

Cardiac Workup in Acute Stroke: What's Essential vs Overused?

Shawn Lee MD

Cardiac Electrophysiologist

31 yo M presenting with left upper extremity weakness and slurred speech

CT imaging identified acute infarct

78 yo F hx of prior TIA, HTN, DM presenting with right sided numbness and tingling

CT imaging identified acute infarct and chronic old infarcts

Typical workup for acute stroke upon initial evaluation

- H&P, vital signs
- 12 lead EKG
- Neurovascular consultation, imaging +/- intervention
- Inpatient telemetry
- Transthoracic echocardiogram + bubble study
- Transesophageal echocardiogram
- Holter/long term monitoring
- *additional imaging/consults at discretion of neurology and primary care team

Stroke subtypes

Ischemic

- Atherosclerosis
- Small vessel disease
- Cardiac pathology
- Other causes (rare diseases)
- Dissection

Hemorrhagic

Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Wolf ME, Hennerici MG. The ASCOD phenotyping of ischemic stroke (Updated ASCO Phenotyping). *Cerebrovasc Dis.* 2013;36(1):1-5. doi:10.1159/000352050

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Workup of Cardioembolic Stroke

- The presence of a potential major cardiac source of embolism in the absence of significant arterial disease remains the mainstay of clinical diagnosis
- ***Although cardiac and arterial disease often coexist (such as atrial fibrillation and ipsilateral carotid atheroma/small vessel atherosclerosis)**

Significance of cardioembolic stroke

Scope of the problem:

High incidence

*Sagrat Cor Hospital of Barcelona
Stroke Registry, 1840 patients

- 18% of ischemic strokes

Subtype of Cerebral Infarction (n = 1840)	Years of Age			
	< 65 (n= 314)	65-74 (n=501)	75-84 (n=722)	≥ 85 (n=303)
Cardioembolic	46 (14.6)	100 (20)	213 (29.5)	109 (36)

High in-hospital mortality

- 27.3%
 - Frequently non-neurologic causes
 - Sepsis
 - pneumonia

Arboix A, Alió J. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. Curr Cardiol Rev. 2010 Aug;6(3):150-61. doi: 10.2174/157340310791658730. PMID: 21804774; PMCID: PMC2994107.

Early embolic recurrence (7 days)

- 3.9%

When to suspect cardioembolic stroke?

1. Sudden neurologic deficits maximal at onset due to acute interruption of blood flow

(vs. Stuttering course in atherothrombotic disease)

Rapid regression of symptoms due to early recanalization

2. Wernicke's like aphasia or global aphasia without hemiparesis
3. and other clinical factors...

Timsit SG, Sacco RL, Mohr JP, Foulkes MA, Tatemichi TK, Wolf PA, et al. Early clinical differentiation of cerebral infarction from severe atherosclerotic stenosis and cardioembolism. Stroke. 1992;23:486-91.

Arboix, A., Oliveres, M., Massons, J., Pujades, R. and García-Eroles, L. (1999), Early differentiation of cardioembolic from atherothrombotic cerebral infarction: a multivariate analysis. European Journal of Neurology, 6: 677-683.

Table 1. Results of univariate analysis: differences between patients with cardioembolic infarction versus atherothrombotic stroke

Variables	Cardioembolic (n = 956)	Atherothrombotic (n = 945)	p value
Demographics			
Female patients	602 (63%)	471 (49.8%)	
Age, years, mean (SD)	80 (9.14)	77.01 (9.75)	0.000
85 years old or more	317 (33.2%)	219 (23.2%)	0.001
Risk factors (%)			
Hypertension	513 (53.6)	643 (68.0)	0.001
Diabetes mellitus	177 (18.5)	307 (32.5)	0.001
Ischemic heart disease	224 (23.4)	66 (7.0)	0.001
Atrial fibrillation	711 (74.3)	132 (14.0)	0.000
Congestive heart failure	100 (10.4)	48 (5.1)	0.000
History of transient ischemic attack (TIA)	96 (10.0)	133 (14.1)	0.007
History of cerebrovascular disease	174 (18.2)	190 (20.1)	0.286
Previous cerebral hematoma	11 (1.1)	9 (1.0)	0.674
Chronic obstructive pulmonary disease	84 (8.8)	97 (10.3)	0.269
Chronic renal disease	57 (6.0)	32 (3.4)	0.008
Peripheral vascular disease	91 (9.5)	81 (8.6)	0.476
Chronic liver disease	20 (2.1)	22 (2.3)	0.724
Hyperlipidemia	130 (13.6)	234 (24.8)	0.000
Heavy smoking (> 20 cigarettes/day)	42 (4.4)	123 (13.0)	0.000
Clinical features (%)			
Sudden onset	625 (65.3)	401 (42.4)	0.000
Headache	73 (7.6)	116 (12.3)	0.001
Dizziness	27 (2.8)	51 (5.4)	0.005
Early seizures	17 (1.8)	17 (1.8)	0.970
Nausea/vomiting	62 (6.5)	84 (8.9)	0.048
Altered consciousness	264 (27.6)	186 (19.7)	0.000
Motor symptoms	762 (79.6)	718 (76.0)	0.056
Sensory symptoms	346 (36.2)	360 (38.1)	0.381
Visual disturbances	202 (21.1)	225 (23.8)	0.158
Speech disturbances	589 (61.5)	518 (54.8)	0.003
Ataxia	40 (4.2)	78 (8.3)	0.000
Cranial nerve palsy	43 (4.5)	64 (6.8)	0.031

