Scope of the Problem: Etiology of Cryptogenic Stroke

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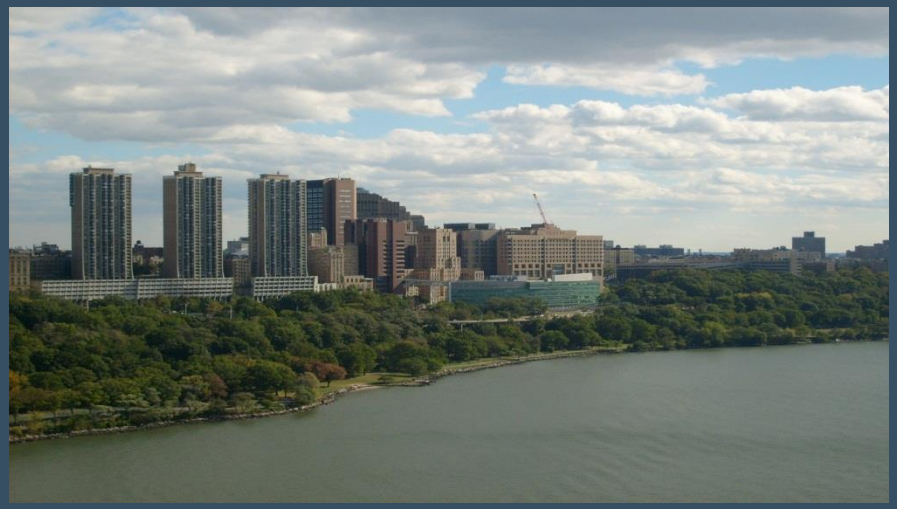

Disclosure Information

Mitchell S. V. Elkind, MD, MS, FAAN, FAHA

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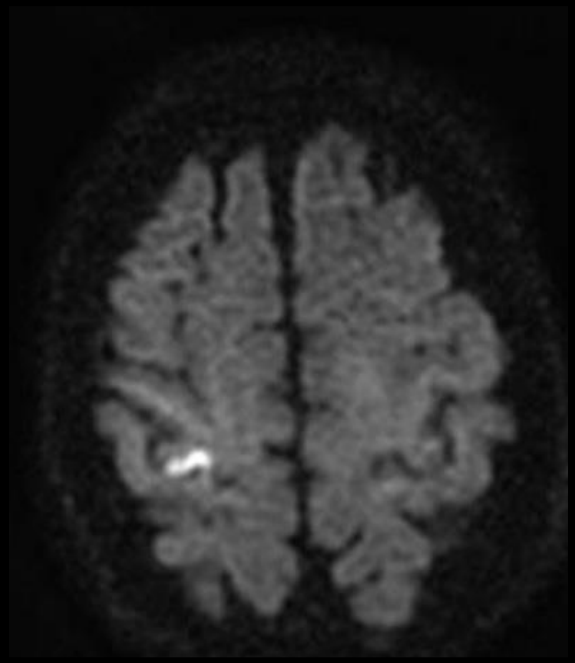
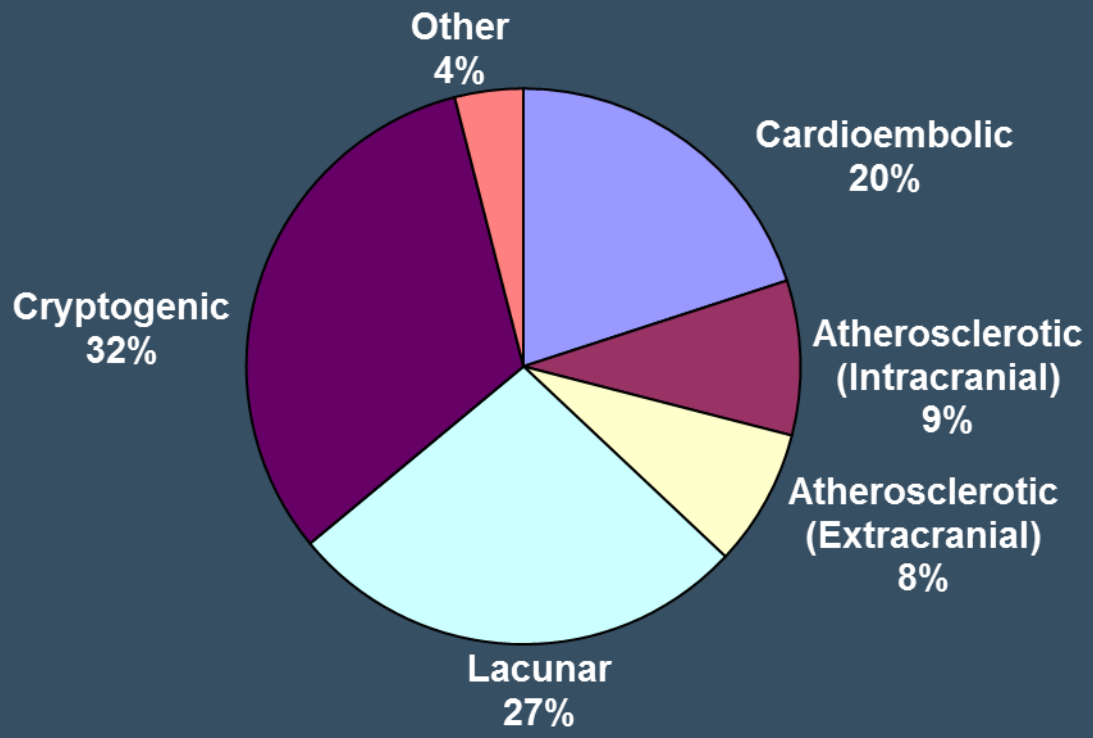
Janssen (rivaroxaban)
Sanofi-Regeneron Partnership (alirocumab)
Biogen IDEC (natalizumab)
Merck/Organon; BMS-Sanofi Partnership

Case

57 year old male economist with no significant past medical history with acute onset of left arm and hand weakness and numbness



Etiologic subtypes ("Causes") of ischemic stroke: The Northern Manhattan Stroke Study



Stroke Numbers in US

	Prevalence over age 20	Incidence	30 day Mortality	90 day Recurrence
Ischemic Stroke	**6.4 million**	**800,000 per year**	**5-12%**	**7%**
Cryptogenic Stroke	**~2 million**	**~200,000-250,000 per year**	**10-15%**	**4-6%**

