Update on Cryptogenic Stroke Evaluation & Treatment

Fadi B. Nahab MD
Associate Professor, Department of Neurology & Pediatrics
Emory University School of Medicine
Stroke Quality Director, Emory Healthcare

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EMORY
UNIVERSITY
SCHOOL OF
MEDICINE

Department of Neurology

Disclosures

- Dr. Nahab
  - Honoraria: AHA/ASA
  - Consultant: Expert witness

Case

- 65yo RH lady presents with acute left MCA syndrome, NIHSS 20, within 4.5 hour time window. NCCT shows no hemorrhage and no early ischemic changes. Gets IV tPA and goes for thrombectomy with complete (TICI 3) reperfusion.
- 24 hr NIHSS= 1
- “Stroke Workup” completed and no cause identified.
- Discharged on aspirin 325mg daily, atorvastatin 80mg daily.

Case

- Patient: “Doctor, what caused my stroke?”
- Doctor: “Not sure”
- Patient: “How do you know that aspirin and atorvastatin will prevent a future stroke if you don’t know what caused my stroke?”

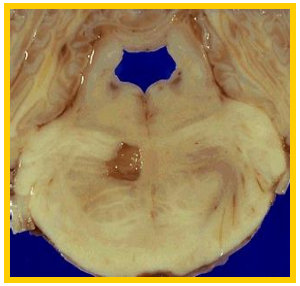
Cerebrovascular Disease: Pathogenesis

Ischemic Stroke (88%)

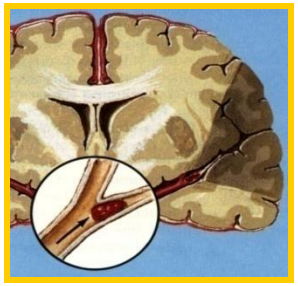
Atherothrombotic Cerebrovascular Disease (20%)

Cryptogenic (30%)

Lacunar (30%)
(small vessel disease)

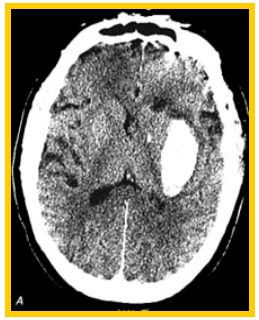


Cardioembolic (20%)

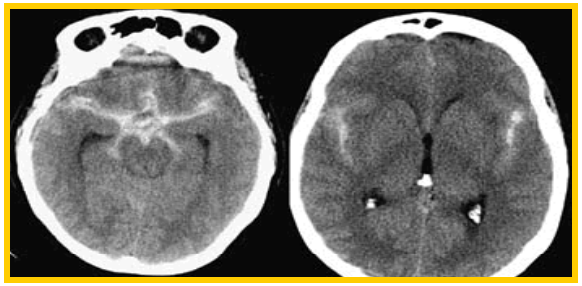


Hemorrhagic Stroke (12%)

Intracerebral Hemorrhage (70%)

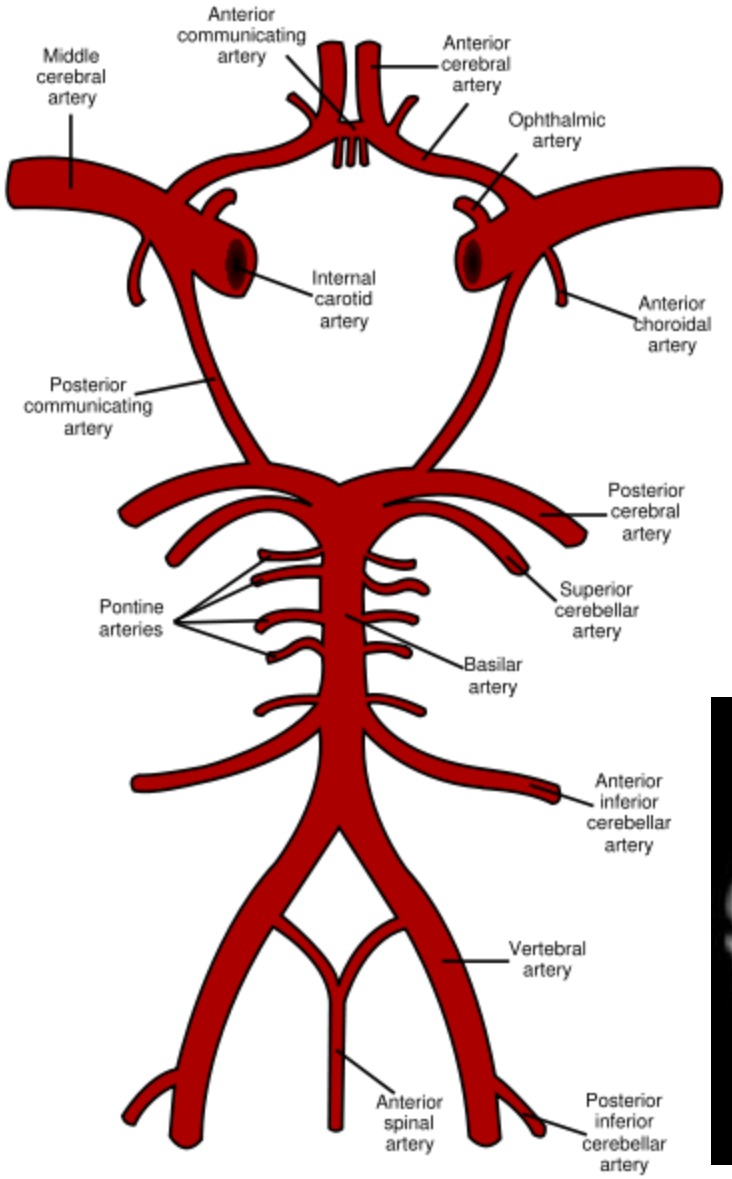


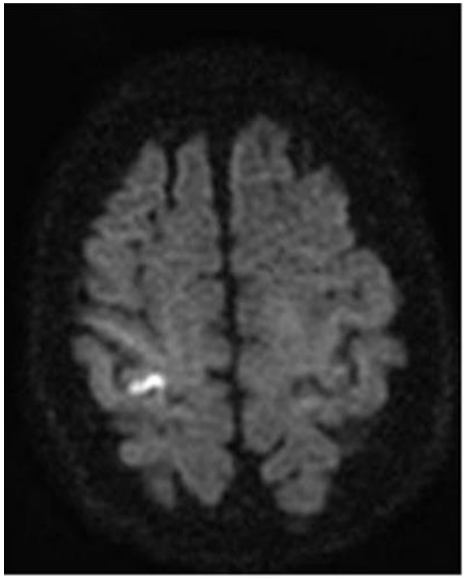
Subarachnoid Hemorrhage (30%)

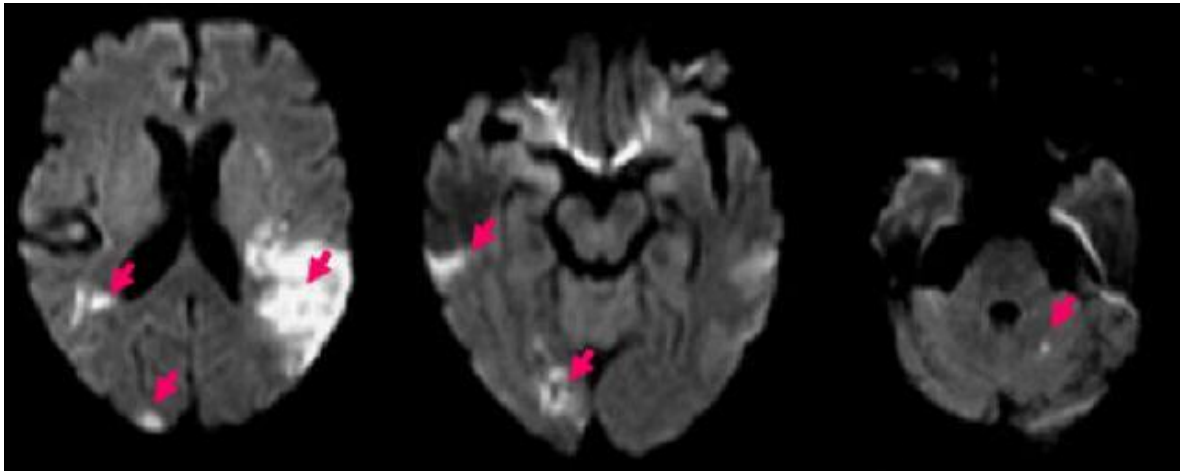


Albers GW et al. *Chest*. 1998;119:683S-698S. Albers GW Personal communication. February 27, 2003.
Rosamond WD et al. *Stroke*. 1999;30:736-743.
Saver J. N Engl J Med 2016;374:2065-74.