Vascular topography (%)

Middle cerebral artery involvement	620 (64.8)	518 (54.8)	0.000
Anterior cerebral artery	45 (4.7)	35 (3.7)	0.278
Posterior cerebral artery involvement	77 (8.0)	87 (9.2)	0.367
Anterior choroidal artery	4 (0.4)	13 (1.4)	0.026
Vertebral artery	19 (2.0)	57 (6.0)	0.000
Basilar artery	23 (2.4)	91 (9.6)	0.000
Internal carotid involvement	24 (2.5)	67 (7.1)	0.000
Posterior inferior cerebellar artery	9 (0.9)	15 (1.6)	0.206

Third model: demographics, risk factors, clinical features, vascular topography, and complications

Atrial fibrillation	2.757	0.133	15.747 (12.145-20.417)	0.000
Ischemic heart disease	1.137	0.188	3.118 (2.157-4.509)	0.000
Sudden onset	0.676	0.125	1.966 (1.538-2.512)	0.000
Cardiac events	0.526	0.269	1.693 (0.999-2.869)	0.050
Female gender	0.445	0.127	1.56 (1.217-2.000)	0.000
Hyperlipidemia	-0.333	0.161	0.717 (0.523-0.983)	0.039
Visual disturbances	-0.57	0.156	0.566 (0.417-0.768)	0.000
Mild neurological deficit at discharge	-0.514	0.147	0.598 (0.448-0.798)	0.000
Visual disturbances	-0.57	0.156	0.566 (0.417-0.768)	0.000
Diabetes	-0.582	0.144	0.559 (0.422-0.74)	0.000
Ataxia	-0.639	0.287	0.528 (0.301-0.926)	0.026
Hypertension	-0.666	0.13	0.514 (0.398-0.663)	0.000
Basilar artery involvement	-1.193	0.309	0.303 (0.166-0.555)	0.000
Internal carotid involvement	-1.24	0.318	0.289 (0.155-0.54)	0.000

Typical workup for acute stroke upon initial evaluation

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- **12 lead EKG**
- Neurovascular consultation, imaging +/- intervention
- **Inpatient telemetry**
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All patients should have 12 lead EKG

Atrial arrhythmia

- Paroxysmal (most common EKG is normal) vs chronic AF*
- CHADS2Vasc score does not account for duration of AF

Myocardial infarction/repolarization abnormalities

- Acute MI vs. late/missed MI
- Left ventricular thrombus

CHA2DS2-VASc		CHA2DS2-VASc	
Risk	Score	Score	Adjusted stroke rate (% / year)
		0	0
CHF or LVEF <40%	1	1	1.3
Hypertension	1	2	2.2
Age > 75	2	3	3.2
Diabetes	1	4	4
Stroke / TIA /			
Thromboembolism	2	5	6.7
Vascular Disease	1	6	9.8
Age 65-74	1	7	9.6
Female	1	8	6.7
		9	15.2

Mechanisms of thrombus formation in atrial fibrillation

Stasis = thrombus formation in LA and LAA

Endocardial changes due to longstanding atrial fibrillation

- “Rough endocardium” (RE) seen macroscopically due to a granular and wrinkled appearance of the endocardium associated with edematous and fibrous thickening
- Mural thrombi and edema with neutrophil infiltration in the subendocardium could be seen under the microscope

Masawa, N., et al. "Diagnosis of cardiac thrombosis in patients with atrial fibrillation in the absence of macroscopically visible thrombi." *Virchows Archiv A* 422.1 (1993): 67-71.

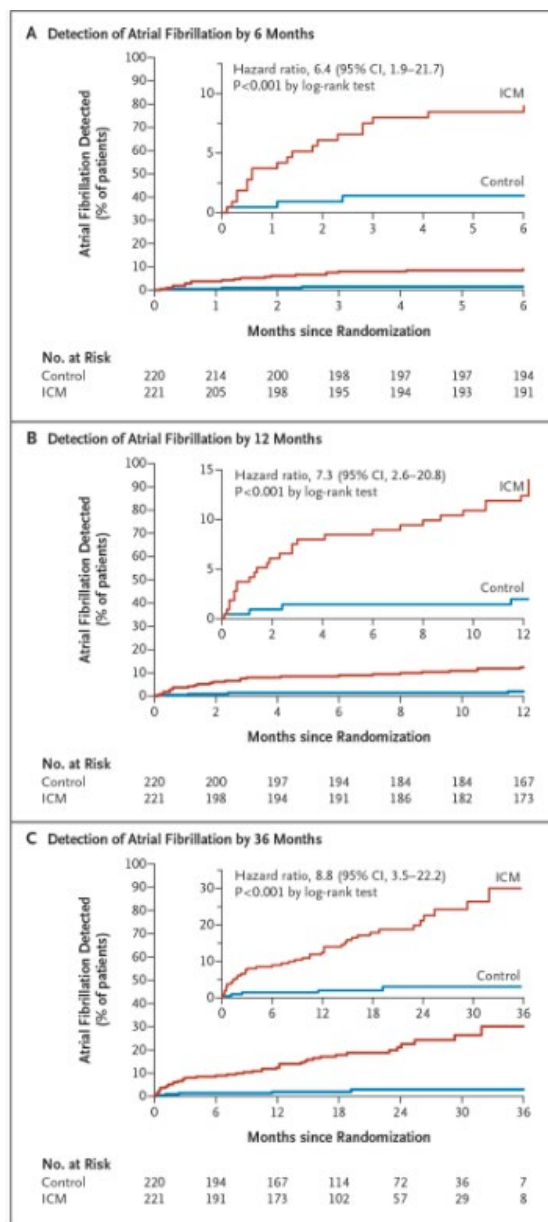
What's essential vs overused?

