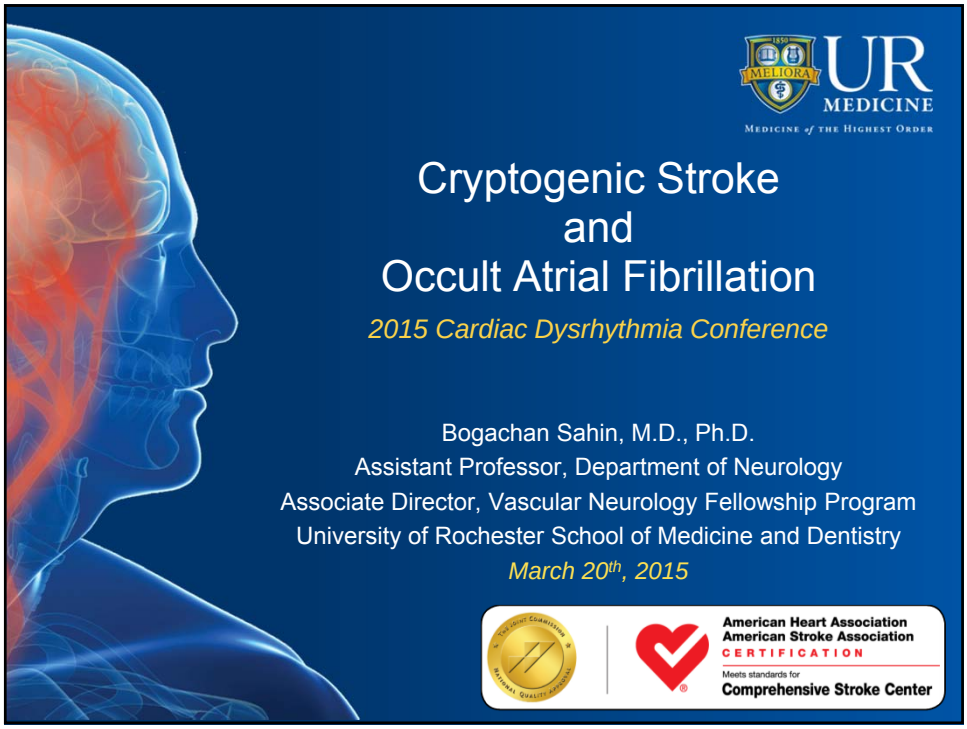
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Cryptogenic Stroke
and
Occult Atrial Fibrillation
2015 Cardiac Dysrhythmia Conference
Bogachan Sahin, M.D., Ph.D.
Assistant Professor, Department of Neurology
Associate Director, Vascular Neurology Fellowship Program
University of Rochester School of Medicine and Dentistry
March 20th, 2015
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DISCLOSURES
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LECTURE OUTLINE

Stroke Basics
Case 1
Stroke Mechanisms
Cryptogenic Stroke
EMBRACE
CRYSTAL AF
Case 2
Outcomes
Conclusions
A Word about Prevention

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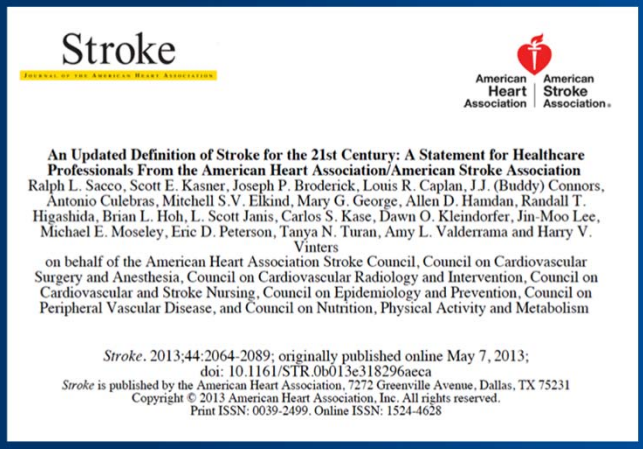
What Is an Acute Ischemic Stroke?



Stroke

Journal of the American Heart Association

American Heart Association | American Stroke Association

An Updated Definition of Stroke for the 21st Century: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

Ralph L. Sacco, Scott E. Kasner, Joseph P. Broderick, Louis R. Caplan, J.J. (Buddy) Connors, Antonio Culebras, Mitchell S.V. Elkind, Mary G. George, Allen D. Hamdan, Randall T. Higashida, Brian L. Hoh, L. Scott Janis, Carlos S. Kase, Dawn O. Kleindorfer, Jin-Moo Lee, Michael E. Moseley, Eric D. Peterson, Tanya N. Turan, Amy L. Valderrama and Harry V. Vinters

on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, and Council on Nutrition, Physical Activity and Metabolism

Stroke. 2013;44:2064-2089; originally published online May 7, 2013;
doi: 10.1161/STR.0b013e318296aeca

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What Is an Acute Ischemic Stroke?