NCHS/NHANES

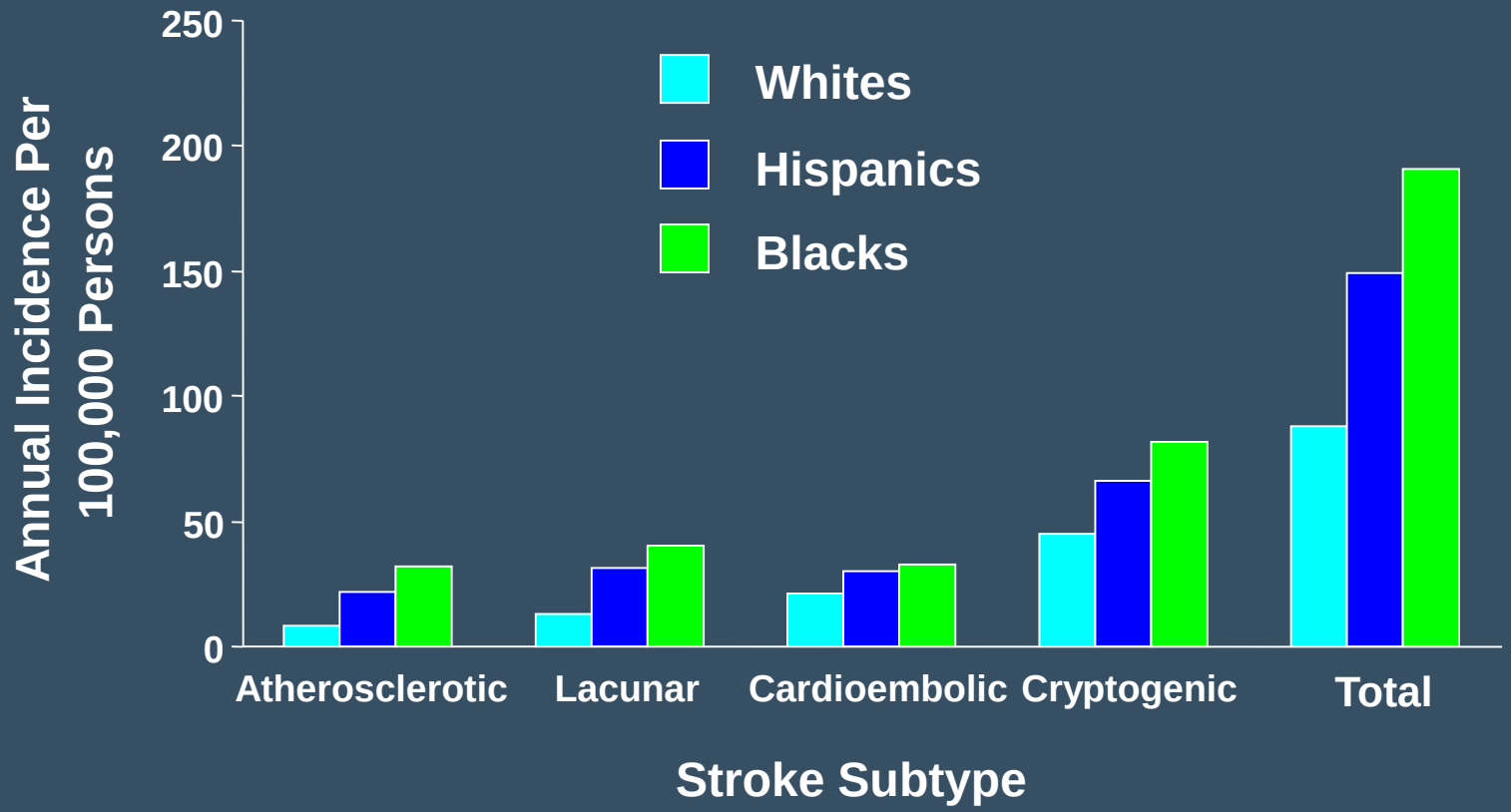
ARIC

Kleindorfer DO, Stroke. 2010;41:1326–1331.

Lovett JK, et al. Neurology 2004;62:569.

Moroney JT et al. Stroke 1998;29:2118.

Racial Imbalance in Ischemic Stroke Incidence

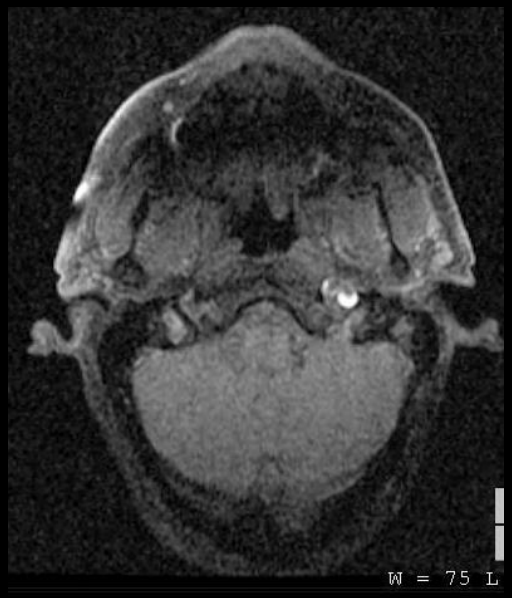


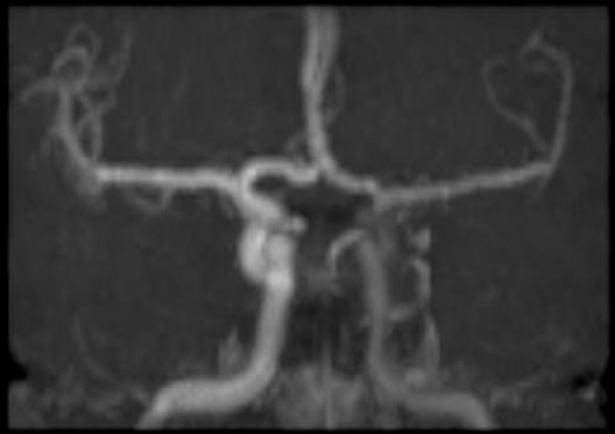
White H, et al. *Circulation.* 2005;111:1327-1331.