Better question: when should we consider long(er) term monitoring

Implantable loop recorder (up to 3 years of monitoring) > extended wearable monitor (30 day holter/mobile cardiac telemetry) > Electrocardiogram (10 seconds) for detection of atrial fibrillation and for decision making of initiation of anticoagulation

- Neurovascular findings suggestive of cardioembolic source
 - o Multiple strokes
 - o Age/chronicity of existing infarcts discovered incidentally
- Association of cardiac symptoms (palpitations) that may suggest atrial arrhythmia, if infrequent or asymptomatic patients
- Higher CHADS2Vasc scores

Longer duration of monitoring = better detection of atrial fibrillation



Sanna T, Diener H-C, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al. (CRYSTAL AF Investigators). Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med*. 2014;2014(370):2478-2486. doi:10.1056/NEJMoa1313600

Should ILR be implanted for every patient with stroke?

Loop Study (2021)

- RCT compared prolonged monitoring (ILR) to usual care (serial EKG) in 6000 patients
- The ILR group experienced a threefold increase in AF diagnosis and subsequent initiation of anticoagulants (31.8% in the ILR group vs. 12.2% in the control group)
- AC started if AF duration > 6 mins

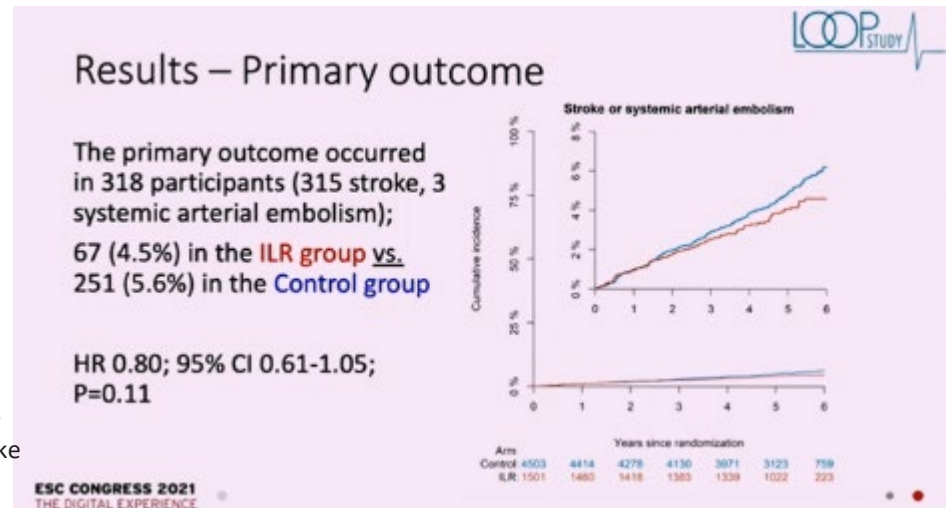
Svensden JH, Diederichsen SZ, Højberg S, et al. Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP Study): a randomised controlled trial. *Lancet*. 2021;398(10310):1507-1516. doi:10.1016/S0140-6736(21)01698-6

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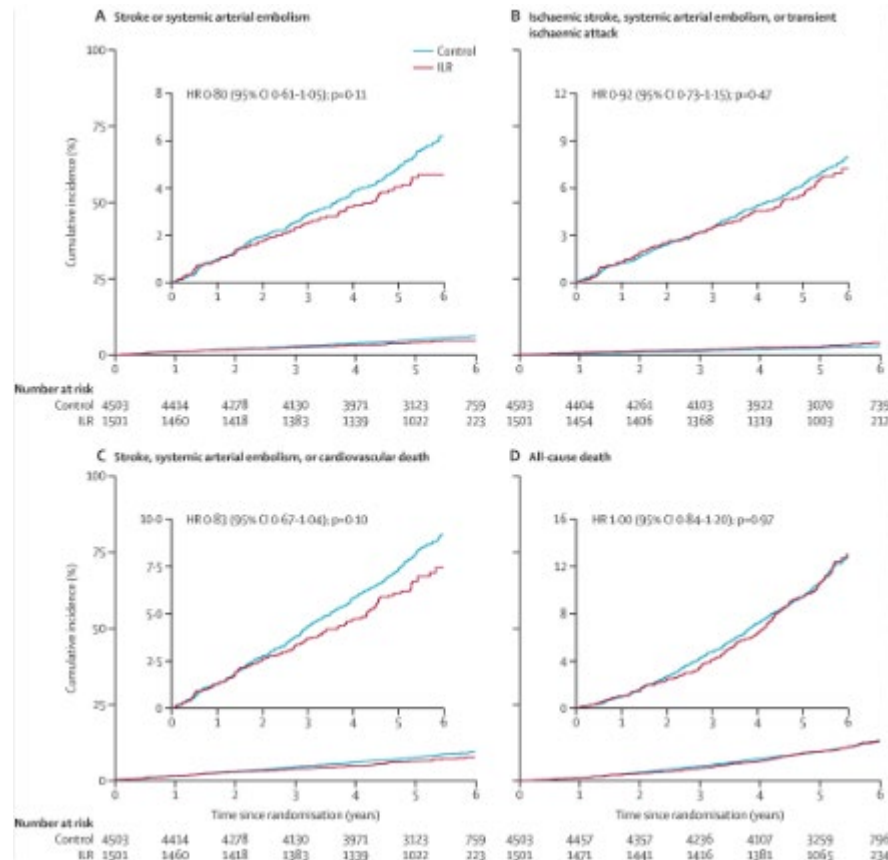
- No statistically significant difference in stroke rates despite initiation of OAC
- **Likely "subclinical" short duration of AF detected (~ 6 mins) may not as important (thrombogenic?) compared to clinically significant AF**