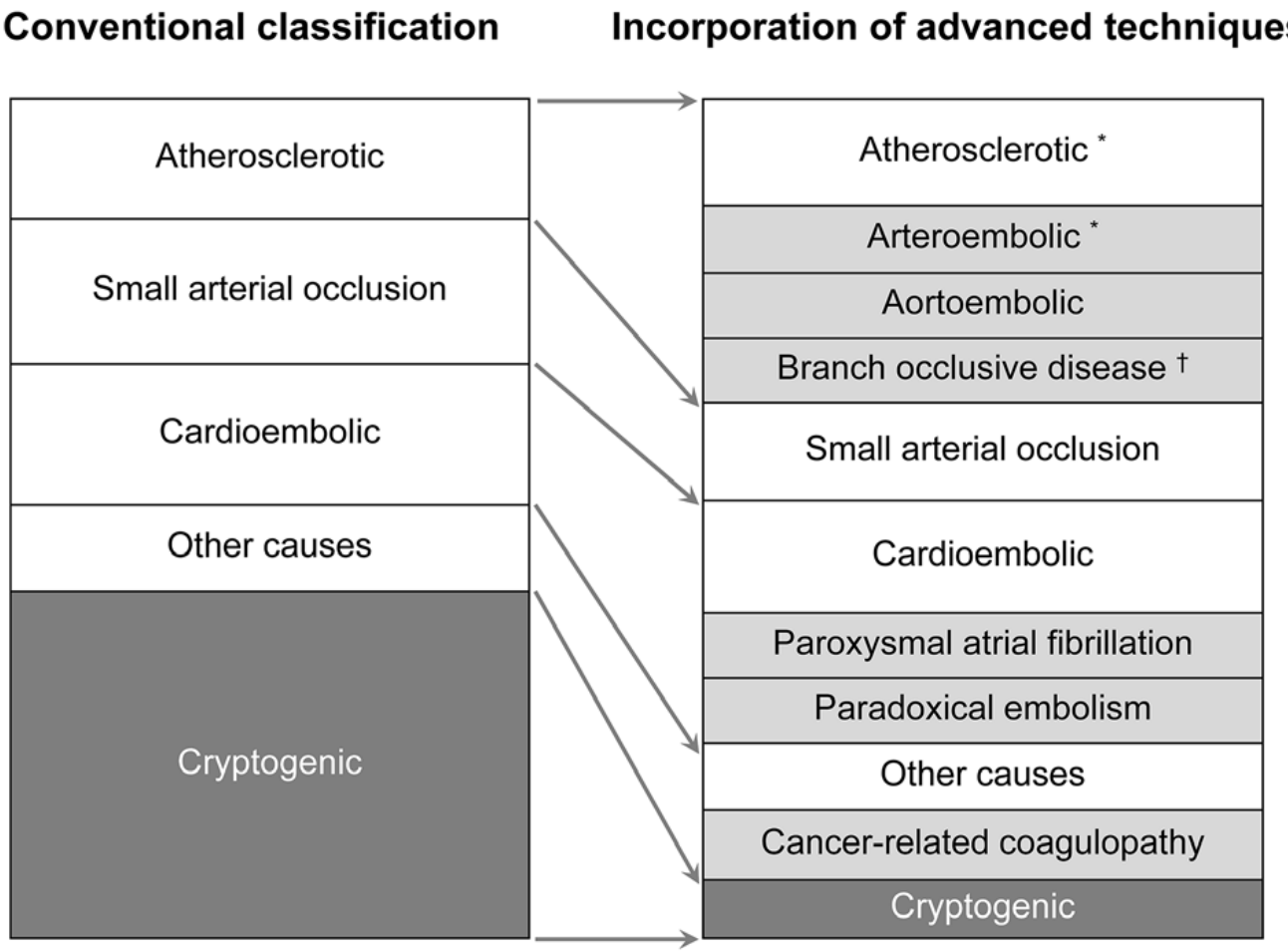
Cryptogenic Strokes on MRI







Cryptogenic Stroke: Causes



Bang OY et al. *Stroke*. 2014;45:1186-1194.

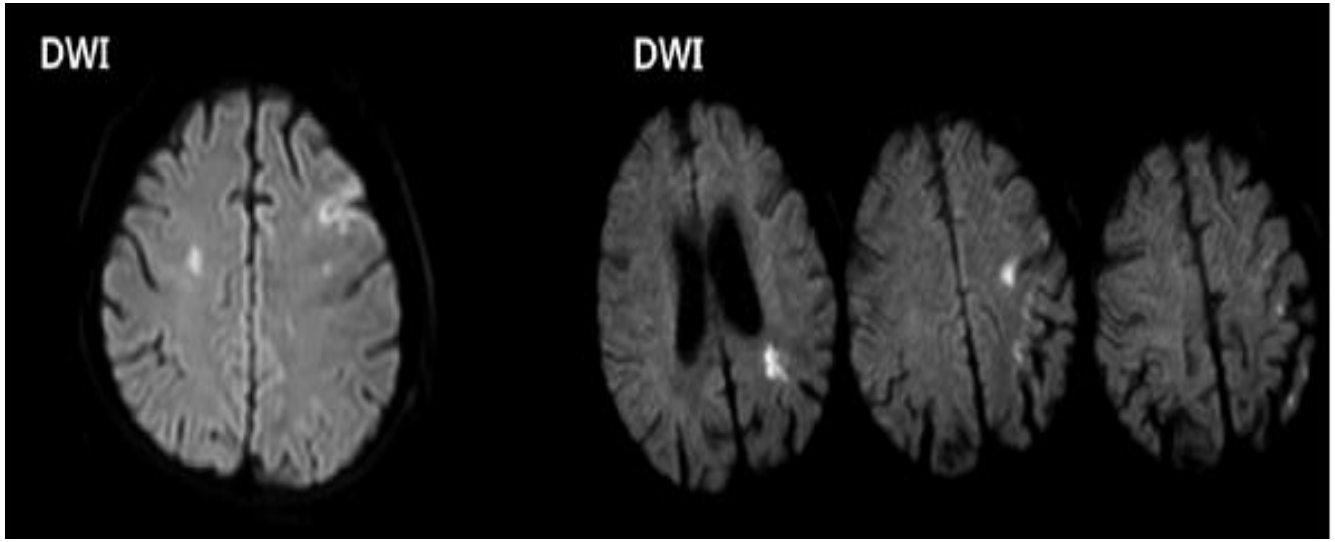
Evaluation of Cryptogenic Stroke

Cryptogenic Stroke vs Embolic Stroke of Undetermined Source (ESUS)

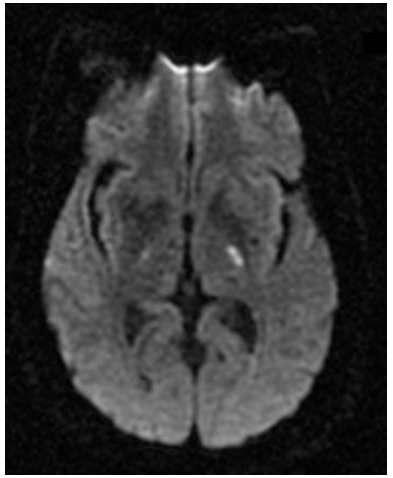
Cryptogenic Stroke	ESUS
Diagnostic Criteria	
No arterial stenosis (≥50%) coupled with non-lacunar infarct, no clinical lacunar syndrome if brain infarct on imaging ≤ 1.5cm, no major risk cardioembolic source	**Non-lacunar >1.5cm (>2cm on DWI) and not in small penetrating artery distribution on imaging**, <50% stenosis proximal to infarct, no major risk cardioembolic source (e.g. PAF, EF<30%, etc), no other identified cause (e.g. arteritis, dissection, vasospasm, drug abuse)
Necessary Diagnostic Assessment	
Not specified	**Brain CT or MRI showing non-lacunar infarct** Transthoracic echocardiography ECG and cardiac monitoring ≥24 hours Imaging of the extra/intracranial arteries supplying the area of brain infarct
Limitations	
Inclusion of variable fraction of lacunar infarcts and intracranial arterial stenosis dependent on extent of testing performed	TEE not recommended and therefore could miss other causes (e.g. aortic arch atherosclerosis)

Lancet Neurol 2014;13:429-438.

Cryptogenic Stroke: Imaging



Infarcts caused by an embolus



Lacunar (non-embolic) infarct

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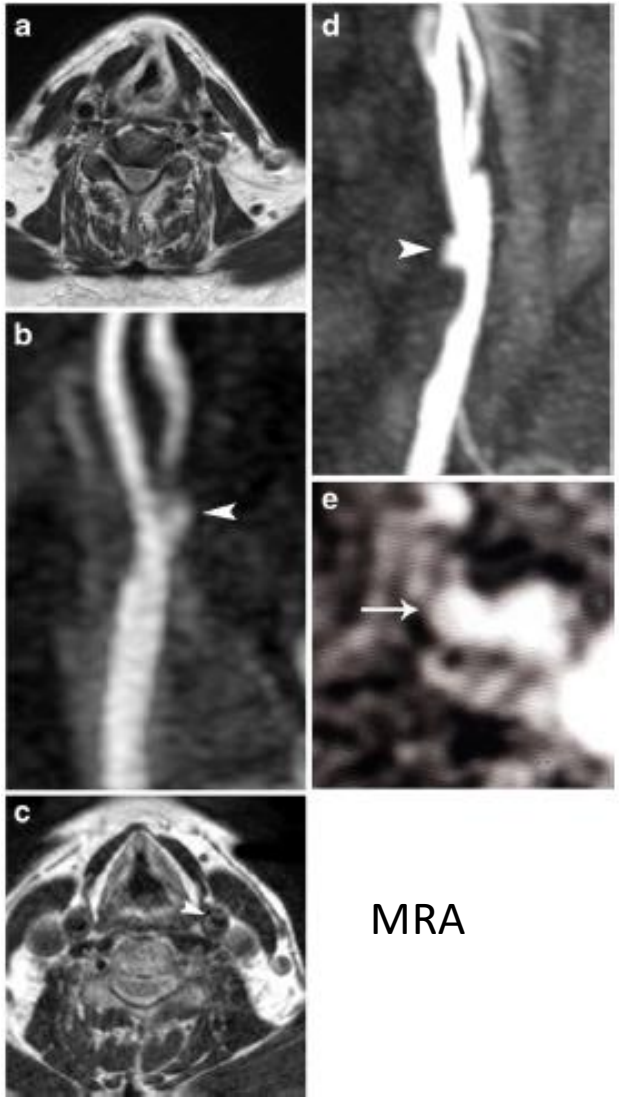
Evaluation of Large Artery (Intracranial/Extracranial) Sources