Classic (clinical) definition:

- Sudden loss of focal neurologic function
- Attributable to ischemia
- Causing a focal neurologic deficit lasting 24 hours or more
- This definition does not capture all instances of CNS infarction.

Updated (tissue) definition:

- Brain, spinal cord, or retinal cell death
- Attributable to ischemia
- Based on evidence of permanent tissue injury
- This definition captures “silent” strokes, MRI-positive TIAs *etc.*

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Stroke in Numbers

- Fifth leading cause of death
- The leading cause of long-term disability in adults
- 800,000 strokes expected in 2015
- Nearly 1/4 recurrent
- Nearly 1/6 expected to die
- 90 strokes and 15 deaths in the U.S. per hour
- 7 strokes and 1 death in Rochester per day
- Up to 2/3 of survivors left with mild to severe disability
- 1/3 of stroke survivors suffer from depression
- Economic burden more than $30 billion per year

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CASE 1

83-year-old man with hypertension, diabetes, and previous stroke 4 months ago with residual right hemiparesis:

- Presents with acute mutism and right-sided flaccid hemiplegia;
- Initial CT unrevealing;
- CTA shows a left MCA occlusion;
- Mechanical embolectomy;
- No clinical improvement;
- Follow-up CT confirms massive left hemispheric infarct;
- Further work-up reveals "new-onset" atrial fibrillation.

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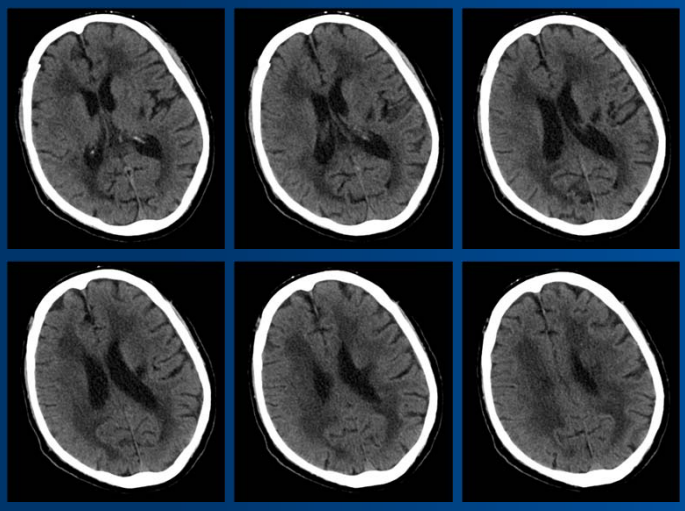

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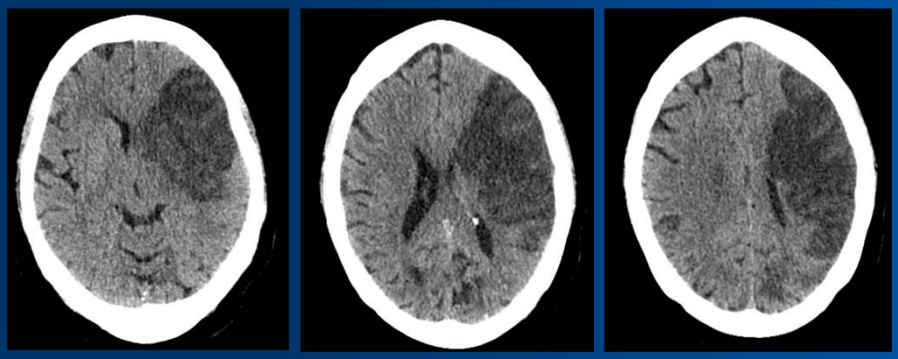

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CASE 1

Could we have prevented this outcome?