Svensden JH, Diederichsen SZ, Højberg S, et al. Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP Study): a randomised controlled trial. *Lancet*. 2021;398(10310):1507-1516. doi:10.1016/S0140-6736(21)01698-6



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Who prolonged monitoring might not be useful for; when it is overused:

Present indication for anticoagulation

- Known, previously diagnosed AF or detected AF during incident event
- Deep venous thrombus/ pulmonary embolism
- Hypercoagulable disorders

Cardioembolic stroke deemed secondary to alternate mechanism

- Severe carotid disease
- Structural heart disorders
 - PFO
 - LV thrombus
 - Aortic atheroma
 - Endocarditis

Poor patient protoplasm for systemic anticoagulation

Should ILR be implanted for every patient with stroke?

Not easy

Yes	No
- One size fits all approach; commitment to anticoagulation if any AF is found - AF is easily missed - AF is a progressive disease and monitoring allows for early intervention	- Unclear duration of AF needed for thrombus formation - Recurrent stroke may not be cardioembolic either in high risk patients (ie. Small vessel disease etc.) - Alternate mechanisms for stroke other than atrial fibrillation DO exist

Typical workup for acute stroke upon initial evaluation

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Echocardiogram

Routinely performed to evaluate for structural heart disease associated with cardioembolic phenomenon

1. For prevention of recurrent stroke, the use of echocardiography is reasonable in some patients with AIS to provide additional information to guide selection of appropriate secondary stroke prevention.

Ila

C-EO

2. Echocardiography is reasonable in selected patients as part of a comprehensive evaluation to determine if they meet the eligibility criteria of the RCTs that investigated mechanical closure of PFO for prevention of recurrent stroke.

Ila

B-R

Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2019;50(12):e344-e418. doi:10.1161/STR.0000000000000211

Intracardiac mass/tumor/thrombus associated with cardioembolic CVA

Left atrial thrombus

- Left atrial appendage thrombus

Left ventricular thrombus

- Dilated cardiomyopathy
- Post myocardial infarct

Infective endocarditis (vegetations)

- Prosthetic valves, native valves

Other intracardiac masses

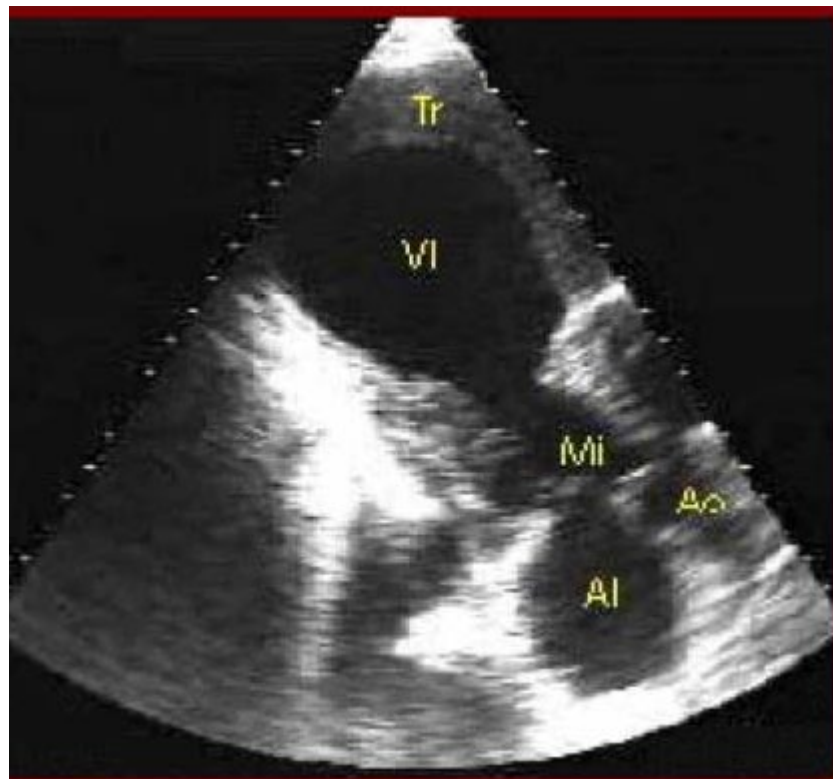
- Atrial myxoma
- Lambl's excrescence (aortic valve)