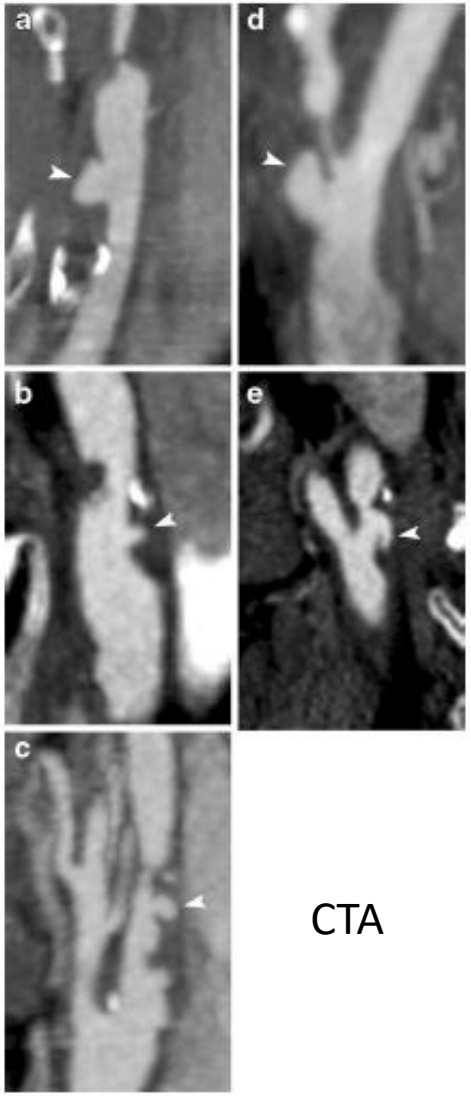
- "Significant" atherosclerotic disease (historical definition ≥50% stenosis)
- Dissection
- Vasculitis

BUT Don't Forget About…

Ulcerative Atherosclerotic Plaques (<50%)



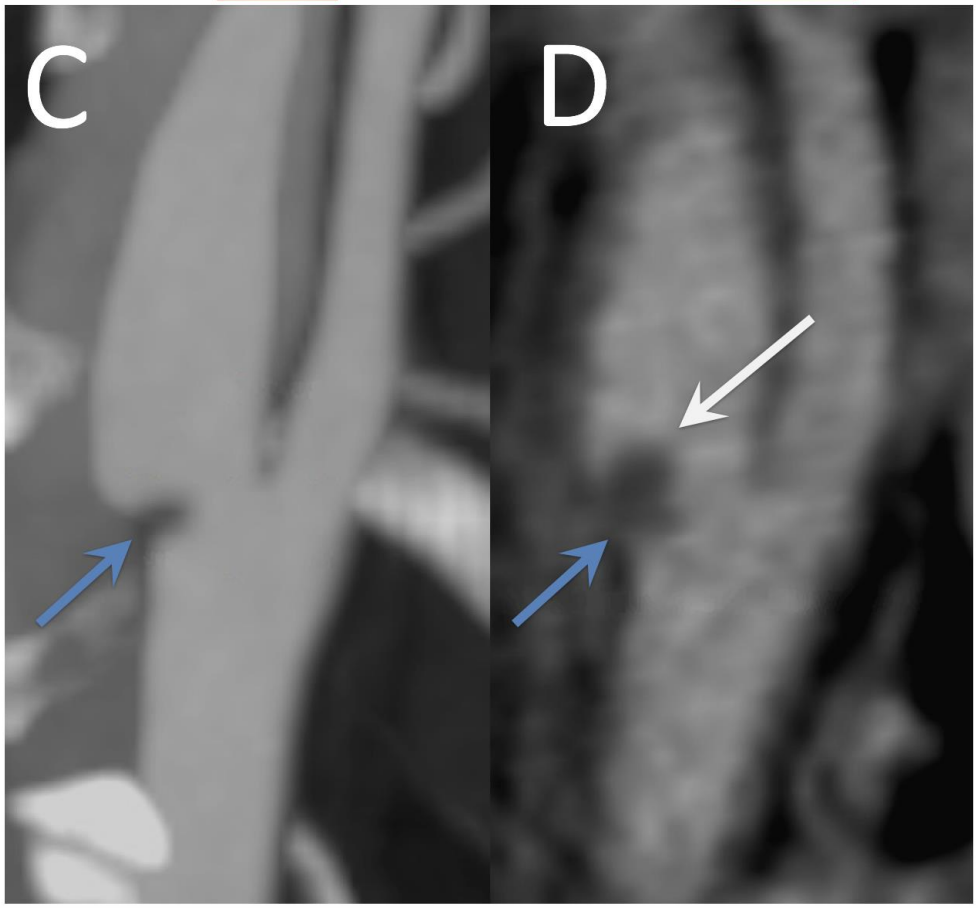
MRA



CTA

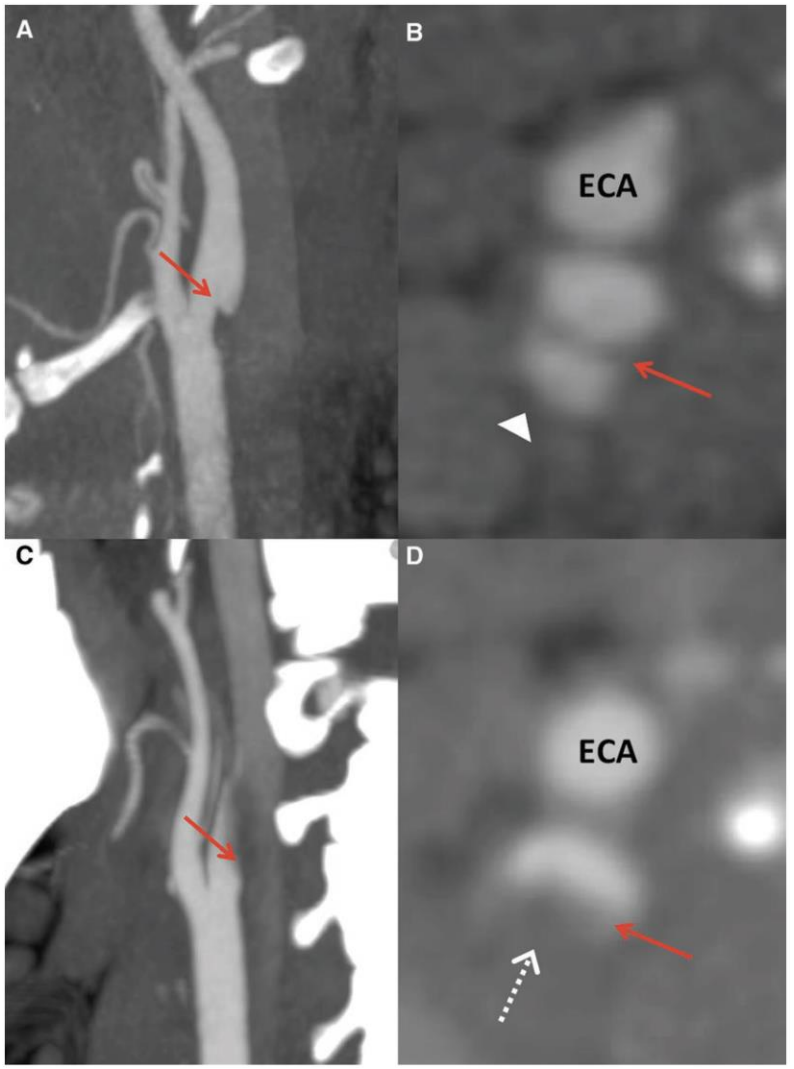
Insights Imaging (2017) 8:213–225

Carotid Web (CaW)



Kim S, Nogueira RG, Haussen DC.

Courtesy of Diogo Haussen MD



Haussen DC et al. Stroke 2017; 48

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Limitations	
Inclusion of variable fraction of lacunar infarcts and intracranial arterial stenosis dependent on extent of testing performed	**Transesophageal echocardiography (TEE)** not recommended and therefore could miss other causes (e.g. aortic arch atherosclerosis)

Lancet Neurol 2014;13:429-438.

