k

Crystal AF_1 : Study Design and End Points

- Randomized, controlled clinical trial with 441 patients
- Compared continuous, long-term monitoring with Reveal™ ICM vs conventional monitoring for AFIB detection in CS patients
- Assessment at scheduled (1 mo, 6 mo, 12 mo, q 6 months) and unscheduled visits
- ECG monitoring performed at the discretion of the site investigator

End Point

Primary

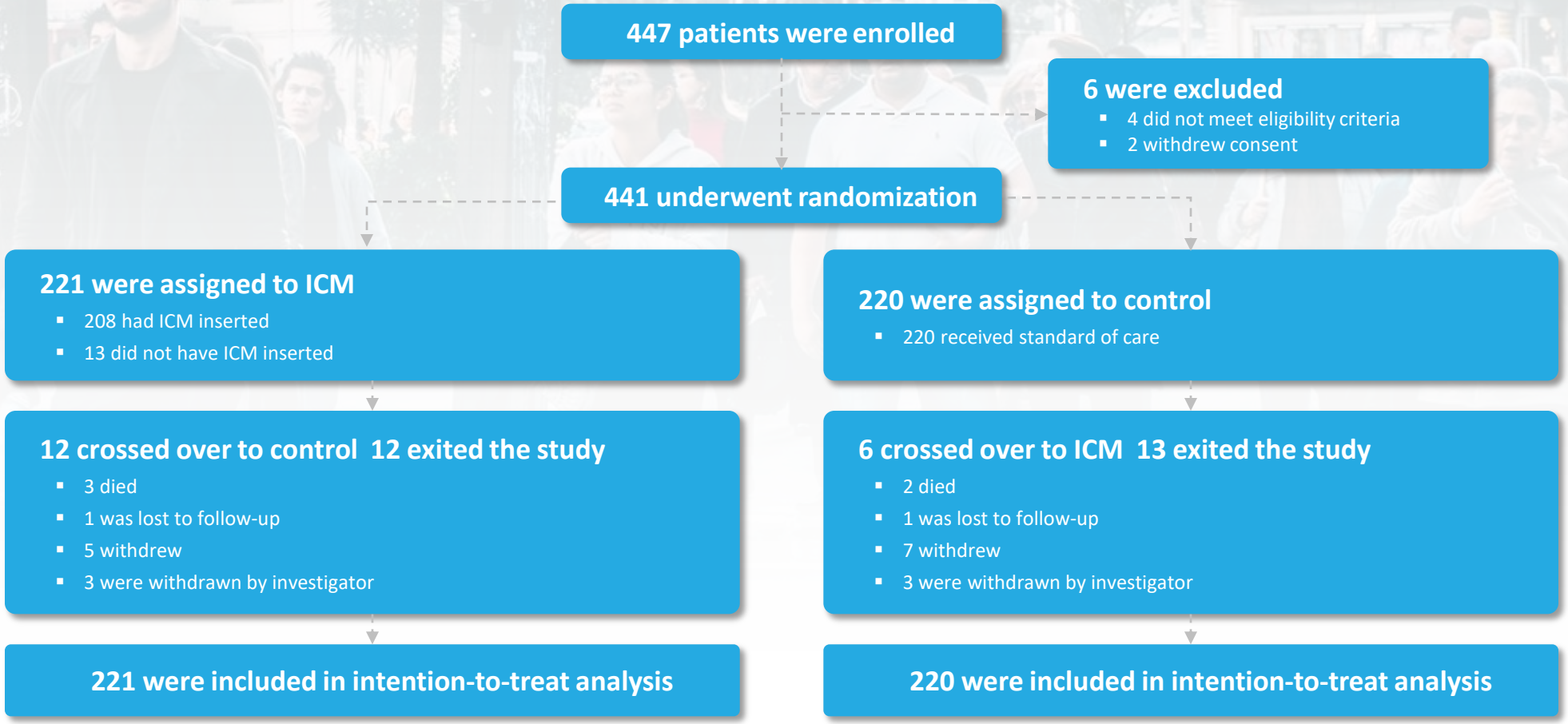
- Time to first detection of AF (>30 secs) at 6 months of follow-up

Secondary

- Time to first detection of AF at 12 months
- Recurrent stroke or TIA
- Change in use of oral anticoagulant drugs

1. Sanna T, et al. *N Engl J Med*. 2014;370:2478-2486.

Crystal AF_1 : Study Population



1. Sanna T, et al. N Engl J Med. 2014;370:2478-2486.

Crystal AF_1: Patients

- Age ≥ 40 years
- Screening for thrombophilic states (in patients < 55 years of age)
- Diagnosis of stroke or TIA occurring within previous 90 days
- Magnetic resonance angiography, computerized tomography angiography, or catheter angiography of head and neck
- Stroke was classified as cryptogenic after extensive testing:
  - 12-lead ECG
  - ≥ 24 hours of ECG monitoring
  - TEE
- Ultrasonography of cervical arteries or transcranial Doppler ultrasonography of intracranial arteries allowed in place of MRA or CTA for patients aged ≥ 55 years

Patients were only categorized with cryptogenic stroke after extensive diagnostic testing.