Aortic diseases

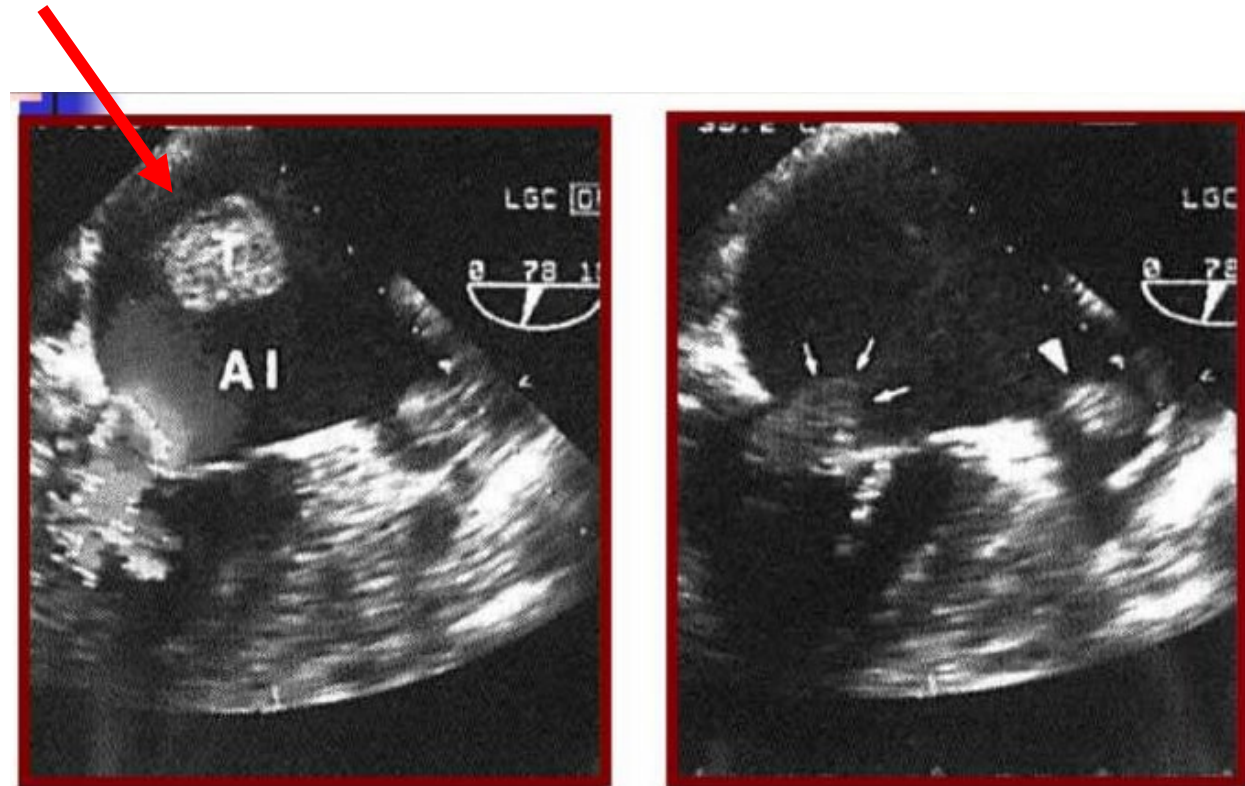
- Atheroma
- Mycotic aneurysm
- Aortic dissection

Post myocardial infarction: LV apical aneurysm

Arboix A, Alió J.
Cardioembolic
stroke: clinical
features,
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disorders and
prognosis. Curr
Cardiol Rev.
2010
Aug;6(3):150-
61. doi:
10.2174/157340
310791658730.
PMID:
21804774;
PMCID:
PMC2994107.