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Mechanisms of Acute Ischemic Stroke

Thrombotic

Lacunar

Embolic

Hemodynamic

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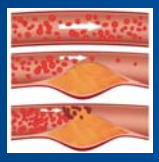
Mechanisms of Acute Ischemic Stroke

Thrombotic:

- Large-vessel occlusive disease
  - Cervical and major intracranial vessels
  - Atherothrombosis
  - Dissection, vasculitis *etc.* less common



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Lacunar:

- Small-vessel occlusive disease
  - Deep penetrators
  - Lipohyalinosis
  - Atherothrombosis

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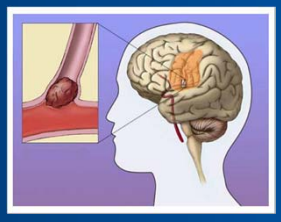
Mechanisms of Acute Ischemic Stroke

Embolic:

- Heart
  - Atrial fibrillation
  - Endocarditis
  - Mechanical valve
  - Low ejection fraction
  - Left ventricular aneurysm
  - Mural thrombus
  - Patent foramen ovale *etc.*
- Aorta
  - Large ulcerated plaque
  - Mobile element
- Cervical and major intracranial arteries
- Thrombophilia



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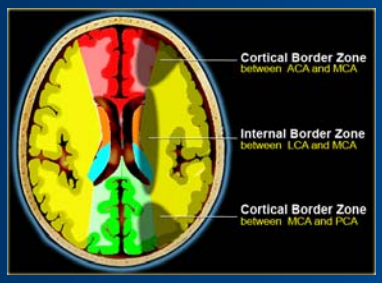
Hemodynamic:

- Systemic or local hypoperfusion
- Classically affects the so-called “watershed” areas.



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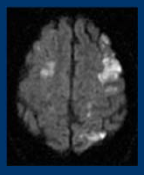
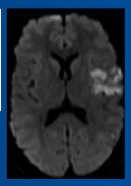
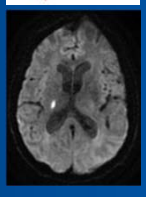




- Atherothrombotic (25-30%)
- Cardioembolic (20%)
- Lacunar (15-20%)
- Cryptogenic (25-30%)
- Other (5-10%, *e.g.* hemodynamic)



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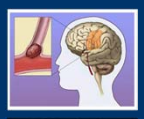
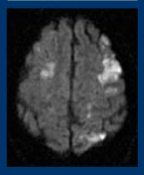

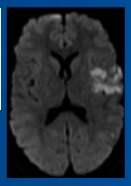

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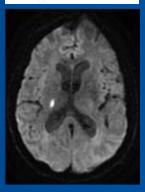

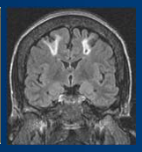

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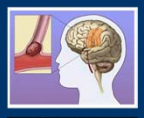
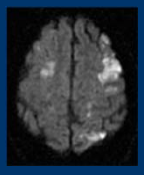

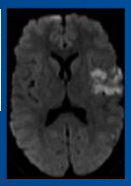

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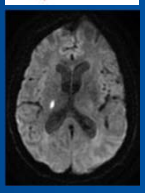

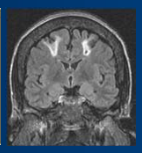

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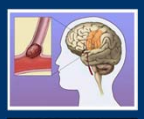
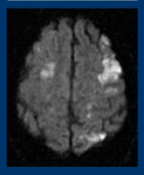

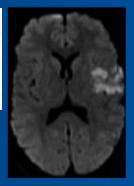

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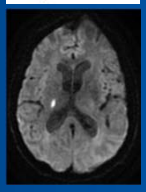


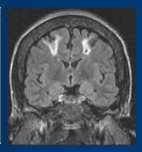

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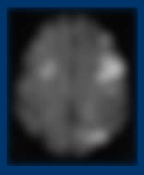

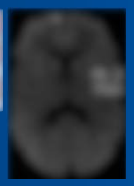

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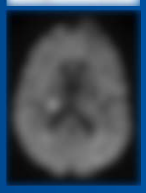

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SOME DEFINITIONS

- Cryptogenic stroke
  Ischemic stroke of unknown cause
- Occult atrial fibrillation
  Unrecognized paroxysmal AF
  It may require prolonged monitoring for detection.

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Cryptogenic Stroke

- 25-30% strokes remain idiopathic after a thorough investigation.
- Some of these patients may have occult AF.
- They are typically treated with antiplatelet agents.
- Detection of AF has the potential to change management.
- Change in management has the potential to improve outcomes.