Diagnostic Evaluation

1. History
2. Examination
3. Blood Tests
4. Electrocardiogram
5. Imaging
   - Brain
   - Blood Vessels
   - Heart

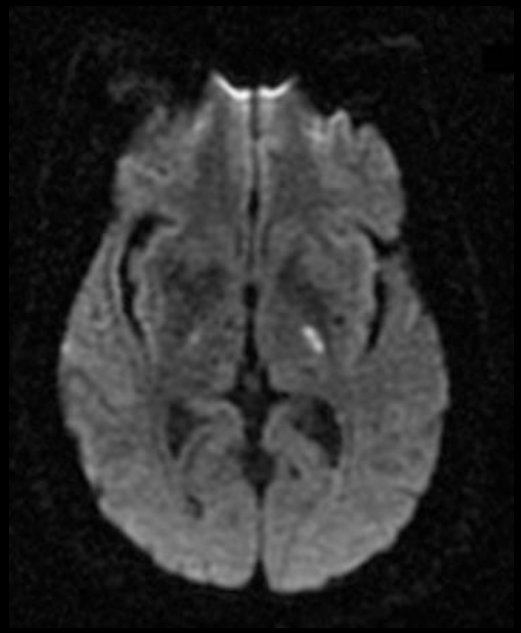
51 yo restaurateur with 10 days severe left-sided temple and orbital headache. Mild difficulty swallowing.

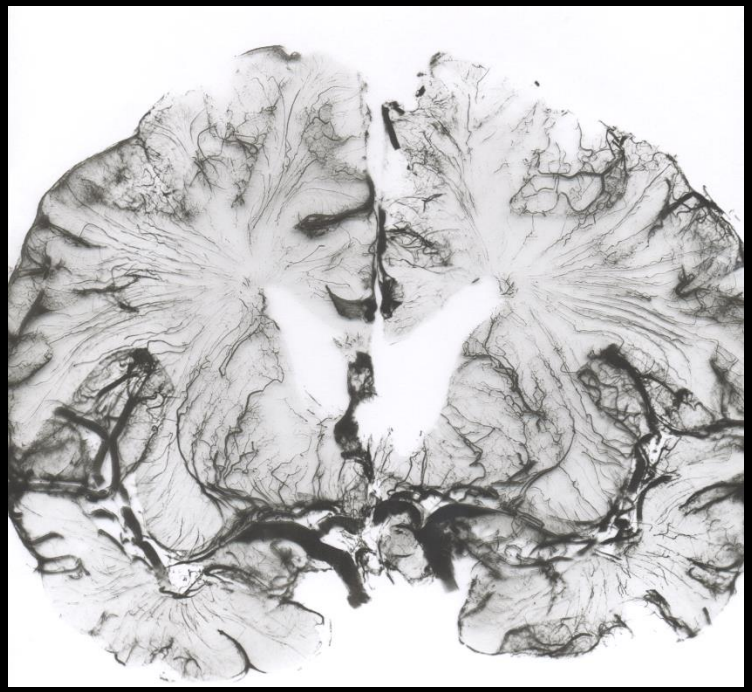




Imaging the Brain

48 year old African American woman with history of untreated hypertension with rapidly progressive right weakness



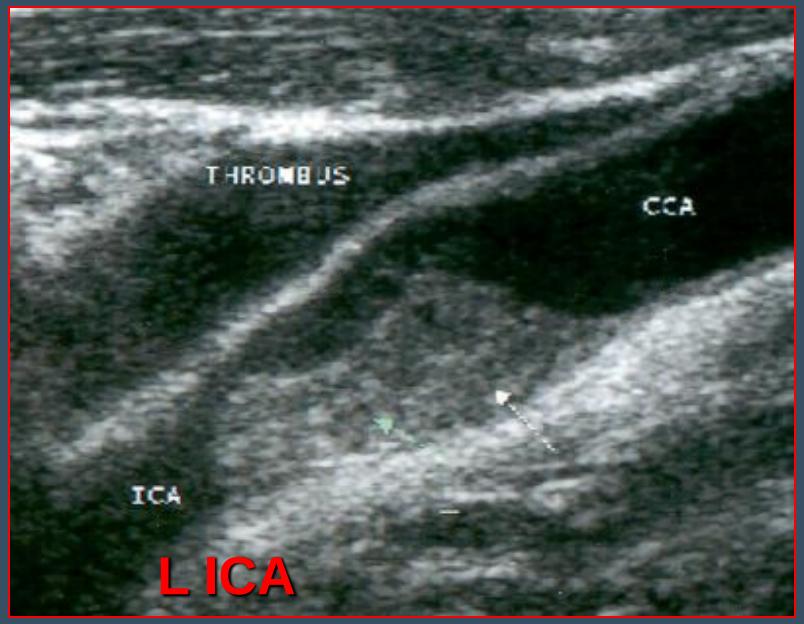


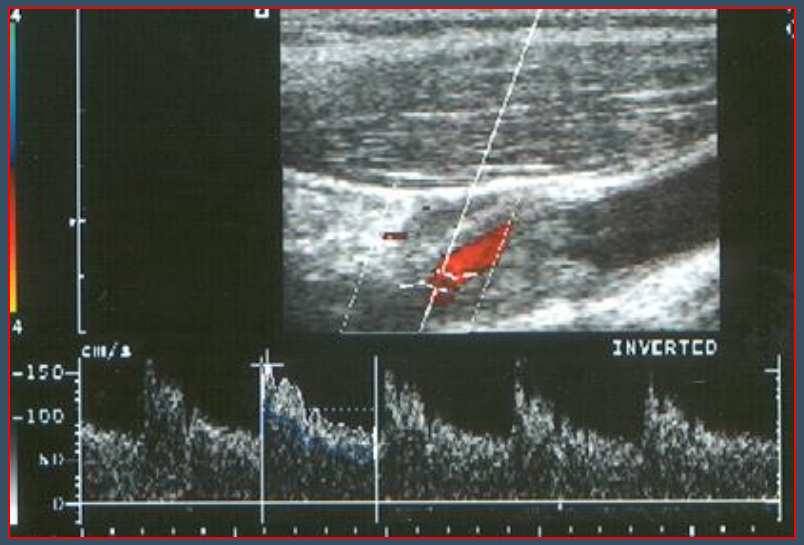
Lacunar infarction: small vessel disease