LA thrombus in mitral valve disease

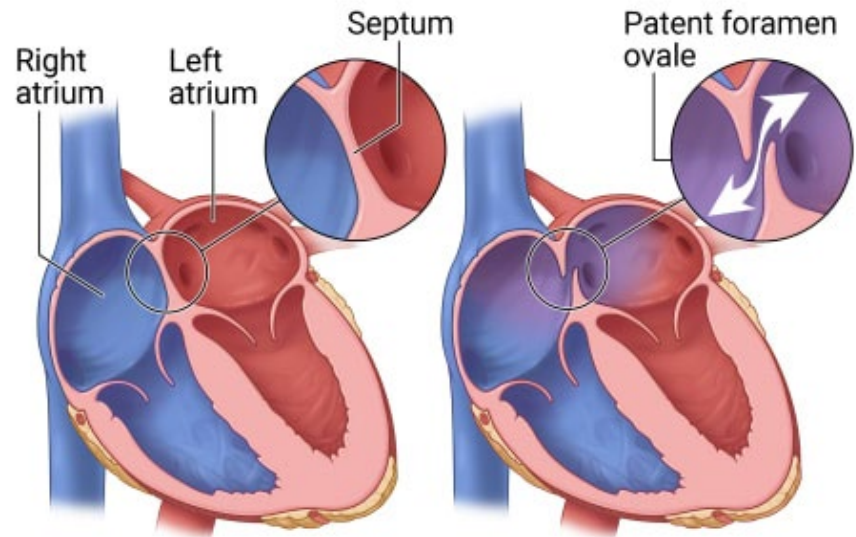


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Patent Foramen Ovale

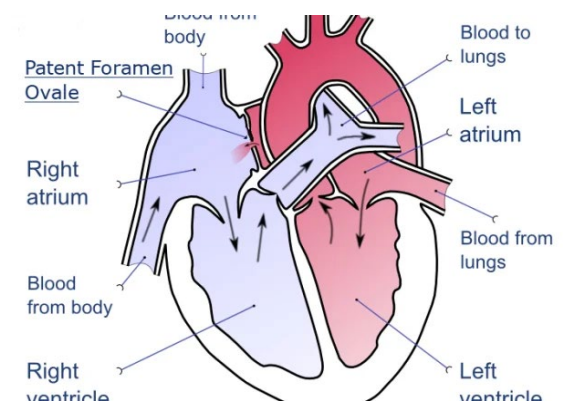
In fetal circulation, *foramen ovale* allows oxygenated blood from the placenta to bypass the non-functional fetal lungs

At birth, pulmonary circulation is established, which causes left atrial pressure (LAP) to exceed right atrial pressure (RAP) leading to functional and subsequent anatomical closure by age 1*



*Pristipino C, et al; Evidence Synthesis Team. European position paper on the management of patients with patent foramen ovale: General approach and left circulation thromboembolism. *Eur Heart J*. 2019;40:3182–3195. doi: 10.1093/eurheartj/ehy649

Patent foramen ovale



Common finding in the healthy population. Autopsy studies suggest a prevalence of 27% in the general population*

Presumed mechanism of stroke is via migration of a thrombus from the venous system to the left atrium with subsequent systemic embolization. Requires the perfect storm:

- Increased RA pressure
- Venous source of thrombus
- Presence of PFO (provides a conduit bypassing pulmonary circulation)

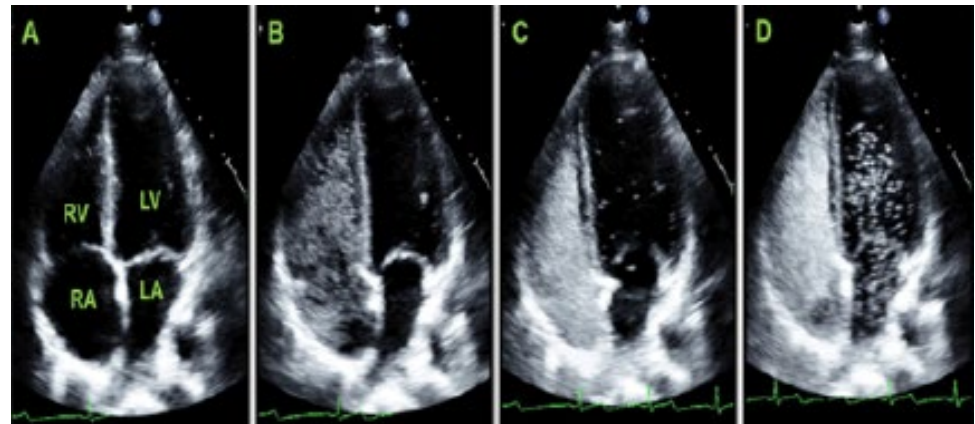
Thus recognized as a cause for cryptogenic cerebrovascular events

Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc 1984;59:17-20.

Patent foramen ovale: bubble study

Transthoracic echo (TTE) – most widely and commonly used ultrasound modality and preferred initial diagnostic modality. Also offers cardiac structural assessment

- Injection of agitated saline through antecubital vein with increased intraabdominal pressure maneuver. Demonstration of bubbles (agitated saline) in left atrium on TTE confirms PFO



Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. Mayo Clin Proc 1984;59:17–20.

Patent foramen ovale

Transthoracic echo (TTE)

- Low sensitivity (45.1%) - but high specificity (99.6%)
- May help in guidance of additional cardiac abnormalities

Transcranial doppler (TCD)

- Sensitivity generally ranges between 93-98%, Specificity (79 – 92%)
- Operator dependent, patient compliance during procedure
- Superior imaging modalities (CT angiography/MRA) etc

Transesophageal echo (TEE) - gold standard

- Sensitivity of 89.2% and specificity of 91.4%
- Best resolution, imaging of other cardiac structures (valves, masses, thrombi)
- Operator dependent, most often requires anesthesia team, resource consuming, more expensive, and often negligible but small risk of traumatic injury



Katsanos AH, et al. Transcranial Doppler versus transthoracic echocardiography for the detection of patent foramen ovale in patients with cryptogenic cerebral ischemia: a systematic review and diagnostic test accuracy meta-analysis. *Ann Neurol*. 2016;79:625-635.