1. Sanna T, et al. *N Engl J Med*. 2014;370:2478-2486.

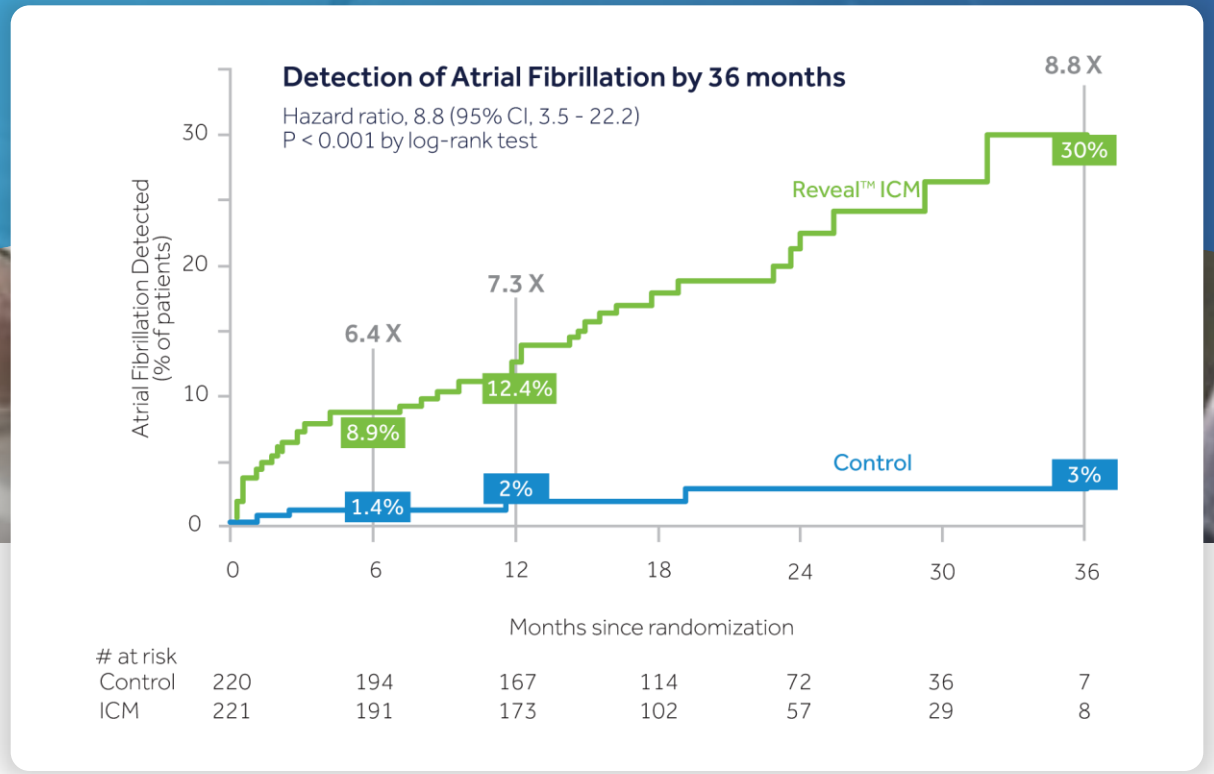
Crystal AF_1: Selected Baseline Patient Characteristics

Characteristic	ICM (n = 221)	Control (n = 220)	P
Age (years)	61.6 ± 11.4	61.4 ± 11.3	0.84
Male	64.3%	62.7%	0.77
White	87.8%	86.8%	0.60
Patent foramen ovale	23.5%	20.9%	0.57
Index event			0.87
Stroke	90.5%	91.4%	
TIA	9.5%	8.6%	

1. Sanna T, et al. N Engl J Med. 2014;370:2478-2486.

Crystal AF: Monitoring With ICM Superior To SOC

For The Detection Of AF[1]



1. Sanna T, et al. N Engl J Med. 2014;370:2478-2486.

6 Month Endpoints

	ICM	Control
Median Time from Randomization to AF Detection	41 days	32 days
Patients found to have AF	19	3
% Asymptomatic Episodes	74%	33%
Oral Anticoagulation Usage, overall	10.1%	4.6%
OAC use in patients with detected AF	94.7%	66.7%
Testing required to detect AF	Automatic AF detection	88 ECGs 20 24-hour Holters 1 event recorder

1. Feng W, et al. Neurology. 2010;74:588–593.

12 Month endpoints

	ICM	Control
Median Time from Randomization to AF Detection	84 days	52.5 days
Patients found to have AF	29	4
% Asymptomatic Episodes	79%	50%
Oral Anticoagulation Usage, overall	14.7%	6.0%
OAC use in AF patients	96.6%	100%
Testing required to detect AF	Automatic AF detection	121 ECGs 32 - 24-hour Holters 1 event recorder
Complications	5 (2 .4%) ICMs removed due to insertion site infection or pocket erosion	NONE

1. Go AS, et al. *Circulation.* 2013;127:e6-e245.

Crystal AF_1: Key Secondary Endpoint

12

Months

97%

of patients in whom AF was detected received oral anticoagulants

1. Go AS, et al. *Circulation.* 2013;127:e6-e245.

Crystal AF_1 : Median Time To Detection of AF

84 Days

in the ICM group
(range 18 to 265 days)

53 Days

in control group
(range 17 to 212 days)

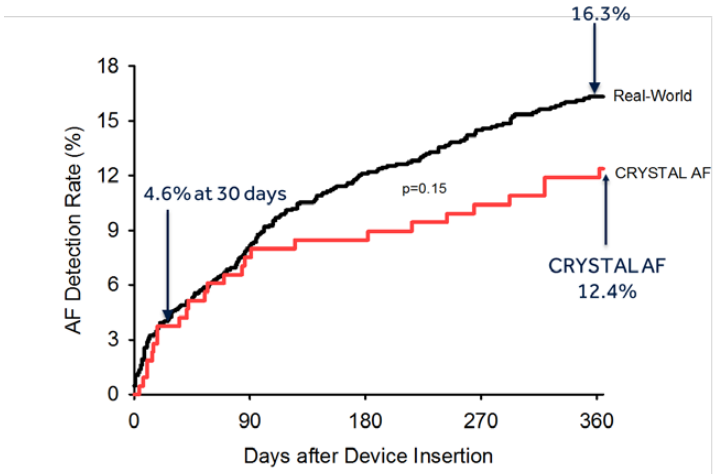
1. Go AS, et al. *Circulation.* 2013;127:e6-e245.