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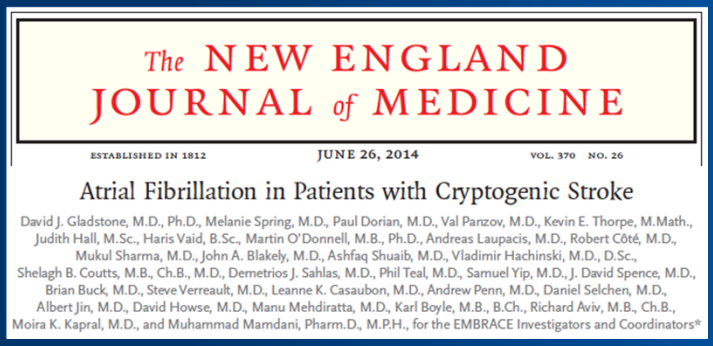
EMBRACE



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Atrial Fibrillation in Patients with Cryptogenic Stroke

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EMBRACE

- Investigator-initiated, open-label, multicenter RCT (Canada)
- Funding source: Academic
- 572 cryptogenic stroke or TIA patients ≥ 55 years
- Randomized to 30-day auto-trigger external cardiac event monitor *vs.* 24-hour Holter monitor
- Primary outcome: AF lasting ≥ 30 seconds within 90 days
- Secondary outcomes:
  - AF lasting ≥ 30 seconds and ≥ 150 seconds
  - AF of any duration
  - Anticoagulation status at 90 days

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- Primary outcome:
  16.1% (intervention) *vs.* 3.2 % (control) of patients

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)

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- Secondary outcomes:
  AF ≥ 30 sec detected in 15.5% (intervention) *vs.* 2.5 % (control)
  AF ≥ 150 sec detected in 9.9% (intervention) *vs.* 2.5 % (control)
  Any AF detected in 19.7% (intervention) *vs.* 4.7 % (control)

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*		
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- Secondary outcomes:
  Anticoagulation status at 90 days
  OAC in 18.6% (intervention) *vs.* 11.6% (control) of patients

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

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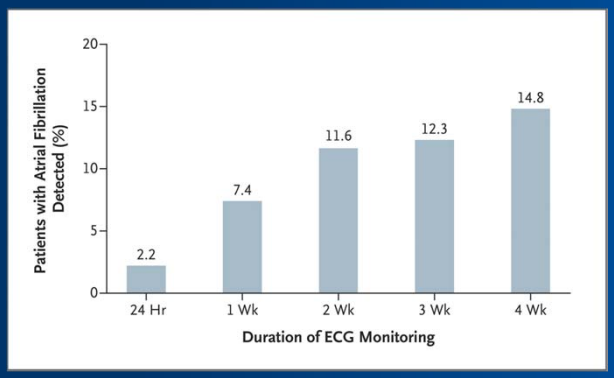
- Duration of monitoring improves diagnostic yield.



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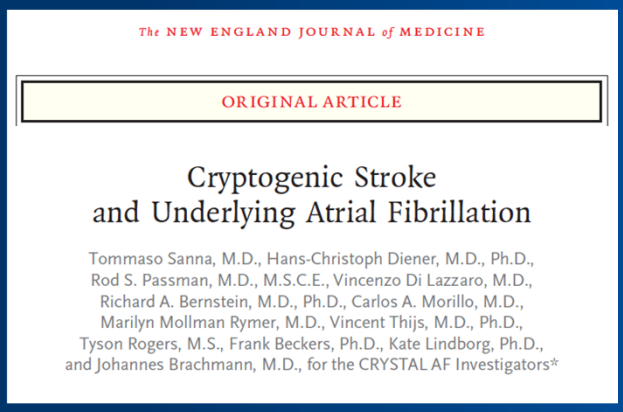
CRYSTAL AF



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cryptogenic Stroke and Underlying Atrial Fibrillation

Tommaso Sanna, M.D., Hans-Christoph Diener, M.D., Ph.D., Rod S. Passman, M.D., M.S.C.E., Vincenzo Di Lazzaro, M.D., Richard A. Bernstein, M.D., Ph.D., Carlos A. Morillo, M.D., Marilyn Mollman Rymer, M.D., Vincent Thijs, M.D., Ph.D., Tyson Rogers, M.S., Frank Beckers, Ph.D., Kate Lindborg, Ph.D., and Johannes Brachmann, M.D., for the CRYSTAL AF Investigators*

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CRYSTAL AF

- Industry-sponsored multicenter RCT (N. America and Europe)
- 441 cryptogenic stroke or TIA patients ≥ 40 years
- Randomized to implantable cardiac monitor (ICM) *vs.* "standard therapy"
- Primary outcome: AF lasting ≥ 30 seconds within 6 months
- Secondary outcomes:
  - AF lasting ≥ 30 seconds within 12 months
  - Recurrent stroke or TIA
  - Initiation of oral anticoagulants