Mojadidi MK, Bogush N, Caceres JD, Msaouel P, Tobis JM. Diagnostic accuracy of transesophageal echocardiogram for the detection of patent foramen ovale: a meta-analysis. *Echocardiography*. 2014;31(6):752-758. doi:10.1111/echo.12462

PFO Closure

Multiple studies support PFO closure after stroke in younger patients (18 – 60 yo)

Older patients: competing vascular risk factors, atrial fibrillation and acquired hypercoagulability from immobility that can lead to paradoxical emboli even if PFO is found

Trial Names	Arms	n	Age (Years), Mean $\pm$ SD	Mean Follow-up (Years)	Conclusions (Closure Superior to Medical Therapy)
CLOSURE I 2012 ²⁷	Closure	447	46.3 $\pm$ 9.6	2	No
	Medical therapy	462	45.7 $\pm$ 9.1		
PC 2013 ²⁸	Closure	204	44.3 $\pm$ 10.2	4.1	No
	Medical therapy	210	44.6 $\pm$ 10.1		
RESPECT 2013 ²⁹	Closure	499	45.7 $\pm$ 9.7	2.6	No
	Medical therapy	481	46.2 $\pm$ 10		
RESPECT (long-term follow-up) 2017 ³	Closure	499	45.7 $\pm$ 9.7	5.9	Yes
	Medical therapy	481	46.2 $\pm$ 10		
CLOSE 2017 ⁴	Closure	238	42.9 $\pm$ 10.1	5.3	Yes
	Medical therapy	235	43.8 $\pm$ 10.5		
REDUCE 2017 ⁵	Closure	441	45.4 $\pm$ 9.3	3.2	Yes
	Medical therapy	223	44.8 $\pm$ 9.6		
DEFENSE-PFO 2018 ¹⁸	Closure	60	49 $\pm$ 15	2.8	Yes
	Medical therapy	60	54 $\pm$ 12		

RoPE (Risk of Paradoxical Emboli score)

The RoPE score assesses the probability that a PFO discovered in the setting of an otherwise-cryptogenic stroke was pathogenically related to the stroke rather than an incidental finding.

>10: 90% probability

0-3: negligible

RoPE score calculator ^a	
Characteristic	Points
No history of hypertension	1
No history of diabetes	1
No history of stroke or transient ischemic attack	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 RoPE score (sum of individual points) = _____	

[Clinical Comparison of Patients with Cryptogenic Stroke or Transient Ischemic Attack and Difficulty in Using the RoPE Score Alone in Older Patients](#)

US Cardiology Review 2021;15:e20.

RoPE (Risk of Paradoxical Emboli score)

Clinical Presentation	Risk Factors	RoPE Score	Chance That Stroke is Due to PFO (%)	2-year Risk of recurrence of TIA or Stroke (%)
38-year-old patient with TIA	None	8	84	6
52-year-old patient with TIA	None	6	62	8
66-year-old patient with TIA	None	5	34	7
52-year-old patient with TIA	Hypertension and diabetes	3	0	20
66-year-old patient with TIA	Hypertension and diabetes	2	0	20

Clinical Comparison of Patients with Cryptogenic Stroke or Transient Ischemic Attack and Difficulty in Using the RoPE Score Alone in Older Patients

US Cardiology Review 2021;15:e20.

When to consider transesophageal echocardiogram (TEE)

There is uncertainty about when to consider TEE vs TTE in acute stroke

TEE is considered a more sensitive test than TTE in detection of major cardiac sources of embolism

- Atrial septum/PFO
- Left atrium
- Aortic arch

TEE is semi-invasive, more resource-intensive and expensive than TTE

Prior data range from 3.4%* to 40%** rate of additional cardiac sources of embolism detected by TEE in patients with stroke compared with TTE alone.

*Cho HJ, et al. Transoesophageal echocardiography in patients with acute stroke with sinus rhythm and no cardiac disease history. *J Neural Neurosurg Psychiatry*. 2010;81:412–415. doi: 10.1136/jnnp.2009.190322

**de Bruijn SF, Agema WR, Lammers GJ, van der Wall EE, Wolterbeek R, Holman ER, Bollen EL, Bax JJ. Transesophageal echocardiography is superior to transthoracic echocardiography in management of patients of any age with transient ischemic attack or stroke. *Stroke*. 2006

CONTEST (Stroke 2022)

Prospective, multicenter, pragmatic, observational study (n=494) to assess diagnostic value of TEE and TTE in regards to treatment in patients with acute ischemic stroke.

July 2017 to June 2019, 5 stroke centers in Germany

Age > 18

Excluded if prior history of AF, symptomatic carotid stenosis and cervical artery dissection

Standard TTE comprised of a bubble test to screen for PFO

Decision to add TEE to TTE was made within the first 24 to 48 hours of stroke unit care (pragmatic study design)

CONTEST (Stroke 2022)

Primary outcome: Treatment relevant findings to justify change of medication, intervention or surgery as a consequence of echocardiographic findings:

- Severely reduced LVEF (<35%), wall motion abnormality
- Intracardiac thrombus (ventricle or atrium)
- Severe valve disease
- Endocarditis
- PFO
- Atrial myxoma