Real World Validation of Crystal AF Results

Rogers, AAN, 2016

- 1247 real-world cryptogenic stroke patients monitored by Reveal LINQ™
- Cryptogenic stroke diagnosis: physician's discretion
- Follow-up: **12 months**
- Diagnostic yield at 12 months: **16.3% (n=147)**
- Median time to detection: **86 days**
  - Analysis supports results of CRYSTAL AF
  - Continuous monitoring for periods longer 30 days may be warranted in CS patients

72% of AF patients would be missed if monitoring stopped at 30 days



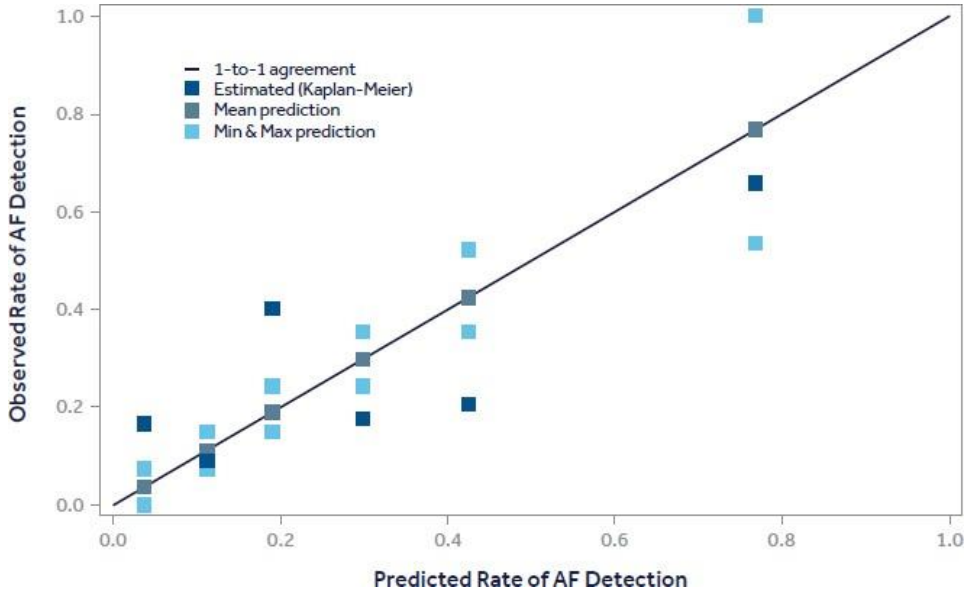
32% relative difference in AF detection rates at 12 months

Predictors Of AF Offer Only Poor Predictive Ability[1]

CRYSTAL AF sub-analysis: Thijs,*Neurology*

PARAMETERS TESTED:

- Age, sex, race
- Body Mass Index,
- Type and severity of index event
- CHADS2 score
- PR-interval
- Diabetes, hypertension
- Congestive heart failure
- Patent foramen ovale
- Premature atrial contractions



Increasing age and a prolonged PR-interval were independently associated with AF, but the predictive ability of these parameters was only moderate

1. Thijs et al. Predictors for Atrial Fibrillation Detection after Cryptogenic Stroke: Results from CRYSTAL AF. Neurology (in press)

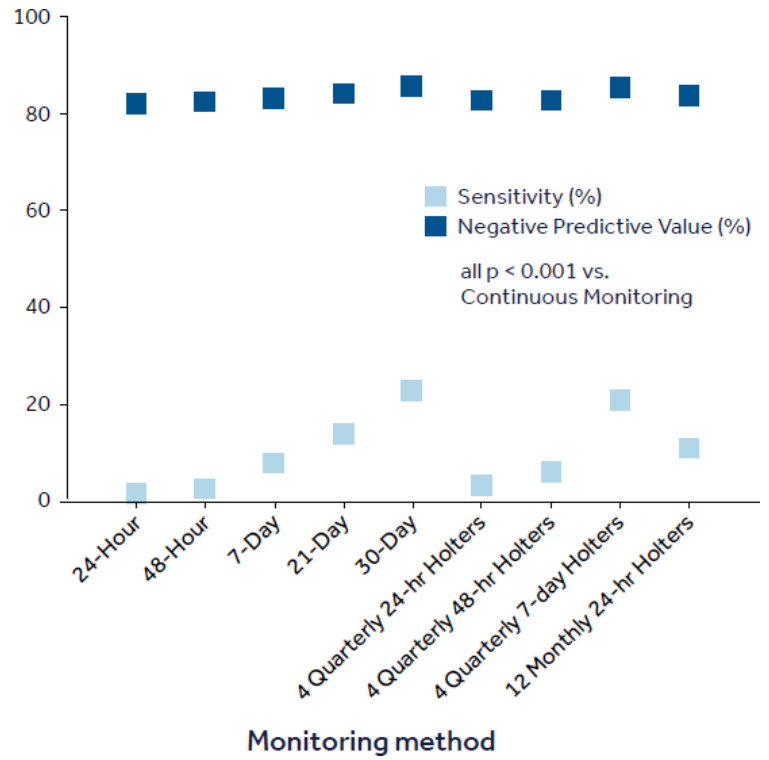
Continuous Monitoring Is Superior to Intermittent[1]

CRYSTAL AF sub-analysis: Choe, Am J Cardiol 2015

Simulated intermittent monitoring was compared to continuous rhythm monitoring in 168 ICM patients

Short – term monitoring	Periodic Monitoring
24 - Hour	Quarterly 24 – hour holters
48 - Hour	Quarterly 48 – hour holters
7 – Day Holter	Quarterly 7 – day holters
21 – Day Event Recorder	Monthly 24 – Hour holters
30 – Day Event Recorder	Monthly 24 – Hour holters