Cardiac Testing

TTE as initial test	TEE as initial test
• Patients ≥45 years with a neurologic event and no identified cerebrovascular disease • Any patient with an abrupt occlusion of a major peripheral or visceral artery • Patients with a high suspicion of left ventricular thrombus • Patients in whom TEE is contraindicated (eg, esophageal stricture, unstable hemodynamic status) or who refuse TEE	• Patients <45 years without known cardiovascular disease (ie, absence of infarction or valvular disease history) • Patients with a high pretest probability of a cardiac embolic source in whom a negative TTE would be likely to be falsely negative • Patients with AF and suspected left atrial or LAA thrombus • Patients with a mechanical heart valve • Patients with suspected aortic pathology

Manning WJ. Available at: http://www.uptodate.com/contents/echocardiography-in-detection-of-cardiac-and-aortic-sources-of-systemic-embolism. Accessed December 15, 2015.

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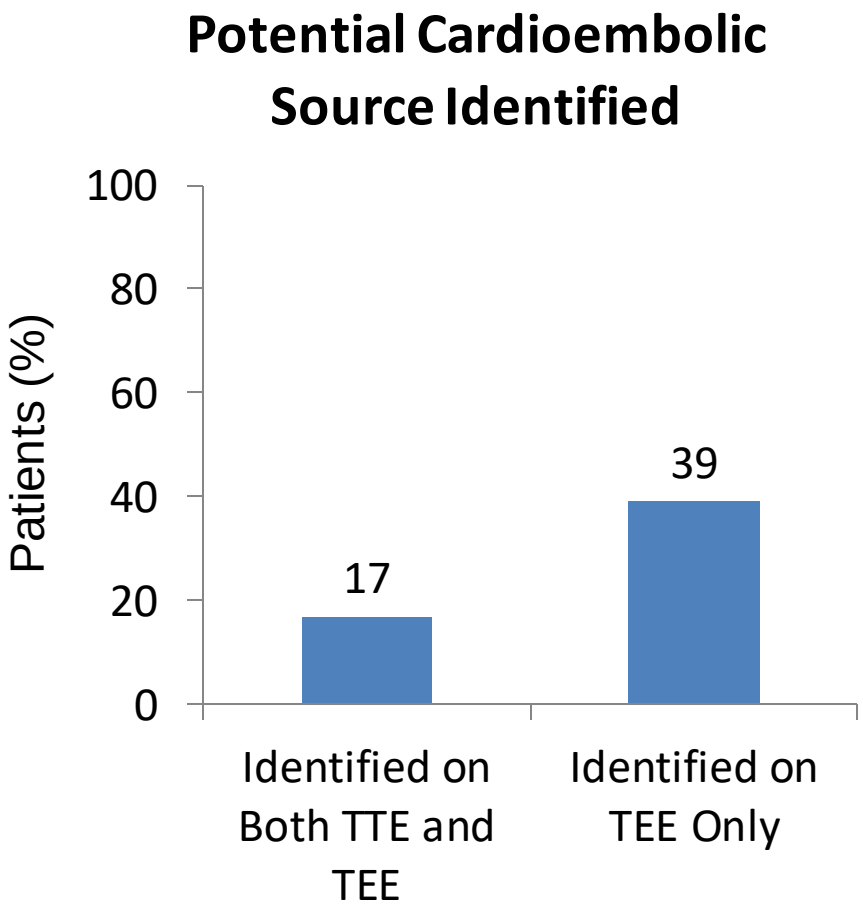
DON'T BELIEVE IT! THERE'S VALUE FROM EACH TEST.

Manning WJ. Available at: http://www.uptodate.com/contents/echocardiography-in-detection-of-cardiac-and-aortic-sources-of-systemic-embolism. Accessed December 15, 2015.

TEE is More Likely to Identify Left Atrial Appendage Thrombus and Significant Aortic Arch Disease



Potential Cardiac Source	TTE	TEE
Major risk factor		
LA cavity thrombus	0	1 (1%)
LA appendage thrombus	1 (1%)	38 (16%)
LV thrombus	2 (1%)	*
Aortic thrombus	0	*
Dilated cardiomyopathy (LVEF<35%)	5 (2%)	*
Mitral valve stenosis	0	*
Minor risk factors		
Mitral valve prolapse	4 (2%)	*
Mitral annular calcification	4 (2%)	*
Calcified aortic stenosis	8 (3%)	*
Patent foramen ovale	3 (1%)	12 (5%)
Spontaneous echo contrast	2 (1%)	5 (2%)
Atrial septal aneurysm	5 (2%)	8 (3%)
LV aneurysm	1 (1%)	*
Aortic aneurysm	0	*
False tendon	0	*
Aortic plaques	1 (1%)	69 (30%)
Other	2 (1%)	*

de Bruijn SF et al. *Stroke.* 2006;37:2531-2534.

TTE Parameters can Identify Patients More Likely to have Occult Atrial Fibrillation

Variable	N	PAF	Non-PAF	P-Value
LA Diameter cm, mean	86	4.2 (n=9)	3.7 (n=77)	0.04
LAVI (mL/m2), mean	68	37.5 (n=7)	29.2 (n=61)	0.07

LA=Left atrium; a'=Tissue Doppler velocity; A=Late mitral inflow Doppler velocity; LAVI=Left atrial volume index; IVSd=Interventricular septal thickness in late diastole.

Kasshout O, et al. Neurohospitalist 2018.

Start with a TTE; if a embolic source isn’t identified, get a TEE.

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Lancet Neurol 2014;13:429-438.

Cardiac Monitoring Strategies

Holter Monitor

Event Recorder

Mobile Cardiac Telemetry

24-48 hours of monitoring	Up to 30 days of monitoring	Up to 30 days of monitoring
External loop recorder	Event-triggered loop recorder	External loop recorder
Saves all cardiac rhythm data	Saves events only	Saves all cardiac rhythm data
	62% patient compliance[1]	53-90% patient compliance[2-5]

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.

Studies of MCOT Monitoring in Cryptogenic Stroke Patients

Study (Year)	N	AF Definition	Monitoring Duration	AF Yield
Tayal (2006)	56	Any duration	MCOT 21 Days	**Overall 23%** AF < 30 sec 18% AF > 30 sec 5%
Gaillard (2010)	98	32 seconds	TTM 30 days	**9%**
Bhatt (2011)	62	30 seconds	MCOT 28 days	**24%** AF > 5 min 9%
Flint (2012)	236	5 seconds	MCOT 30 days	**Overall 11%** AF < 30 sec 4% AF > 30 sec 7%
Kamel (2013)	20	30 seconds	MCOT 21 days	**0%**
Miller (2013)	156	30 seconds	MCOT 30 days	**Overall 17%** AF < 30 sec 12% AF > 30 sec 4%
Gladstone (2014)	572	30 seconds	Event Monitor 30 days vs 24 Holter	**16.1%** in event monitor vs. **3.2%** Holter
Emory (2015)	132	30 seconds	MCOT 30 days	**13%**

Glotzer TV, Ziegler PD. *Heart Rhythm*. 2015;12:234-241.
Kasshout O, et al. Neurohospitalist 2018

Reveal LINQ ™ ICM

The Smallest ICM to Provide Continuous and Wireless Data Collection and Trending

No wires or leads

Proven AF algorithm accurately detects AF in 98.5% of patients[1]

Three-year longevity for long-term monitoring[2]

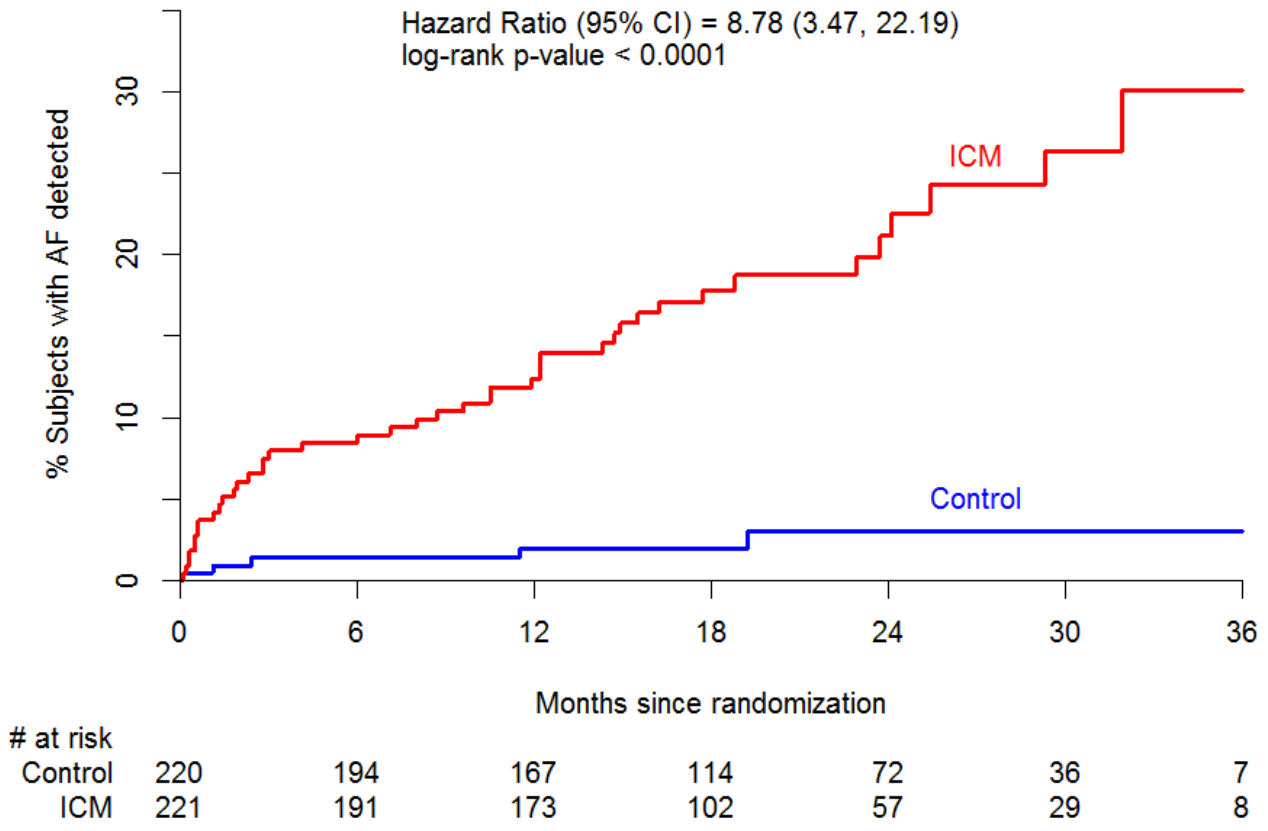
MR Conditional at 1.5 and the only ICM at 3.0 Tesla with no post-insertion waiting required‡