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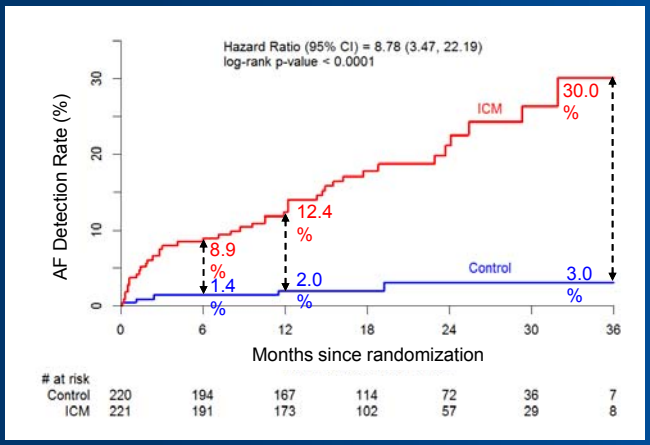
CRYSTAL AF

- Primary and secondary outcomes:



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CRYSTAL AF

- Secondary outcomes cont.:

Parameter	6 Months	12 Months	36 Months
Time to AF detection	41 days	84 days	252 days
Asymptomatic episodes	74%	79%	81%
Anticoagulant use among patients found to have AF	94.7%	96.6%	90.0%
Patients with > 6 min of AF on 1 day	93.8%	92.3%	94.9%

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EMBRACE *vs.* CRYSTAL AF

- The external event monitor detected AF in 16.1% of patients at 90 days in EMBRACE.
- The implantable event monitor detected AF in 8.9% of patients at 180 days in CRYSTAL AF.
- There were differences in initial stroke work-up.
  - TEE or intracranial imaging not required in EMBRACE
  - Less pre-enrollment ECG monitoring in EMBRACE
- There were differences in the control arms.
  - "ECG monitoring performed at the discretion of the site investigator" in the control arm CRYSTAL AF
- Average age 73 *vs.* 61 in EMBRACE *vs.* CRYSTAL AF

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Selection criteria for implantable loop recorder placement in hospitalized patients with cryptogenic stroke

Patient Selection:

1. Age ≥ 40
2. Brain imaging consistent with cardioembolic stroke
3. No identifiable thromboembolic source after a thorough work-up
4. No history of atrial fibrillation or atrial flutter
5. No indication or contraindication for lifelong anticoagulation

Diagnostic Approach:

Patients ≥ 40 and < 55 should be offered an implantable loop recorder.
Patients ≥ 55 may be offered a 30-day cardiac event monitor *or* an implantable loop recorder, with the understanding that if the 30-day cardiac event monitor is unrevealing, an implantable loop recorder would be the next recommended step.

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LECTURE OUTLINE

Stroke Basics
Case 1
Stroke Mechanisms
Cryptogenic Stroke
EMBRACE
CRYSTAL AF
Case 2
Outcomes
Conclusions
A Word about Prevention

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CASE 2

71-year-old woman with no known past medical history:

- Presented with transient slurred speech;
- CT showed old embolic infarcts;
- CTA showed no significant atherosclerotic disease;
- MRI showed acute multifocal embolic left MCA infarcts;
- TTE: Left atrial enlargement;
- TEE: Biatrial enlargement, no LAA thrombus;
- Discharged on ASA and statin therapy;
- Referred to Cardiology for implantable loop recorder placement;
- Paroxysmal AF detected, patient started on apixaban.

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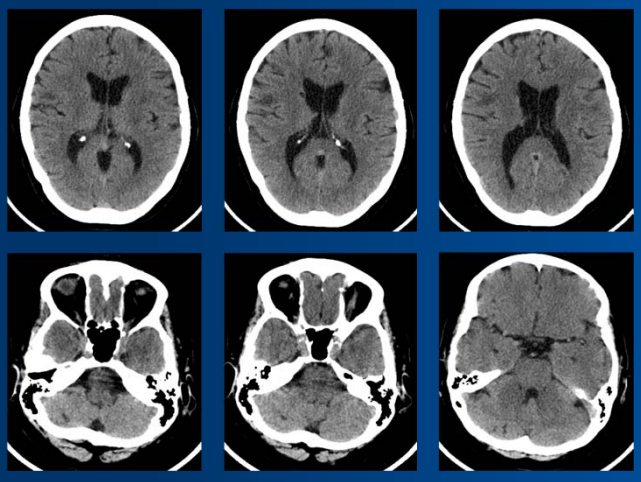
CASE 2