Sensitivity was low: 1.3-22.8%
Negative predictive value: 82.3-85.6%



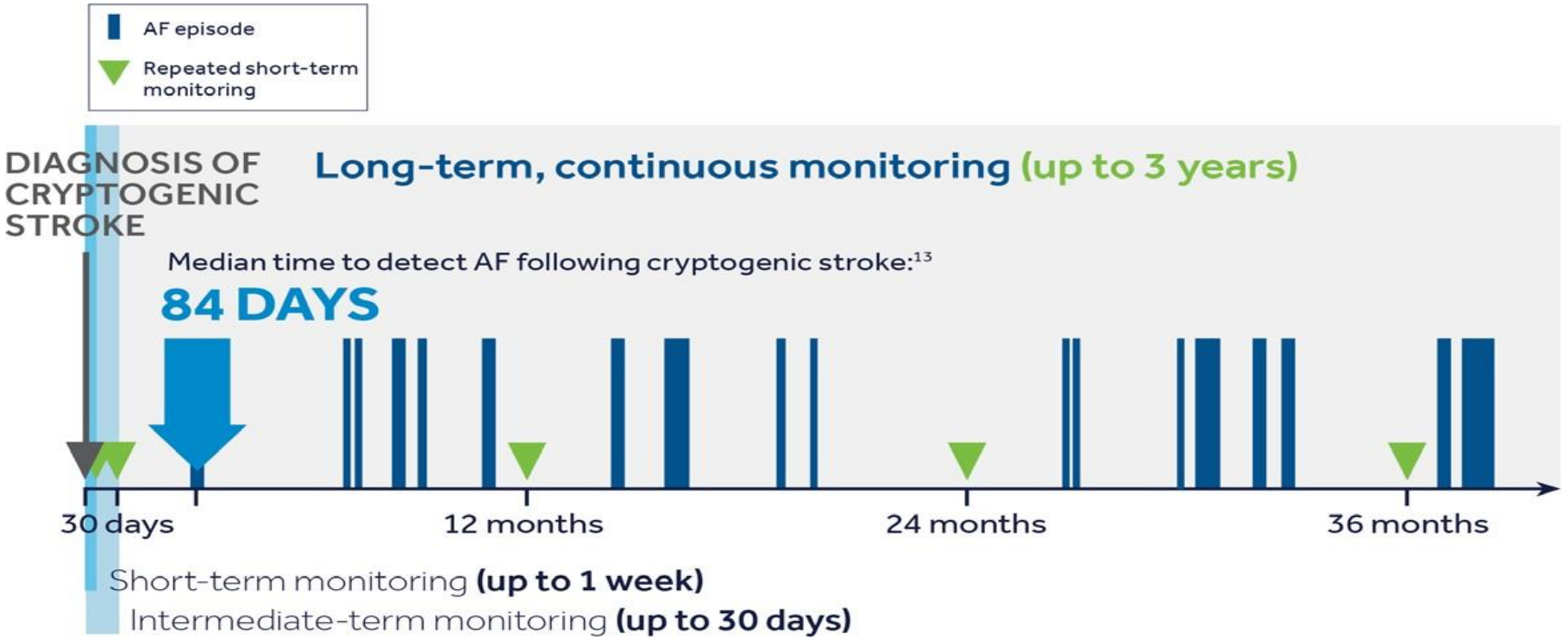
"Intermittent rhythm monitoring would have failed to identify previously undiagnosed AF in the vast majority of CS patients"

1. Choe et al. A comparison of atrial fibrillation monitoring strategies after cryptogenic stroke (from the CRYSTAL AF trial). Am J Cardiol. 2015;116:889-93.

Why Extended Monitoring?

SHORT- AND INTERMEDIATE-TERM MONITORING MAY MISS MANY PATIENTS WITH PAROXYSMAL AF[1]

79% of first AF episodes were asymptomatic at 12 months[1]



Note: For illustrative purposes only. 1. Sanna T, et al. N Engl J Med. 2014;370:2478-2486.

ICM IIa Recommendation For Cryptogenic Stroke

2016 ESC GUIDELINES FOR THE MANAGEMENT OF AF

Recommendation	Class	Level
In stroke patients, additional ECG monitoring by long-term non-invasive ECG monitors or implanted loop recorders should be considered to document silent atrial fibrillation.	IIa	B

AF = atrial fibrillation; AHRE = atrial high rate episodes; ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; TIA = transient ischaemic attack.
[a]Class of recommendation. [b]Level of evidence.

ICM IIa Recommendation For Cryptogenic Stroke

2019 AHA/ACC/HRS Focused Update for the Management of Patients With Atrial Fibrillation

Recommendation	Class	Level
In patients with cryptogenic stroke (i.e., stroke of unknown cause) in whom external ambulatory monitoring is inconclusive, implantation of a cardiac monitor (loop recorder) is reasonable to optimize detection of silent AF.	IIa	B-R

AF = atrial fibrillation; AHRE = atrial high rate episodes; ECG = electrocardiogram; ICD = implantable cardioverter defibrillator; TIA = transient ischaemic attack.
[a]Class of recommendation. [b]Level of evidence.

PROLONGED CARDIAC MONITORING IN SECONDARY STROKE PREVENTION[1]

Objectives

Evaluate the impact of prolonged cardiac rhythm monitoring (PCM) on secondary stroke prevention using data from available-to-date randomized clinical trials (RCTs) and observational studies.

Methods

- A comprehensive literature search of MEDLINE, SCOPUS, CENTRAL, and conference proceedings was conducted to identify studies reporting stroke recurrence rates in patients with a history of cryptogenic stroke or TIA receiving PCM as compared to patients receiving conventional (non-PCM) cardiac monitoring.
- Literature search was performed on October 14, 2018.
- Quality control and bias identification were performed by two independent reviewers with the Cochrane risk-of-bias tool[2] and all emerging conflicts were resolved with consensus.
- Small-study effect (i.e., publication bias) across individual studies was graphically evaluated for the primary outcome of interest (recurrent stroke/TIA) with funnel plot inspection and assessed with the Egger's test.[3]

Conclusion

The use of prolonged cardiac monitoring has a potential impact on secondary stroke prevention, as patients with cryptogenic IS/TIA undergoing PCM had higher rates of AF detection and anticoagulant initiation, and lower stroke recurrence.