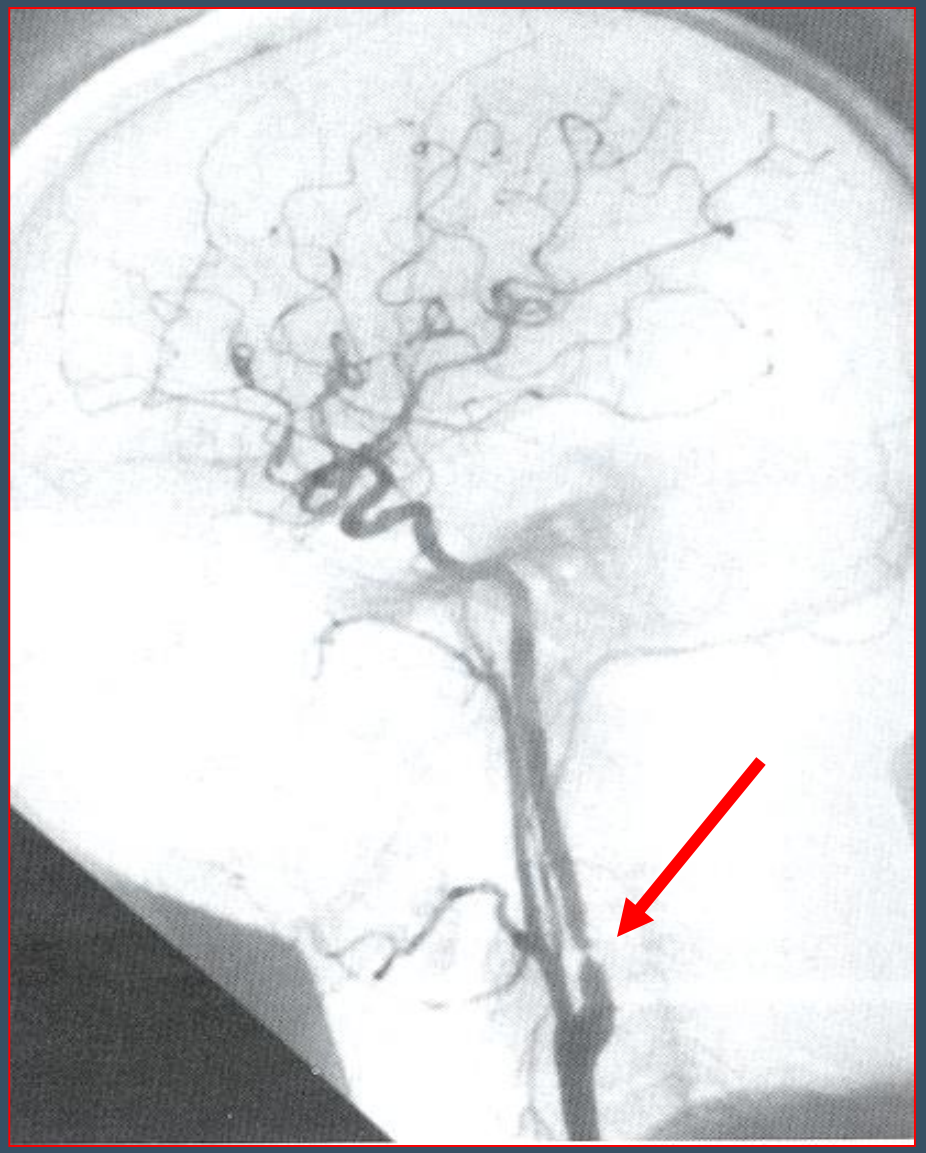
Atherosclerotic stroke: Imaging the Vessels

- Duplex Doppler
- Transcranial Doppler
- MRI neck/brain
- MRA neck/brain
- CT angiography neck/brain
- Conventional angiography