Reveal LINQ ICM is 1/3 the width of an AAA battery

† Reveal LINQ ICM has been demonstrated to pose no known hazards in a specified MR environment with specified conditions of use. Please see Reveal LINQ ICM clinician manual or MRI Technical Manual for more details.

1. Hindricks G, Pokushalov E, Urban L, et al. Performance of a new leadless implantable cardiac monitor in detecting and quantifying atrial fibrillation: Results of the XPECT Trial. *Circ Arrhythm Electrophysiol*. April 2010;3(2):141-147.
2. See the Reveal LINQ ICM clinician manual for usage parameters

CRYSTAL AF: Detection of AF at 36 Months



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

Treatment Approaches to Cryptogenic Stroke

Cryptogenic Stroke (ESUS) Studies: Aspirin vs Direct Oral Anticoagulant

RE-SPECT ESUS[1]	NAVIGATE ESUS[2]
• ~6000 patients • Randomized to dabigatran 110 or 150 mg or ASA • ~3 years • Primary end point: Time to first recurrent stroke (ischemic, hemorrhagic, or unspecified)	• ~7000 patients • Randomized to rivaroxaban or ASA • ~3 years • Primary end point: Time to first recurrent stroke (ischemic, hemorrhagic, or unspecified) or TIA

1. ClinicalTrials.gov. NCT02239120. Accessed Dec 15, 2015
2. ClinicalTrials.gov. NCT02313909. Accessed Dec 15, 2015.

NAVIGATE-ESUS Trial Stopped Early

- No reduction in recurrent stroke with Xarelto 15mg daily (vs aspirin 100mg daily) and increased risk of ICH and major systemic bleeding

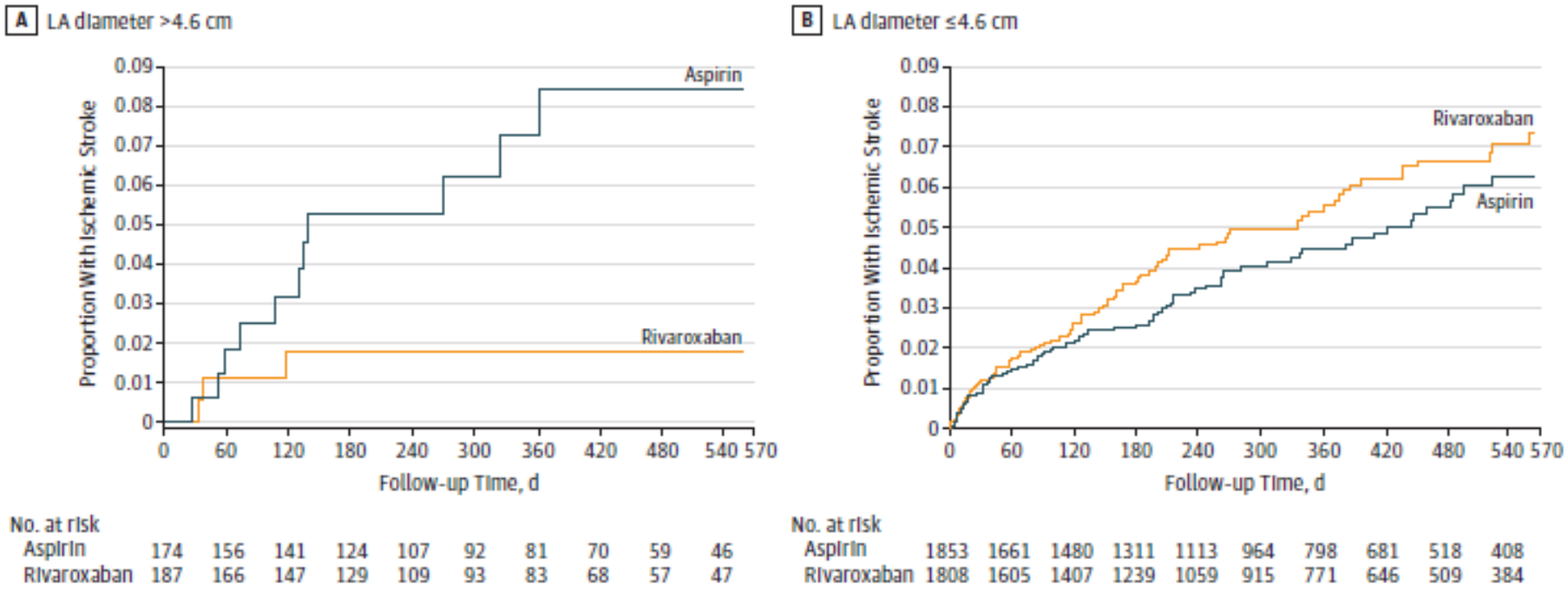
Table 2. Efficacy Outcomes.*

Outcome	Rivaroxaban Group (N=3609)	Aspirin Group (N=3604)	Hazard Ratio (95% CI)†
	no. of patients (annualized rate)		
Primary efficacy outcome: any recurrent stroke or systemic embolism	172 (5.1)	160 (4.8)	1.07 (0.87–1.33)
Secondary efficacy outcomes			
Any recurrent stroke‡	171 (5.1)	158 (4.7)	1.08 (0.87–1.34)
Ischemic stroke‡	158 (4.7)	156 (4.7)	1.01 (0.81–1.26)
Hemorrhagic stroke§	13 (0.4)	2 (0.1)	6.50 (1.47–28.8)
Systemic embolism	1 (<0.1)	2 (0.1)	0.50 (0.05–5.51)
Any recurrent stroke, myocardial infarction, death from cardiovascular causes, or systemic embolism¶	207 (6.2)	195 (5.8)	1.06 (0.87–1.29)
Any disabling stroke	41 (1.2)	29 (0.8)	1.42 (0.88–2.28)
Myocardial infarction	17 (0.5)	23 (0.7)	0.74 (0.39–1.38)
Death from any cause	65 (1.9)	52 (1.5)	1.26 (0.87–1.81)
Death from cardiovascular causes¶	34 (1.0)	23 (0.7)	1.48 (0.87–2.52)

Hart R, et al. N Engl J Med 2018;378:2191-2201.

NAVIGATE-ESUS & LA diameter

Figure 2. Kaplan-Meier Curves for Time to First Ischemic Stroke



*LA diameter >4.6cm (5% of NAVIGATE ESUS cohort, 2% of Emory cohort) was associated with a significantly increased risk of stroke on aspirin compared with rivaroxaban (6.5% vs 1.7%, p=0.02)

JAMA Neurol. doi:10.1001/jamaneurol.2019.0617
Published online April 8, 2019.