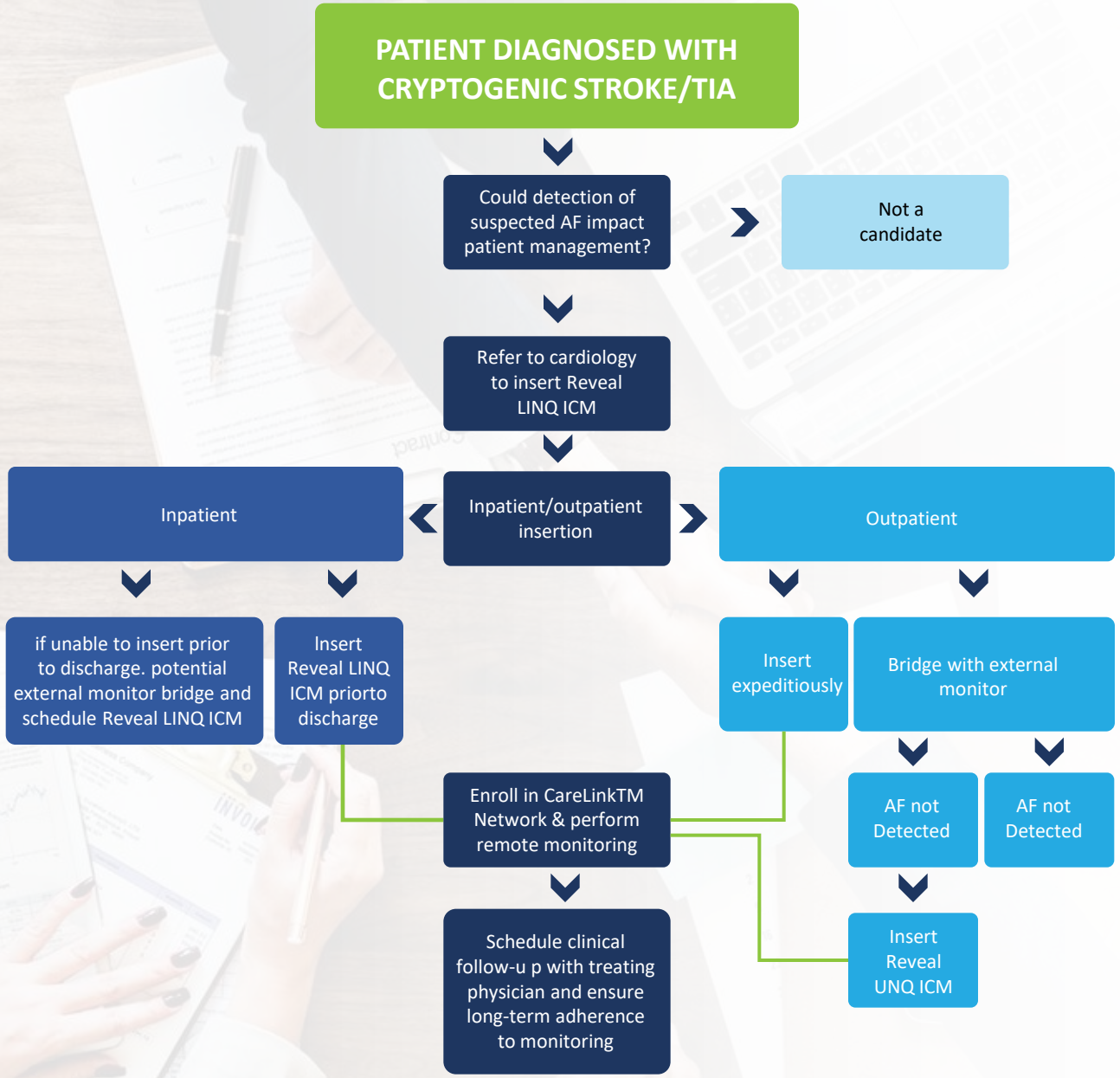
RESULTS

Patients who underwent PCM compared to conventional cardiac monitoring show:

- **2.5x increased incidence of AF detection** (n = 1,102, RR = 2.46, 95% CI: 1.61-3.76, and P < 0.0001)
- **2.1x increased incidence of anticoagulant initiation** (n = 956, RR = 2.07, 95% CI: 1.36-3.17, and P = 0.0008)
- **55% decreased risk of recurrent stroke** (n = 1,102, RR = 0.45, 95% CI: 0.21-0.97, and P = 0.04)

[1] Tsivgoulis G, Katsanos AH, Grory BM, et al. Prolonged Cardiac Rhythm Monitoring and Secondary Stroke Prevention in Patients With Cryptogenic Cerebral Ischemia. *Stroke*. Published online June 20, 2019.
[2] Higgins JP, et al. BMJ. 2011;343:d5928.
[3] Sterne JA, et al. *BMJ*. 2011;343:d4002.