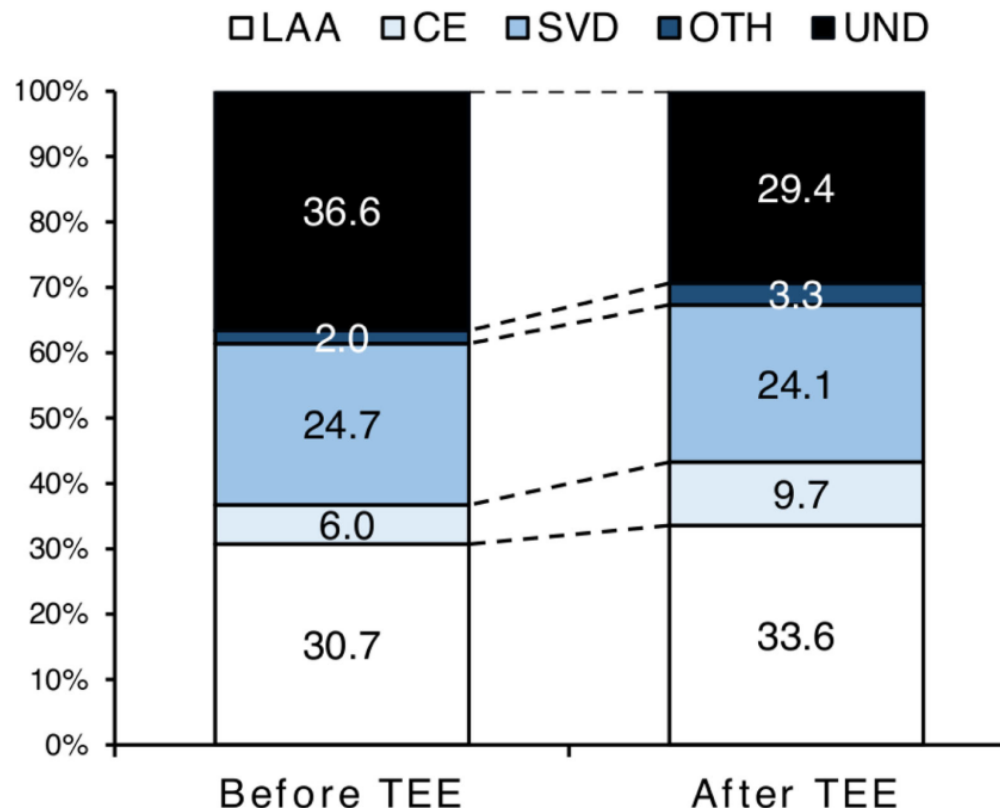
Secondary outcome: diagnostic findings in TEE not captured by TTE that led to immediate change in acute treatment or strategy for secondary prevention and change in assessment of cause of stroke according to TOAST criteria

CONTEST (Stroke 2022)

Findings	TTE (n=454)	TEE (n=454)
Treatment relevant		
Reduced left ventricular ejection fraction, $\leq 35\%$ or qualitative	8 (1.8)	8 (1.8)
Regional wall motion abnormality	19 (4.2)	13 (2.9)
Intracardiac thrombi (ventricle or atrium)	3 (0.7)	5 (1.1)
Severe valve disease	6 (1.3)	7 (1.5)
Signs of endocarditis	1 (0.2)	4 (0.9) †
PFO, age ≤ 60 or >60 y but meeting PFO closure treatment criteria	28 (6.2)	52 (11.5)
Signs of right ventricular overload	1 (0.2)	1 (0.2)
Signs of cardiomyopathy	3 (0.7)	2 (0.44)
Atrial myxoma	...	...
Total*	64 (14.1)	86 (18.9)
Not treatment relevant		
PFO without treatment consequence	29 (6.4)	42 (9.3)
Mild to moderate valve disease	8 (1.8)	10 (2.2)
Aortic thrombus	...	2 (0.4)
Aortic atheroma or plaques	4 (0.9)	74 (16.3)
Other findings of the aorta (ectasy, aneurysm)	7 (1.5)	6 (1.3)
Other	15 (3.3)	23 (5.1)

Thomalla G, Upneja M, Camen S, et al. Treatment-Relevant Findings in Transesophageal Echocardiography After Stroke: A Prospective Multicenter Cohort Study. *Stroke*. 2022;53(1):177-184. doi:10.1161/STROKEAHA.121.034868

Stroke etiology according to TOAST criteria



38 yo M presenting with left upper extremity weakness and slurred speech

CT imaging identified acute infarct

- EKG: NSR, inpatient telemetry unremarkable
- TTE: + bubble study, normal left atrial size
- TEE: + PFO
- Underwent PFO closure
- No further monitoring due to elucidation of mechanism of CVA

78 yo F hx of prior TIA, HTN, DM presenting with right sided numbness and tingling

CT imaging identified acute infarct and chronic old infarcts

- EKG: NSR, inpatient telemetry unremarkable
- TTE: negative bubble study, enlarged left atrium, normal LVEF
- TEE: negative for left atrial thrombus or aortic plaque
- Discharged home with loop recorder
- Detection of AF in 3 months with subsequent initiation of oral AC

Take Home Points

A TTE is a very good screening tool and is of great diagnostic value

Atrial fibrillation is the most common cause of cardioembolic stroke and should be judiciously evaluated for

- Advanced age and risk factors for cardiovascular disease might help in deciding additional monitoring

PFO closure is best assessed with TEE for evaluation and for subsequent management, but that doesn't mean every patient needs one

- Young age, less risk cardiovascular risk factors, and a (good) bubble study might help in pursuing a TEE