EMORY HEALTHCARE

RE-SPECT ESUS

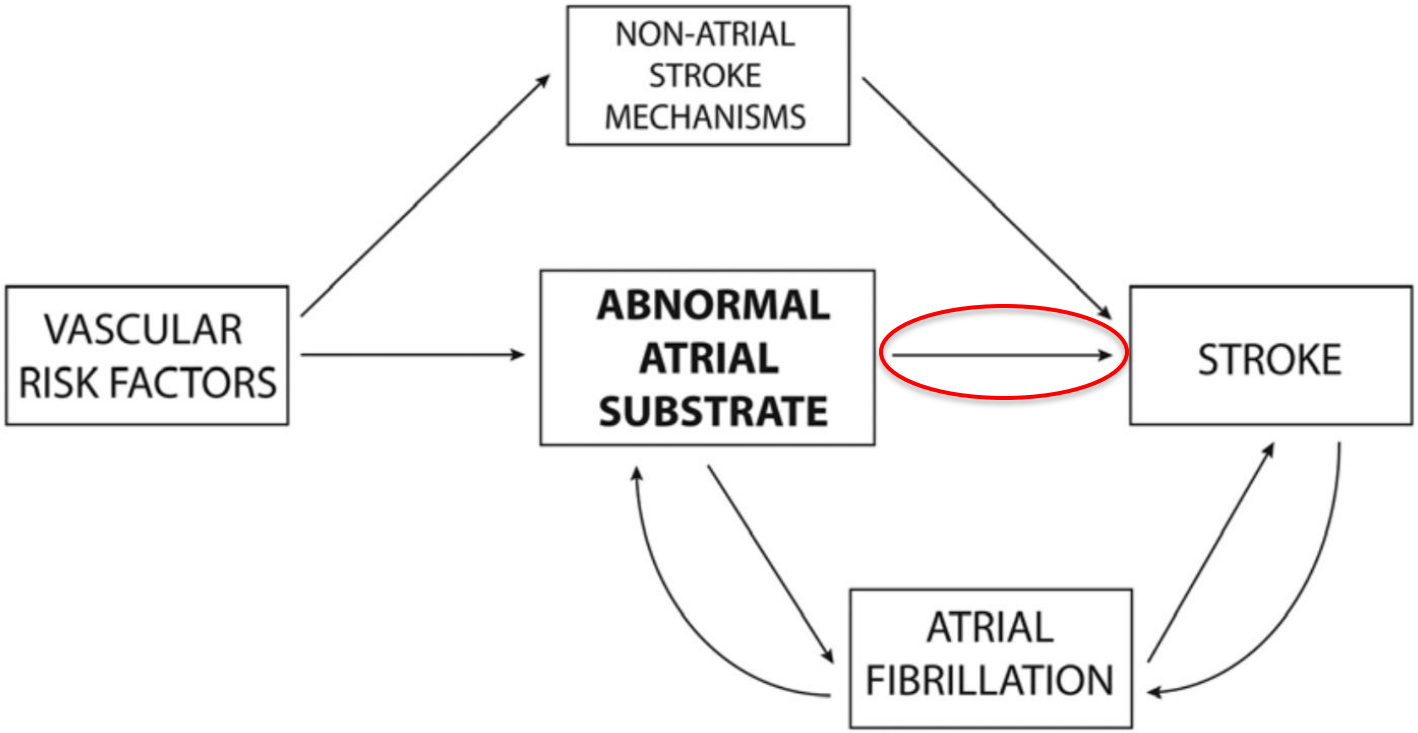
- 5390 ESUS patients randomized to aspirin 100mg daily vs dabigatran 150mg BID for prevention of recurrent stroke.
  - 110mg BID for moderate CKD or age >75 years
- Mean follow-up: 19 months
- Recurrent stroke per year:
  - Dabigatran 4.1%, Aspirin 4.8% (HR 0.85, p=0.1)
- Major bleeding per year:
  - Dabigatran 1.7%, Aspirin 1.4%

N Engl J Med 2019; 380:1906-1917

Apixaban for treatment of embolic stroke of undetermined source (ATTICUS)

- Researchers aimed to determine whether the direct oral factor Xa inhibitor apixaban, started within 28 days after index stroke, is superior to aspirin in preventing new ischemic lesions in subjects with remote cardiac monitoring. Primary endpoint was detection of new ischemic lesions in flair and diffusion-weighted (DWI) MRI at 12-months follow-up.
- ESUS patients with risk profile for cardiac thromboembolism (ie, left atrium [LA] size > 45 mm, spontaneous echo contrast in LA appendage, LA appendage flow velocity ≤ 0.2 cm/s, atrial high-rate episodes, CHA2DS2-Vasc score ≥ 4, patent foramen ovale).
- Findings showed no difference in the primary outcome of new ischemic lesions on follow-up MRI, and no difference in the secondary outcome of clinical cerebrovascular event.

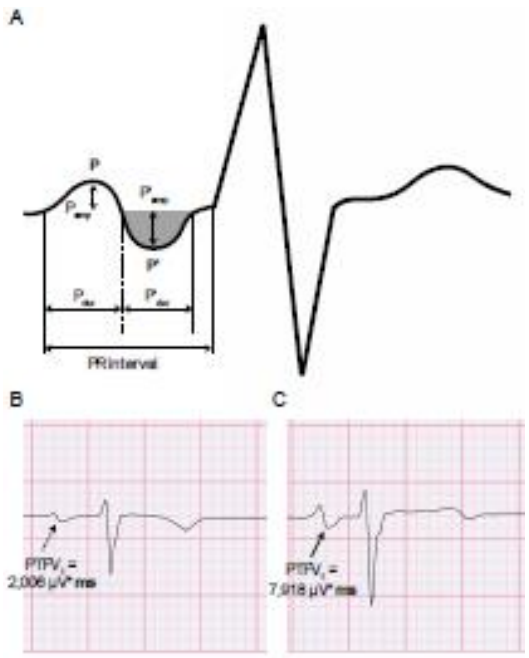
Atrial Cardiopathy:
A New Thromboembolic Model



ARCADIA Trial

(AtRial Cardiopathy and Antithrombotic Drugs In prevention After cryptogenic stroke)

- Randomize patients with Atrial Cardiopathy to Eliquis vs Aspirin
  - Atrial Cardiopathy defined by 1 of the following:
    - $PFTV_1$ >5000 µV*ms on 12-lead ECG
    - Left atrial diameter/BSA ≥ 3 cm/m^2 on echo (severe enlargement)
    - Serum NT-proBNP >250 pg/mL
- Primary endpoint: Recurrent stroke



Emory PI: Fadi Nahab MD

PFO Closure in Cryptogenic Stroke: What is it's role?

Cryptogenic Stroke & PFO: Risk of Recurrence is Low in Young Patients

Age	+PFO 2-yr stroke or death rate	-PFO 2-yr stroke or death rate	P-value
<55 yrs	2.0%	9.3%	0.15
55-64 yrs	10.0%	13.9%	0.70
≥65 yrs	37.9%	14.5%	0.01

Multiple randomized controlled trials of PFO Closure in cryptogenic stroke have consistently shown very low risk of recurrent stroke in younger patients regardless of treatment.

Stroke 2004;35:2145-2149.

REDUCE PFO Closure Trial

- 664 patients (age ≤ 60 yrs) randomized 2:1 in PFO closure with GORE device vs medical therapy (anticoagulants not allowed)
  - Freedom from recurrent clinical ischemic stroke at 24 months
  - Incidence of new brain infarct on MRI at 24 months

NEJM 2017;377:1033-1042

REDUCE PFO Closure Trial

Endpoint	Closure group (n=441)	Medical group (n=223)	Hazard ratio (95% CI)	P value
Annualized recurrent stroke rate (per 100 person-years)	0.39	1.70	0.23 (0.09-0.62)	0.001
New Brain infarct 24 mos, n (%)	22 (5.7)	20 (11.3)	0.51 (0.29-0.91)	0.024
Silent infarct at 24 months, %	4.4	4.5	0.98 (0.43-2.23)	0.97
Atrial Fibrillation	6.6%	0.4%		
Serious Device Adverse Events	6 (1.4%) 3 device dislocations, 2 device thromboses, 1 aortic dissection			

NEJM 2017;377:1033-1042

CLOSE PFO Closure Trial

- 663 patients (age ≤ 60 years) with PFO and either atrial septal aneurysm (ASA) or large shunt (≥30 bubbles within 3 cardiac cycles)
- Randomized to 3 groups: PFO closure, oral anticoagulant, or antiplatelet therapy
- Mean follow-up 5 years

NEJM 2017;377:1011-1021.

CLOSE PFO Closure Trial

Endpoint	Closure group	Antiplatelet group	Hazard ratio (95% CI)	P value
Total strokes over 5 years, number	0	4	0.03 (0.00-0.25)	<0.001
Atrial Fibrillation	4.6%	0.9%		0.02
Major Device Complications	14 (5.9%) 9 atrial fibrillation, 1 atrial flutter, 2 SVT, 1 air embolism, 1 hyperthermia			

NEJM 2017;377:1011-1021.

Meta-analysis of PFO randomized studies with antiplatelet vs anticoagulant

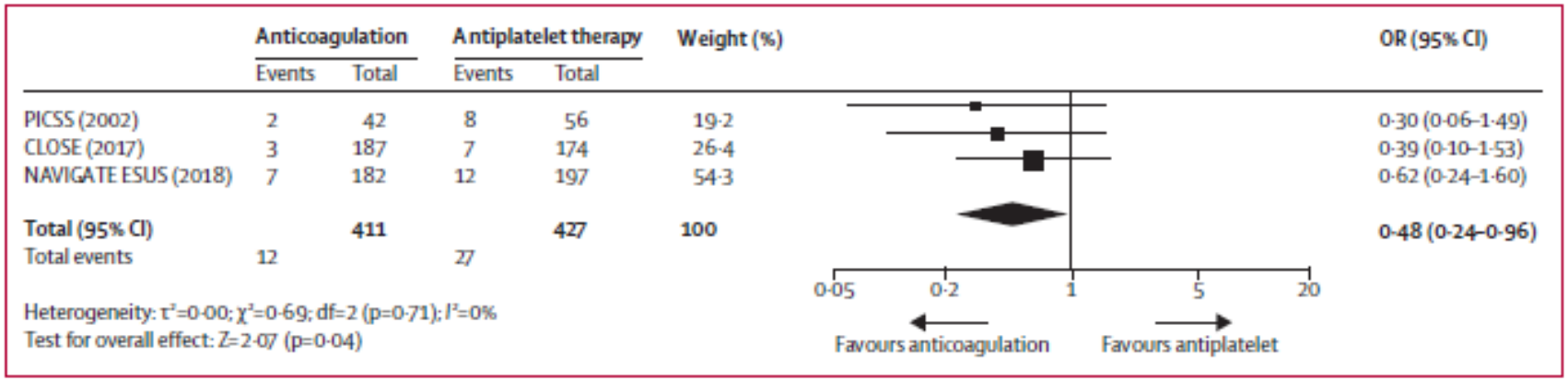


Figure 2: **Forest plot of randomised comparisons of anticoagulation or antiplatelet therapy for patients with patent foramen ovale**
OR=odds ratio.