As published in *Stroke*, June 2019[1]



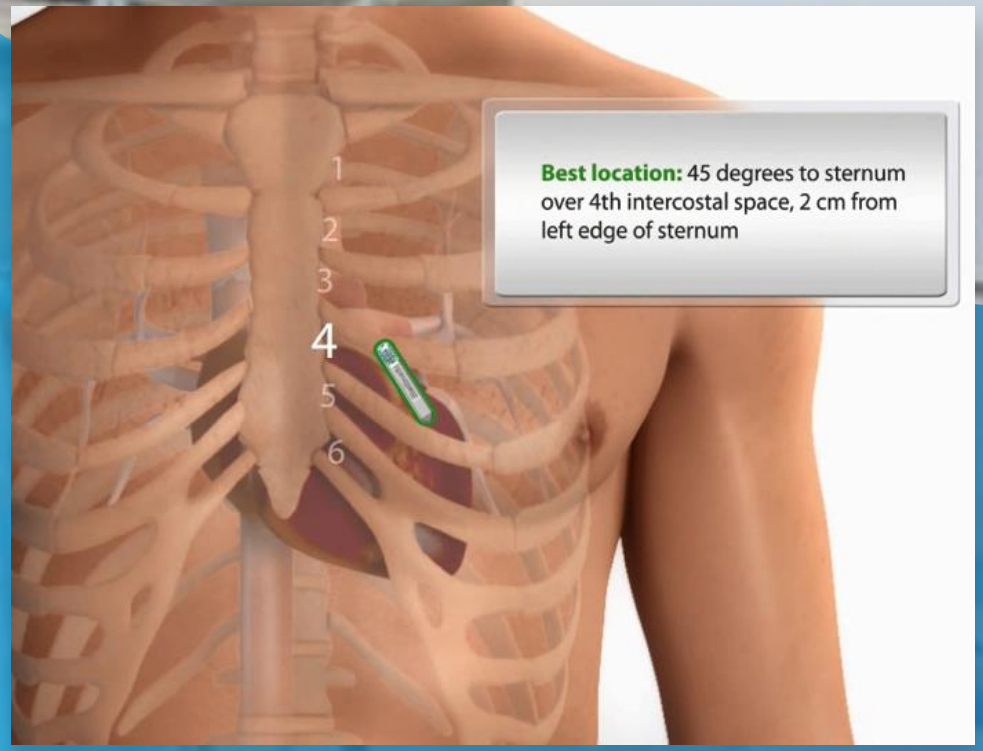
Cryptogenic Stroke Pathway

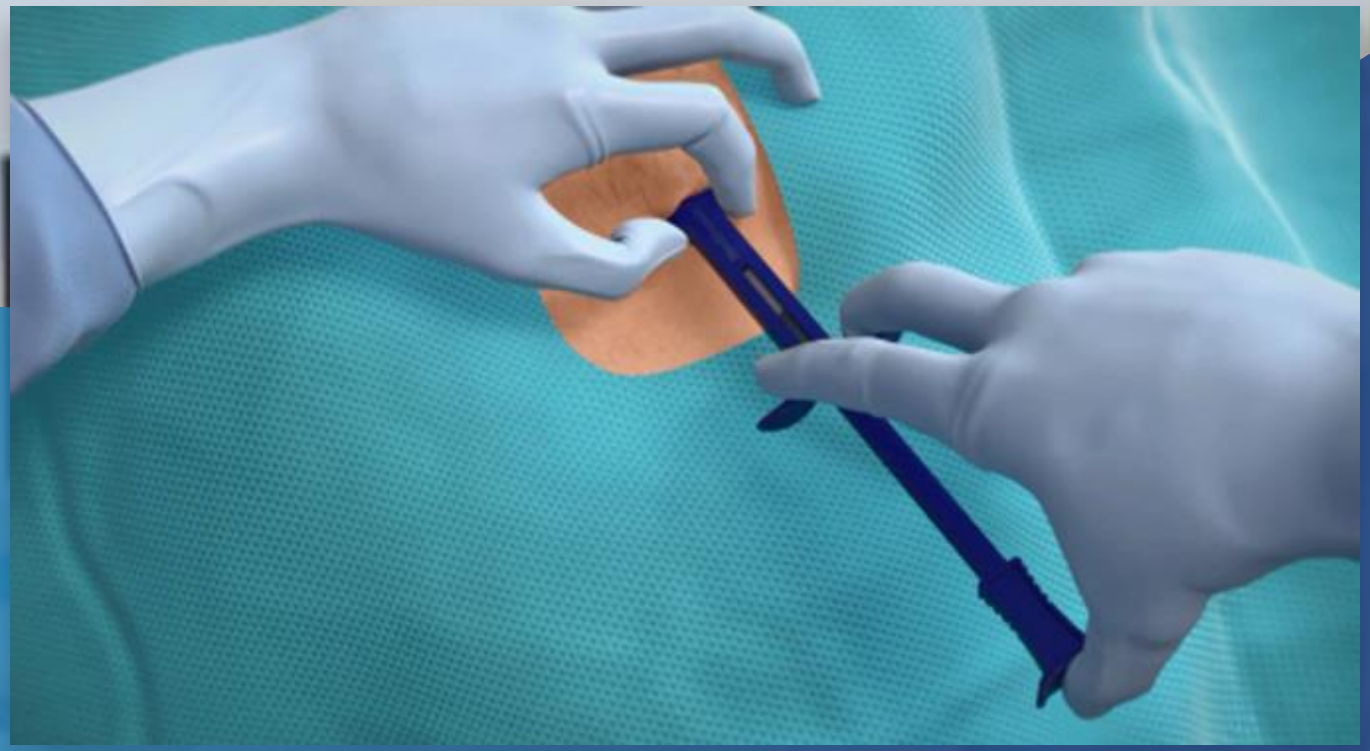
Pathway based on the consensus of the Cryptogenic Stroke Pathway steering committee. February 2016.

Medtronic Disclosure Statement: This pathway is provided for educational purposes and should not be considered the exclusive source for this type of information. It is the responsibility of the practitioner to exercise independent clinical judgment.

Refer to the brief statement for indications, warnings/precautions, and complications for the Reveal LINQ™ ICM.