Extracranial 80-90% L ICA stenosis



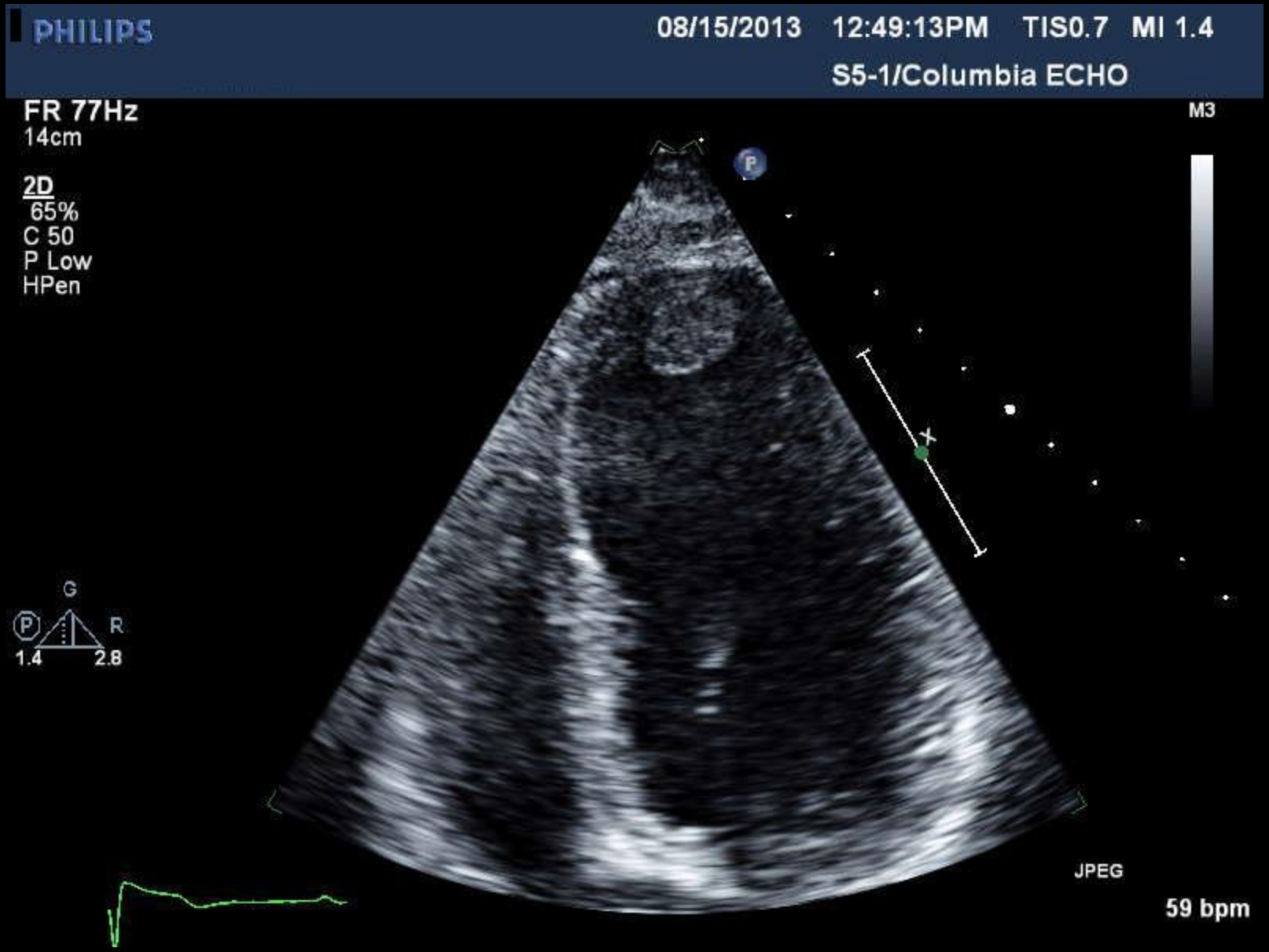




TR 9/2000

Cardioembolic Stroke: “Imaging” the Heart

- EKG
- Transthoracic echocardiography
- Transesophageal echocardiography
- Bubble echocardiography/TCD
- Holter monitoring
- Cardiac MRI
- Extended monitoring


PHILIPS
08/15/2013 12:49:13PM TIS0.7 MI 1.4
S5-1/Columbia ECHO
FR 77Hz
14cm
2D
65%
C 50
P Low
HPen
M3
G
P
R
1.4
2.8
JPEG
59 bpm

Well-established sources of cardiac embolism

- Atrial fibrillation
- LA thrombus/LV thrombus
- Acute MI
- Ischemic/non-ischemic cardiomyopathy
- Prosthetic valves
- Valvular vegetations
- Tumors (myxoma)

Etiologic subtypes ("Causes") of ischemic stroke: The Northern Manhattan Stroke Study

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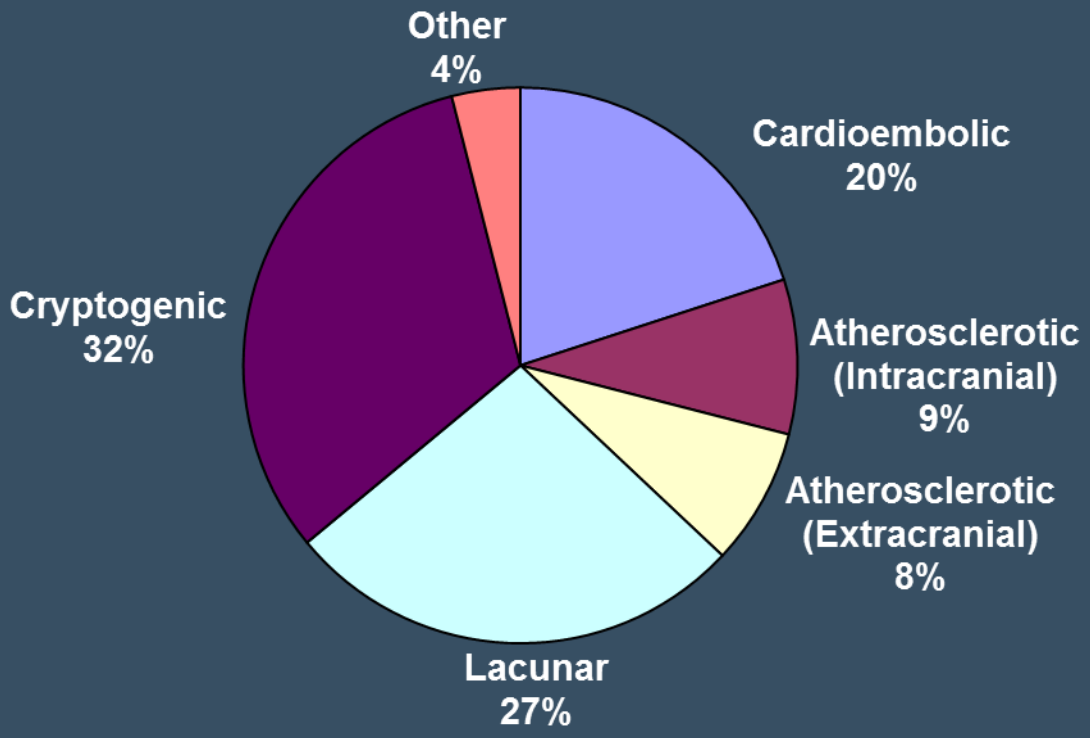


Definition of Cryptogenic Stroke

Stroke of Undetermined Origin:
Brain infarct *not* attributed to a definite source of large-vessel atherosclerosis, cardioembolism, or small-vessel disease, in the presence of:

(1) extensive cardiac, vascular, hematologic, and serologic evaluation;

(2) incomplete evaluation; or

(3) evidence of more than one competing cause.

--"TOAST criteria"

Adams HP Jr, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial. TOAST: Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35–41.

A bit of wisdom…

**“There are known knowns.
These are things we know that we know.
There are known unknowns.
That is to say, there are things that we know we don't know.
But there are also unknown unknowns.
There are things we don't know we don't know.”**

Donald Rumsfeld

Embolic stroke of undetermined source (ESUS)

Requires full evaluation to establish the following:

- Non-lacunar stroke detected by CT or MRI
- Absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying territory
- No major-risk cardioembolic source of embolism based on TTE and ≥24 hr monitoring (AF/flutter, prosthetic valve, LVEF<30%, etc.)
- No other specific cause identified (dissection, vasculitis, spasm, etc.)

Hart RG et al. ***Lancet Neurol* 2014; 13: 429–38.**

Embolic Stroke of Undetermined Source (ESUS):