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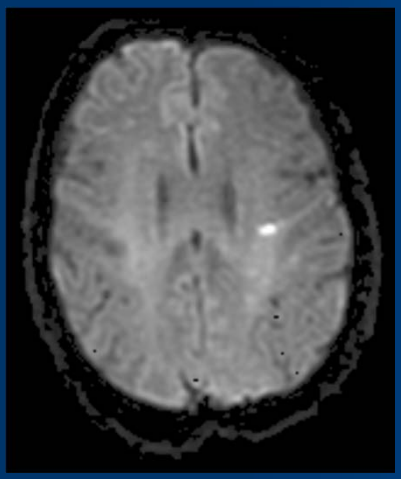
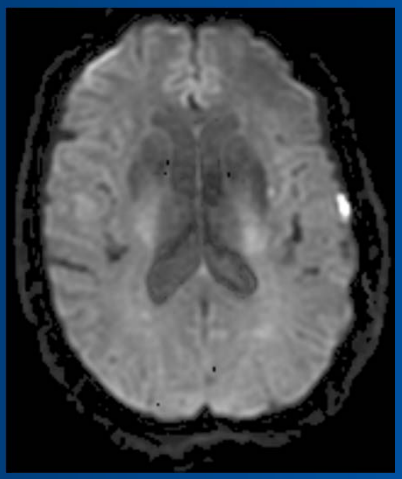
MRI





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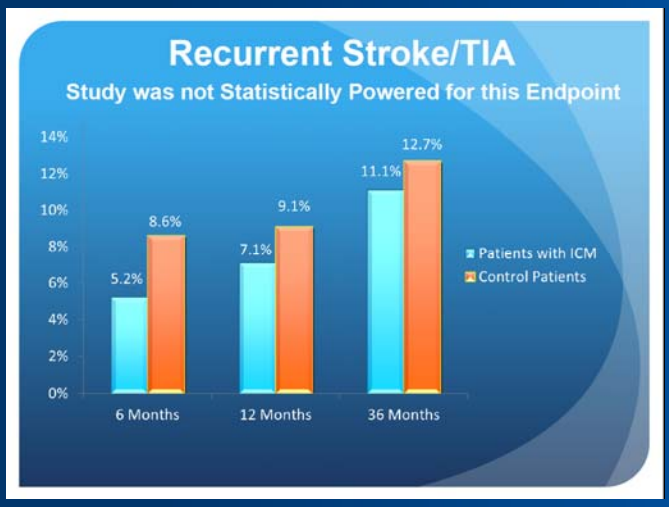

Adopted from Richard Bernstein at Northwestern University, personal communication

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CONCLUSIONS

- Continuous monitoring increases diagnostic yield.
- AF detection changes management in most cases.
- It is unclear if this improves patient outcomes.

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Continuum of Stroke Therapy

- Primary prevention
- Acute therapies (recanalization, neuroprotection *etc.*)
- Prevention of immediate complications
- Recovery and rehabilitation
- Secondary prevention

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Continuum of Stroke Therapy

- No proven acute treatments beyond the first few hours
- Intravenous rt-PA still the gold standard of acute care
- Only 10% of ischemic stroke patients eligible
- Not all eligible patients treated (*e.g.* 77% in 2011)
- Only 12% of treated patients expected to benefit
- That is fewer than 1% (about 0.8%) of all ischemic strokes.

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Continuum of Stroke Therapy

- Reducing blood pressure reduces stroke risk by 35 to 40%.
- Exercise can reduce stroke risk by 40%.
- Statins reduce stroke risk even in people with mildly elevated LDL.
- Smoking doubles the risk of stroke.
- Risk of stroke is 2 to 6 times higher in diabetics.

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Continuum of Stroke Therapy

- Nearly 800,000 strokes are expected in U.S. in 2015.
- About 680,000 of these will be ischemic strokes.
- Up to 200,000 will have no clear source.
- Up to 60,000 may be due to paroxysmal AF.
- Annual risk of recurrent stroke at least 4% in this group (2,400).
- Antiplatelets may reduce that risk to 3% (1,800).
- Anticoagulants expected to reduce it to 1.3% (800).
- At least 1,000 fewer strokes per year going forward.
- 1,500 assuming one other risk factor on average.
- 2,200 assuming two other risk factors on average.

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