Insertion


1
2
3
4
5
6
Best location: 45 degrees to sternum over 4th intercostal space, 2 cm from left edge of sternum



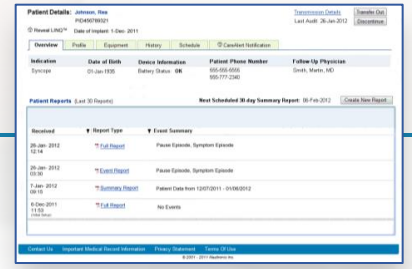
The Complete Monitoring Solution

ICM

Wireless

MyCareLink™ Patient Monitor

Cellular

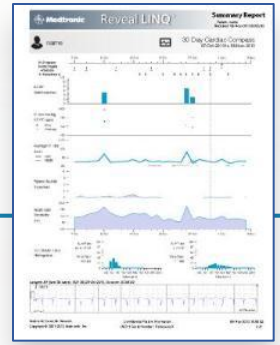


CareLink™ User Interface

Simplified Insertion Procedure

Patient Assistant

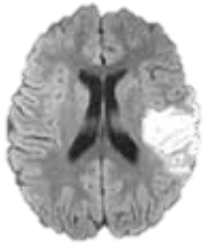
Mobile Alerts



Streamlined Reports

Case Study

62 y/o man who presented with aphasia and R sided hemiparesis s/p TPA. MRI demonstrated a left MCA stroke.



Workup

Vessel imaging, TTE/TEE, hypercoag panel, inpatient telemetry, 14 day event monitor did not reveal etiology of stroke.

Referral to EP

ILR implantation

Treatment

Neurology placed patient on Plavix 75 mg daily

Medtronic Reveal LINQ™ **Current Report: Episodes**

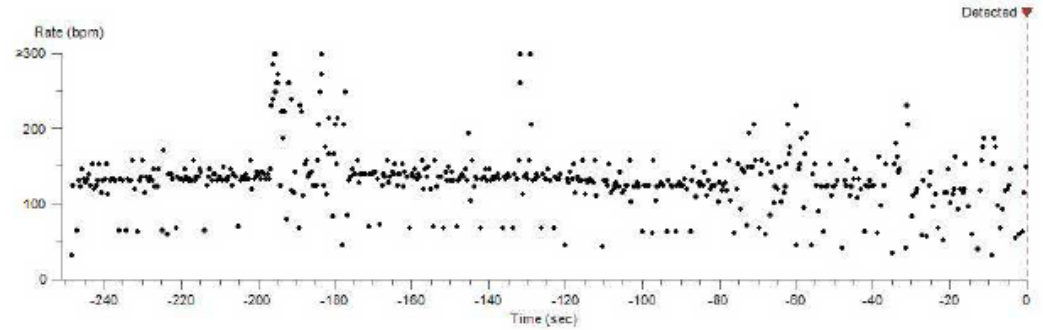
Episode List

Assessment Legend: ■ Appropriate ■ Indeterminate ⊗ Inappropriate

ID#	Assessment Type	Date	Detected hh:mm	Duration hh:mm:ss	Max V. Rate	Median V. Rate	Episode Details
11	AF	28-Sep-2015	11:38	00:02:00	167 bpm	98 bpm	ECG
10	AF	28-Sep-2015	11:34	00:02:00	231 bpm	130 bpm	ECG
9	Pause	31-Aug-2015	11:31	00:00:03		115 bpm	ECG
8	AF	24-Aug-2015	11:32	00:08:00	250 bpm	122 bpm	ECG
7	Tachy	24-Aug-2015	11:25	00:03:07	273 bpm	240 bpm	ECG