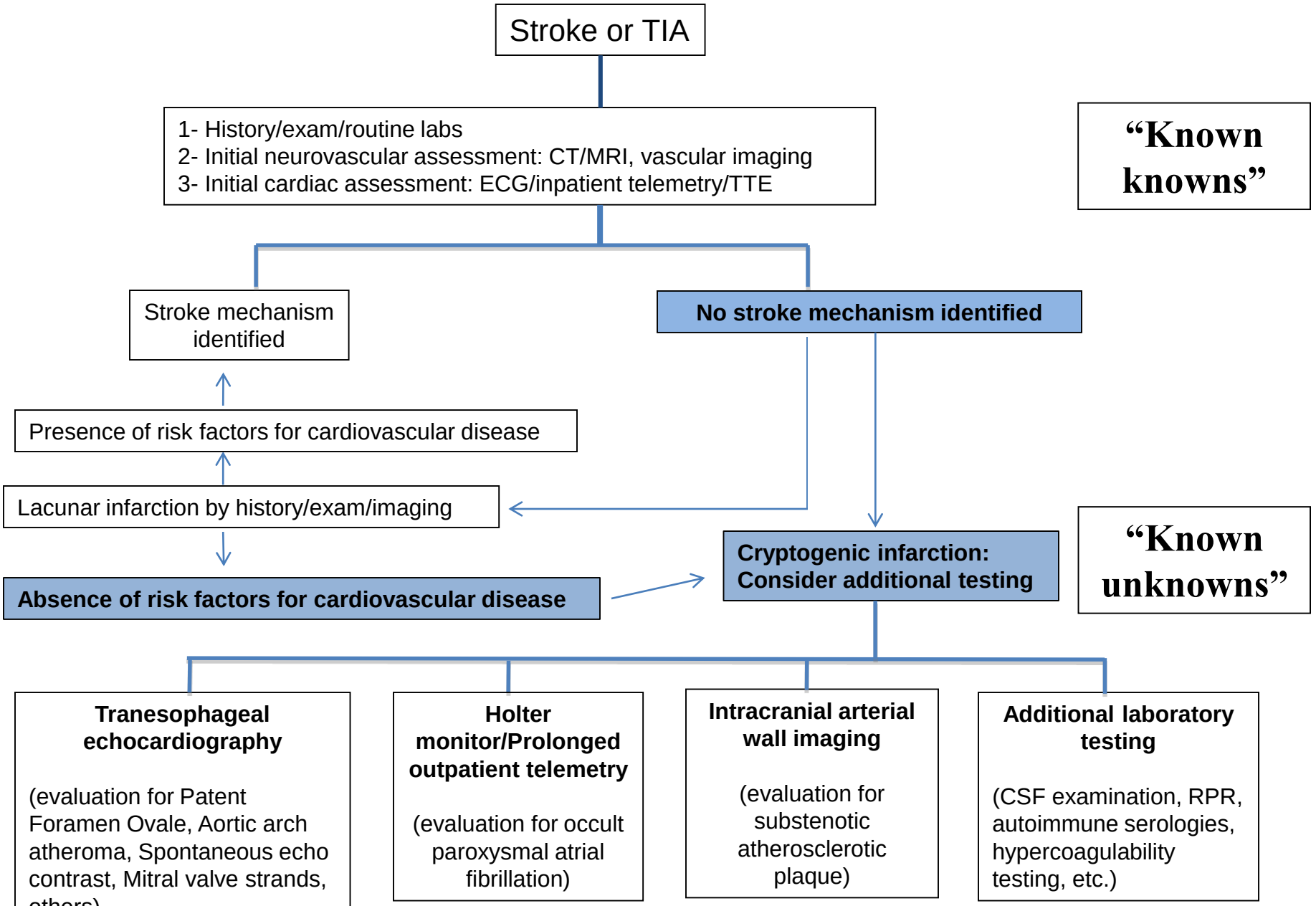
Panel 3: Proposed diagnostic assessment for embolic stroke of undetermined source*

- Brain CT or MRI
- 12-lead ECG
- Precordial echocardiography
- Cardiac monitoring for ≥24 h with automated rhythm detection†
- Imaging of both the extracranial and intracranial arteries supplying the area of brain ischaemia (catheter, MR, or CT angiography, or cervical duplex plus transcranial doppler ultrasonography)

*Imaging of the proximal aortic arch is not needed; special blood tests for prothrombotic states only if the patient has a personal or family history of unusual thrombosis or associated systematic signs or disorder. †Cardiac telemetry is not sufficient.

Hart RG et al. Lancet Neurology 2014;13:429-438.

Suggested approach to the identification and further evaluation of cryptogenic stroke



Yaghi S, Elkind MSV. Cryptogenic Stroke: A Diagnostic Challenge. Neurology Clinical Practice 2014;4(5):386-39.

Potential causes of cryptogenic stroke

- Migraine
- Genetic disorders
  - Fabry disease
  - CADASIL
  - Collagen mutations
  - Actin mutations
- Vasculopathies
  - Vasculitis
  - Reversible Vasoconstriction Syndrome
  - Inflammation (CRP)
- Infections
  - Syphilis
  - HIV
  - Varicella zoster virus
  - Occult Endocarditis
- Homocysteine
- Sleep apnea
- Hypercoagulable states
  - Factor V Leiden
  - Antiphospholipid antibodies
- Cardiac diseases
- Patent foramen ovale
- Atrial septal aneurysm
- Aortic arch atheroma
- Valvular strands
- Mitral annular calcification

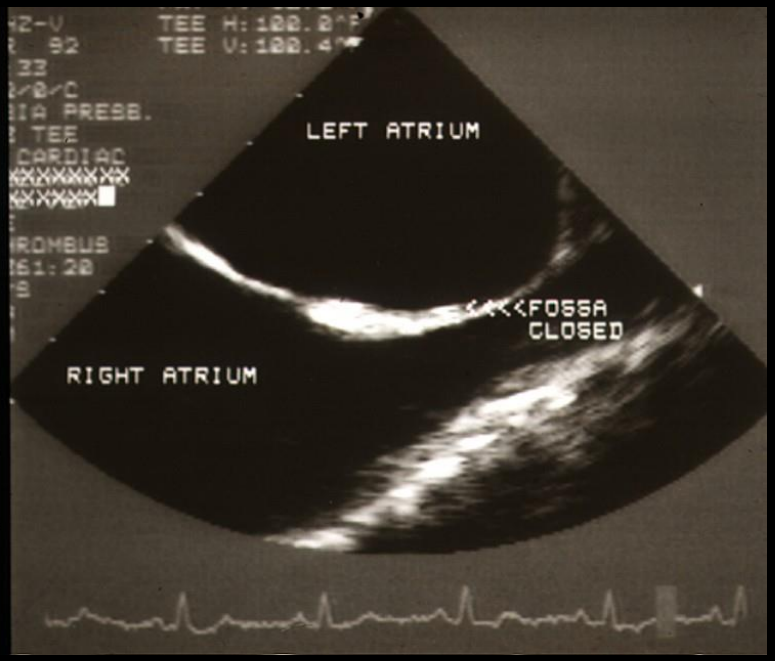
Etc.