- Summary OR of 0.48 (95% CI 0.24-0.96) in favor of anticoagulation to reduce recurrent ischemic stroke.

Lancet Neurol 2018; 17: 1053–60

JAMA Neurology | Special Communication

Proposal for Updated Nomenclature and Classification of Potential Causative Mechanism in Patent Foramen Ovale-Associated Stroke

Akram Y. Elgendy, MD; Jeffrey L. Saver, MD; Zahid Amin, MD; Konstantinos Dean Boudoulas, MD; John D. Carroll, MD; Islam Y. Elgendy, MD; Iris Q. Grunwald, MD; Zachary M. Gertz, MD; Ziyad M. Hijazi, MD, MPH; Eric M. Horlick, MD; Scott E. Kasner, MD; David M. Kent, MD; Preetham Kumar, MD; Clifford J. Kavinsky, MD, PhD; David S. Liebeskind, MD; Helmi Lutsep, MD; Mohammad K. Mojadidi, MD; Steven R. Messé, MD; Jean-Louis Mas, MD; Heinrich P. Mattle, MD; Bernhard Meier, MD; Ahmad Mahmoud, MD, MSc; Ahmed N. Mahmoud, MD; Fabian Nietlispach, MD, PhD; Nimesh K. Patel, MD; John F. Rhodes, MD; Mark Reisman, MD; Robert J. Sommer, MD; Horst Sievert, MD; Lars Søndergaard, MD; Muhammad O. Zaman, MD; David Thaler, MD; Jonathan M. Tobis, MD, MSCAI

IMPORTANCE Recent epidemiologic and therapeutic advances have transformed understanding of the role of and therapeutic approach to patent foramen ovale (PFO) in ischemic stroke. Patent foramen ovale is likely responsible for approximately 5% of all ischemic strokes and 10% of those occurring in young and middle-aged adults.

OBSERVATIONS Randomized clinical trials have demonstrated that, to prevent recurrent ischemic stroke in patients with PFO and an otherwise-cryptogenic index ischemic stroke, PFO closure is superior to antiplatelet medical therapy alone; these trials have provided some evidence that, among medical therapy options, anticoagulants may be more effective than antiplatelet agents.

CONCLUSIONS AND RELEVANCE These new data indicate a need to update classification schemes of causative mechanisms in stroke, developed in an era in which an association between PFO and stroke was viewed as uncertain. We propose a revised general nomenclature and classification framework for PFO-associated stroke and detailed revisions for the 3 major stroke subtyping algorithms in wide use.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: A complete list of the Patent Foramen Ovale Associated Stroke International Working Group authors appears at the end of the article.

Corresponding Author: Jonathan M. Tobis, MD, MSCAI, David Geffen School of Medicine, Division of Cardiology, Department of Medicine, University of California, Los Angeles, 10833 Le Conte Ave, Factor Bldg CHS, Room B-976, Los Angeles, CA 90095 (jtobis@mednet.ucla.edu).

Proposal for Classifying PFO Association with ESUS

Table 2. Proposed Flexible Clinical Practice Approach to Classifying Patent Foramen Ovale Causal Association in Patients With Embolic Infarct Topography and Without Other Major Stroke Sources[a]

Risk source	Features	RoPE Score	
		Low[b]	High[b]
Very high	A PFO and a straddling thrombus	Definite	Definite
High	(1) Concomitant pulmonary embolism or deep venous thrombosis preceding an index infarct combined with either (2a) a PFO and an atrial septal aneurysm or (2b) a large-shunt PFO	Probable	Highly probable
Medium	Either (1) a PFO and an atrial septal aneurysm or (2) a large-shunt PFO	Possible	Probable
Low	A small-shunt PFO without an atrial septal aneurysm	Unlikely	Possible

Abbreviations: PFO, patent foramen ovale; RoPE, the Risk of Paradoxical Embolism Score.

[a] The algorithm in this table is proposed for use in flexible clinical practice, when application of an entire formal classification system is not being conducted.

[b] The RoPE score includes points for 5 age categories, cortical infarct, absence of hypertension, diabetes, prior stroke or transient ischemic attack, and smoking. A higher RoPE score (≥7 points) increases probability of causal association.

- RoPE Score: Age, Cortical Infarct, Absence of HTN or DM, Prior stroke or TIA, Smoking.

Risk of Recurrence is Low in Young Patients with PFO and Cryptogenic Stroke on Medical Therapy

Endpoint	REDUCE Trial Medical Therapy (Antiplatelet) (n=223)	CLOSURE PFO Trial Medical Therapy- (Antiplatelet) (n=409)*	CLOSURE PFO Trial Medical Therapy- (Anticoagulant) (n=187)**
Annualized recurrent stroke rate (per 100 person-years)	1.7	1.3 (per-protocol) 1.2 (intention to treat)	0.3 (per-protocol) 0.3 (intention to treat)

*Kaplan-Meier 5 year cumulative estimate of stroke was 4.9%.

**Kaplan-Meier 5 year cumulative estimate of stroke was 1.5%.

NEJM 2017;377:1033-1042.

NEJM 2017;377:1011-1021.

Emory Experience

Emory Cryptogenic Stroke/ESUS Recommended Diagnostic Testing

Markers of Coagulation

- D-dimer
  - Marker of fibrinolysis; byproduct of fibrin degradation
- Fibrin monomer (soluble fibrin)
  - Marker of coagulation activation; byproduct of fibrinogen conversion to fibrin
- Prothrombin fragment 1.2 (F 1+2)
  - Marker of coagulation activation; peptide released during conversion of prothrombin to thrombin
- Thrombin-antithrombin complex (TAT)
  - Marker of coagulation activation; complex formed during thrombin formation

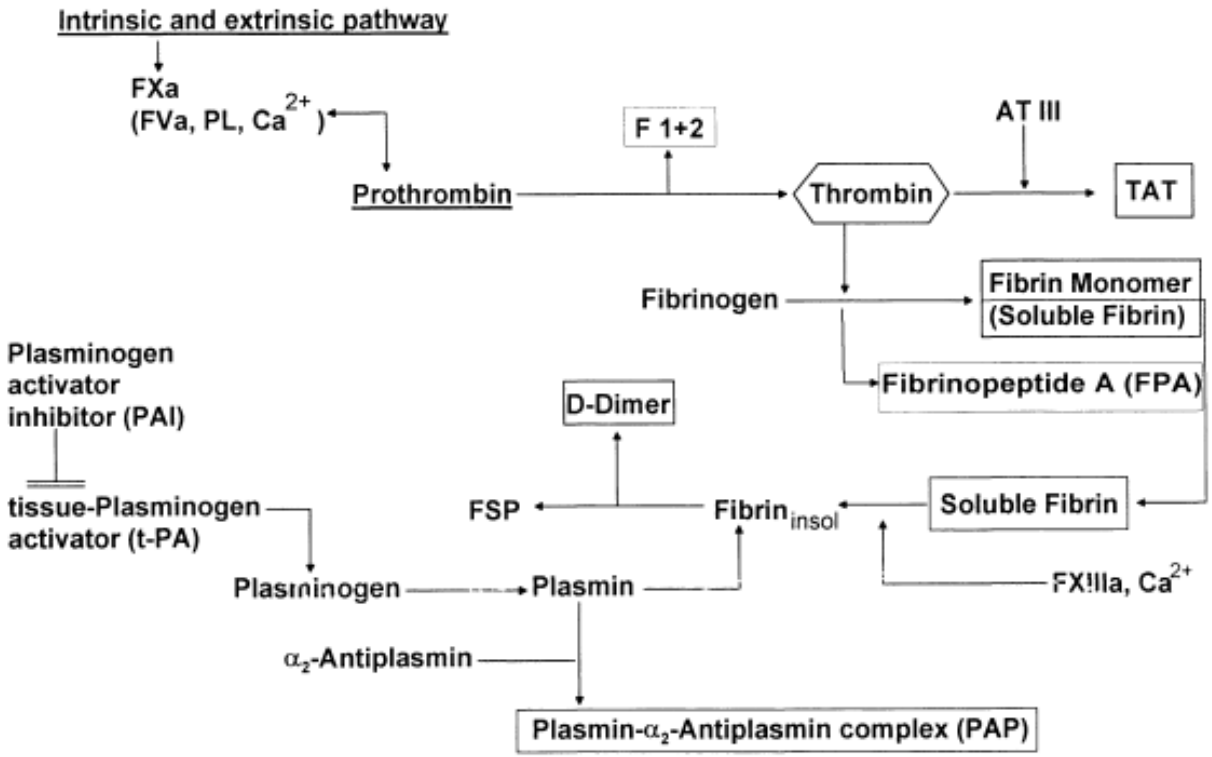


FIG. 1. Pathway of formation of activation markers of coagulation and fibrinolysis.