Medtronic Reveal LINQ™ **Current Report: Episodes**

Episode Detail: *AF (ID# 11)*

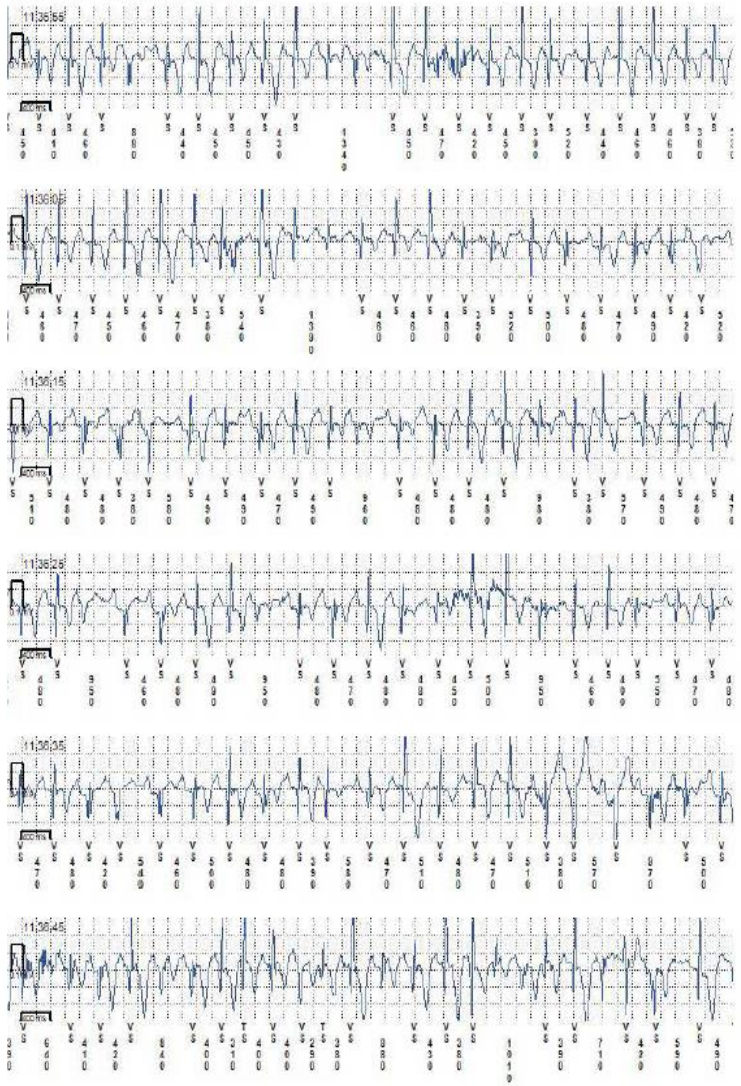


Assessment Legend: ■ Appropriate ■ Indeterminate ⊗ Inappropriate

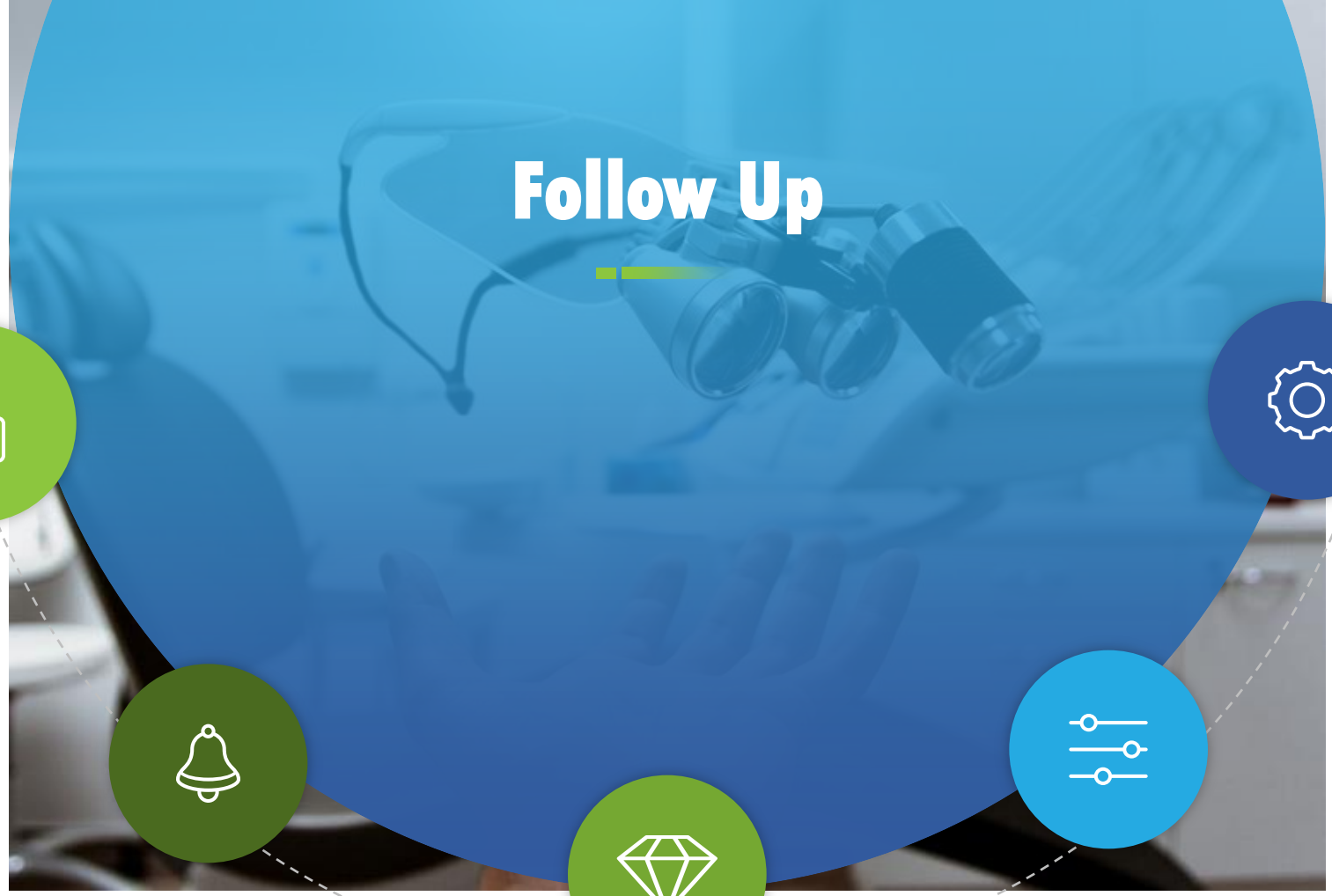
ID#	Assessment Type	Date	Detected hh:mm	Duration hh:mm:ss	Max V. Rate	Median V. Rate
11	AF	28-Sep-2015	11:38	00:02:00	167 bpm	98 bpm

Medtronic Reveal LINQ™ **Current Report: Episo**

ECG Detail: *AF (ID# 11)*, 28-Sep-2015



Follow Up



Immediately started on oral anticoagulation with Eliquis.

Continued remote monitoring with our office until his monitor was transferred to his new EP in Arizona.

Lives in an RV.

Moved to Tucson, Arizona– in his RV.

Following on Carelink with bedside monitor.

Conclusions

Epidemiology:

- Stroke is the leading cause of disability and 5th leading cause of death.
- Secondary prevention is key, especially in patients with atrial fibrillation.

Cryptogenic stroke:

- 30% of these patients have atrial fibrillation.
- ESUS is a more selective appropriate term for this population .
- In order to be deemed this, an extensive workup in required.

PFOs:

- Within the cryptogenic stroke population, many will have PFOs. It is our job as neurologists to be the gatekeeper for closure as this will only benefit a select portion of these patients.
- Long term monitoring should still be considered.

Long Term Monitoring:

- Short- to intermediate-term cardiac rhythm monitoring may not be enough to detect paroxysmal AF in your cryptogenic stroke patients
- CRYSTAL AF demonstrates superiority of continuous, long-term monitoring of cryptogenic stroke patients with an ICM
- LTM leads to a change in treatment which decreases the risk of recurrent disabling stroke.

Thank You!
Questions!!