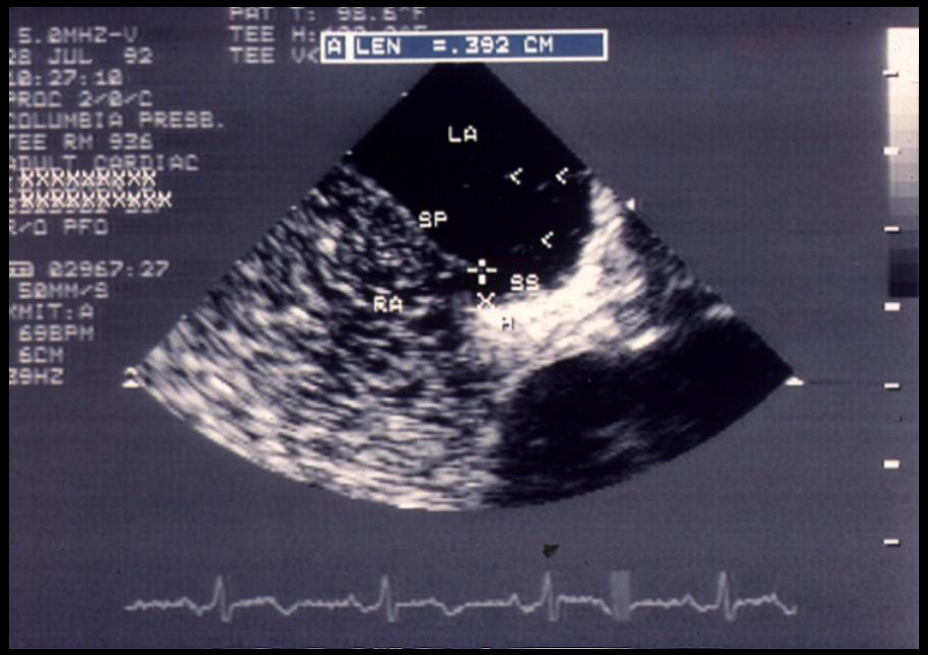
"Unknown unknowns"

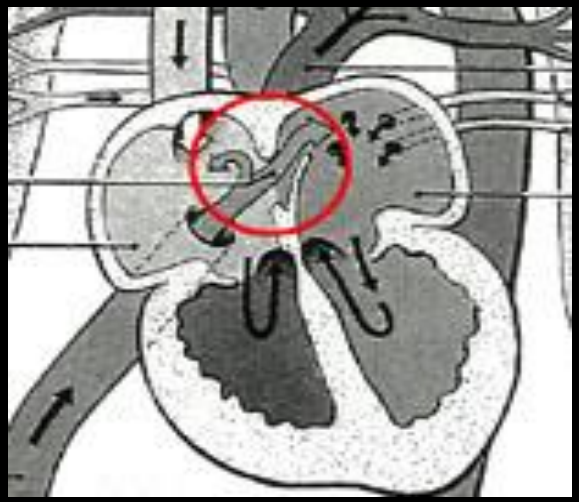
Common **potential causes of cryptogenic stroke ("Known unknowns")**

- Occult atrial fibrillation
- Less well-documented sources of cardiac embolism
  - PFO
  - Aortic arch atheroma
- Vasculopathies
  - Non-stenosing plaque
- Hypercoagulable states