Dati F, et al. Semin Thromb Hemost 1998; 443-448.

Methods: MOCHA Validation Study

- Cohort:
  - Consecutive cryptogenic stroke patients meeting Embolic Stroke of Undetermined Source (ESUS) criteria seen in the Emory Clinic from January 1, 2017 to October 31, 2018
    - Inclusion Criteria:
      - ≥ 18 years
      - Completion of prolonged cardiac monitoring [mobile cardiac outpatient telemetry (MCOT) and/or implantable loop recorder (ILR)] from the Emory cardiac registry.
    - Exclusion Criteria:
      - On anticoagulation therapy
      - Known malignancy, hypercoagulable disorders, VTE
  - The MOCHA profile was obtained ≥ 2 weeks after the index stroke and an abnormal MOCHA profile was defined as **≥2** elevated markers.
  - Prespecified endpoints:
    - **New diagnosis of AF, malignancy, other hypercoagulable disorder, VTE, recurrent stroke and major hemorrhage.**
    - Composite outcome included AF, malignancy, other hypercoagulable disorder or VTE
  - Antithrombotic Treatment:
    - Pilot study: January 1, 2016-December 31, 2016- Maintained on aspirin
    - **Validation study: January 1, 2017-October 31, 2018- Treatment based on physician discretion considering MOCHA profile and left atrial volume index on transthoracic echocardiography**

Neurology® 2020;94:1-e8.

MOCHA **Validation** Study

Table 2 Endpoints stratified by MOCHA markers

Endpoints	Abnormal MOCHA profile (n = 53), n (%)	Normal MOCHA profile (n = 79), n (%)	*p* Value
AF	4 (8)	7 (9)	0.79
Malignancy	11 (21)	0 (0)	<0.001
VTE	5 (9)	0 (0)	0.009
Hypercoagulable disorder	6 (11)	0 (0)	0.004
Composite outcome	24 (45)[a]	7 (9)	<0.001

Abbreviations: AF = atrial fibrillation; MOCHA = markers of coagulation and hemostatic activation; VTE = venous thromboembolism.
[a] Two patients had >1 composite endpoint during follow-up.

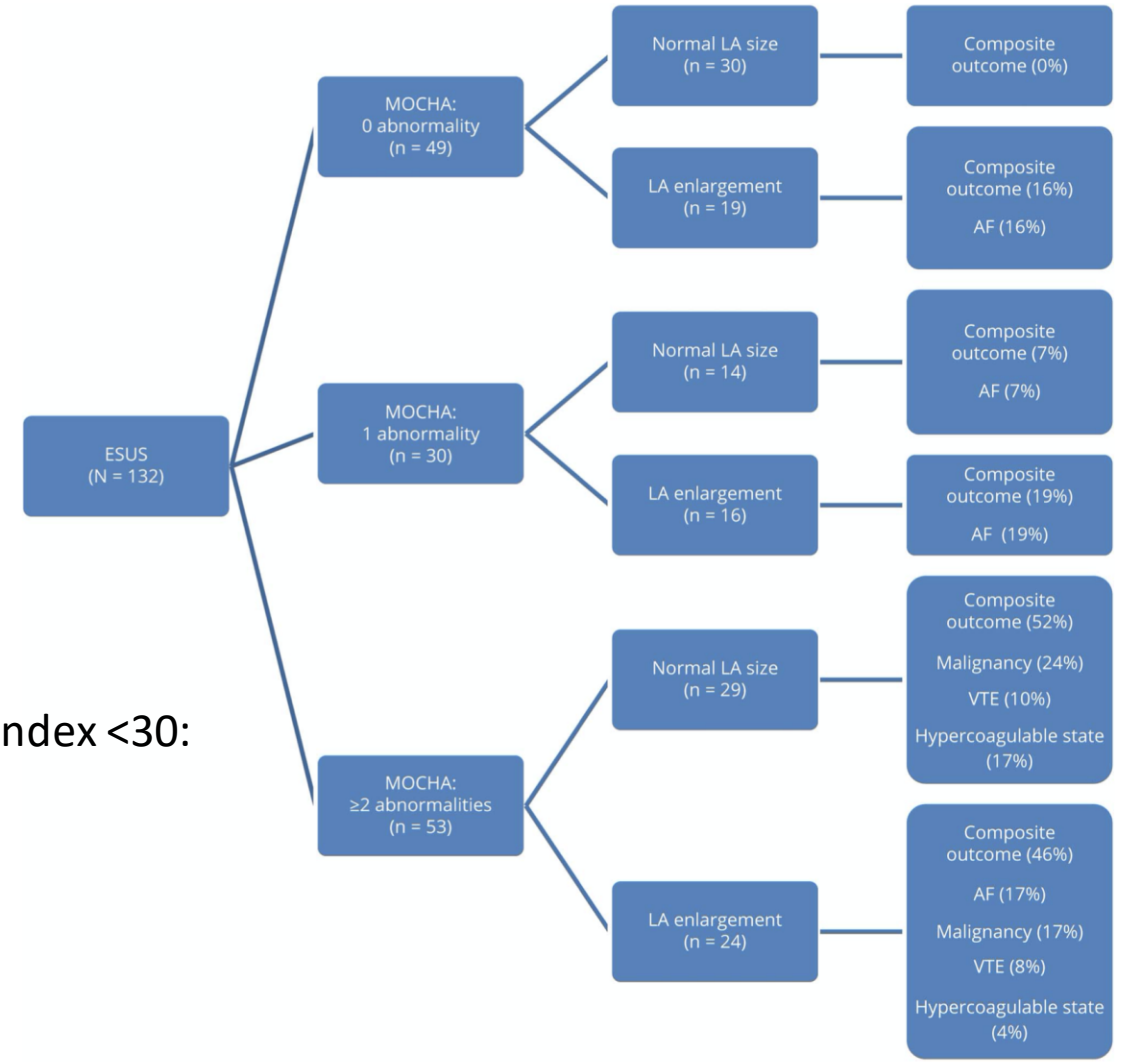
[a]All MOCHA negative patients with AFib had left atrial enlargement
[b]Cancers include prostate, breast, colon, bladder, renal, polycythemia vera, acute myelocytic leukemia
[c]Hypercoagulable disorders included antiphospholipid antibody syndrome, von willebrand factor abnormality, left atrial appendage clot, nephrotic syndrome.

Neurology® 2020;94:1-e8.

MOCHA and LA Size Aid in Identifying Causes of Cryptogenic Stroke

LA diameter <4.0cm <u>AND</u> LA volume index <30: ILR is low yield

Figure 2 Flow diagram of composite outcome incorporating MOCHA and left atrial enlargement



AF = atrial fibrillation; ESUS = embolic stroke of undetermined source; LA = left atrium; MOCHA = markers of coagulation and hemostatic activation; VTE = venous thromboembolism.

Neurology® 2020;94:1-e8.

Proposed Cryptogenic Stroke Treatment Approach

- **Preferred therapy = single antiplatelet agent unless:**
  - **Heart rhythm monitoring shows atrial fibrillation**
    - **Anticoagulation**
  - **TTE with large left atrium (e.g. LAVI ≥ 40) and no prior valvular disease**
    - **Cardiac monitoring; consider ARCADIA trial. Anticoagulation in patients with low bleeding risk may be beneficial.***
  - **MOCHA ≥ 2 markers elevated**
    - **Routine cancer screening; CT chest in 35+ pack-yr smokers and consider pan-CT/PET. Cardiac monitoring. Consider anticoagulation pending further cardiac and malignancy workup.**
  - **Migraine w/ aura**
    - **Headache prophylaxis for frequent HA; present in a high percentage of young cryptogenic stroke patients with normal MOCHA**
  - **Recurrent stroke on antiplatelet agent**
    - **Assess medication adherence, drug-drug interactions (e.g. NSAID use) and opportunity to optimize risk factors before considering PFO closure or anticoagulation**
  - **PFO**
    - **Monitor with prolonged outpatient telemetry; if MOCHA abnormal, assess for VTE (limb ultrasound +/- contrast-enhanced MRV pelvis), malignancy and other hypercoagulability. Anticoagulate if +VTE. Consider PFO closure or anticoagulation if MOCHA abnormal and no VTE.**
  - **COVID-19+ with no VTE**
    - **If age-adjusted d-dimer is elevated (>3000 FEU), consider DOAC x 4 weeks in patients at low risk for bleeding complication. Transition to antiplatelet therapy and 2-4 weeks later repeat d-dimer/MOCHA on antiplatelet therapy to determine longterm antiplatelet therapy (normal d-dimer/MOCHA) or return to DOAC (if d-dimer/MOCHA abnormal).**

*Patel K, et al. Front Neurol 2021.695378.

Summary

- Cryptogenic strokes are common and recurrent strokes are likely to be preventable.
- Ongoing studies will help clarify the best treatment paradigm
- A standardized evaluation of cryptogenic stroke patients will help to identify common risk factors in cryptogenic stroke including atrial fibrillation, malignancy and migraine.