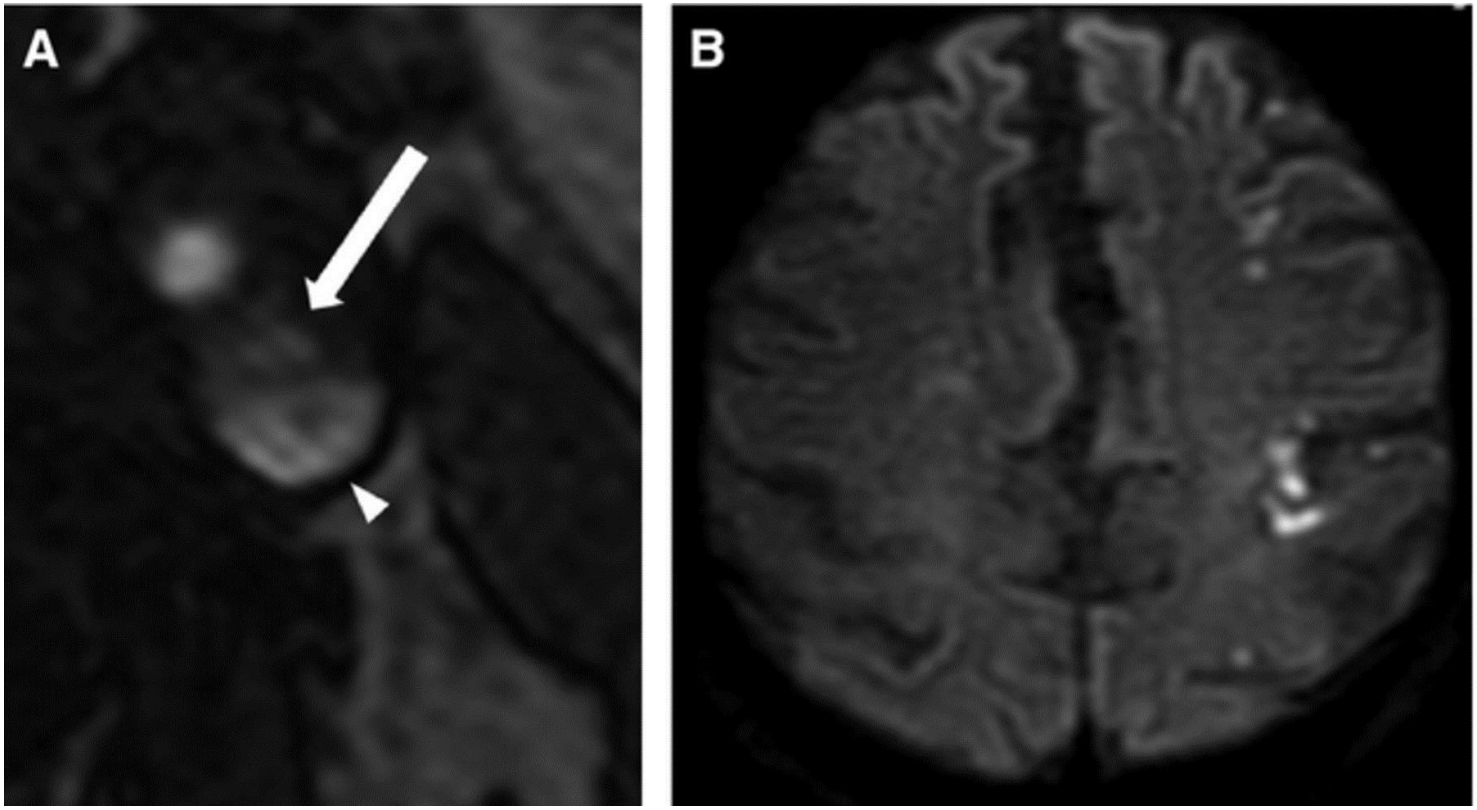
Transesophageal echocardiogram: PFO





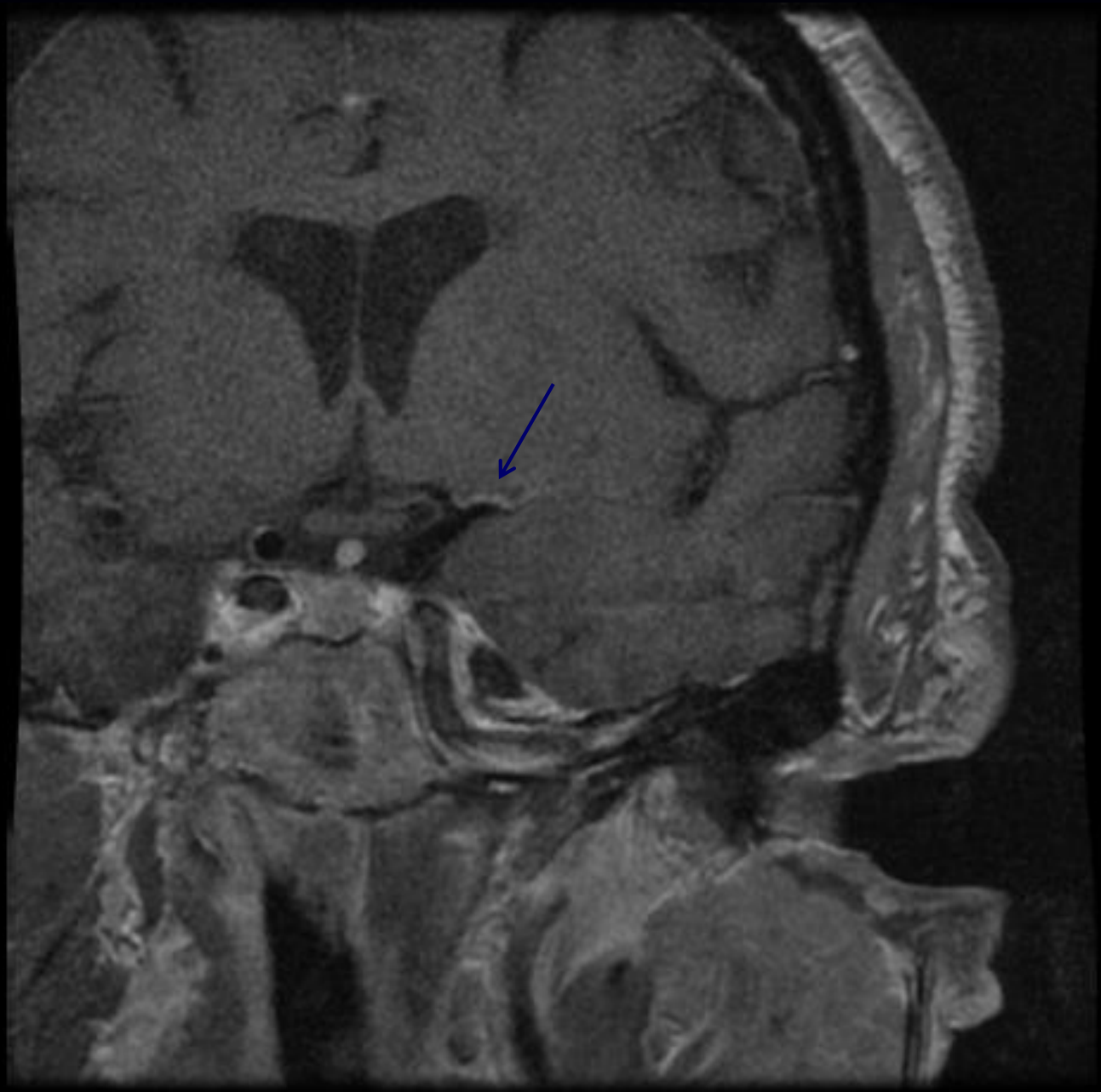


Axial 3D-time-of-flight source image demonstrates signal hyperintensity in the plaque (arrow) of a nonstenosing left-sided carotid artery plaque.

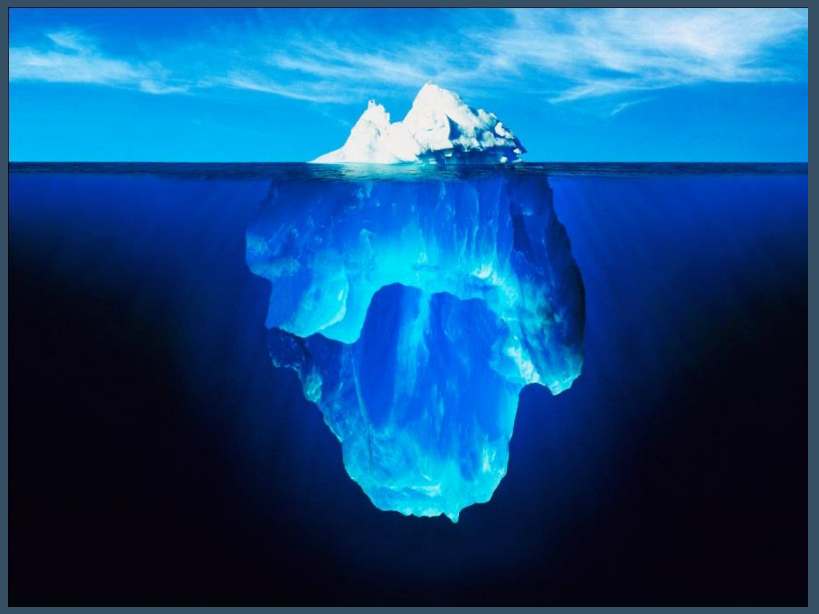


6/27 patients (22.2%) had intraplaque high-intensity signal nonstenosing carotid plaque on side of stroke compared to 0 patients with IHIS-positive plaques on opposite side (p=0.01).

Ajay Gupta et al. J Am Heart Assoc 2015;4:e002012



Atrial fibrillation as a cause of stroke



Atrial fibrillation

Chronic AF

Paroxysmal AF

"Occult" AF

Other arrhythmias

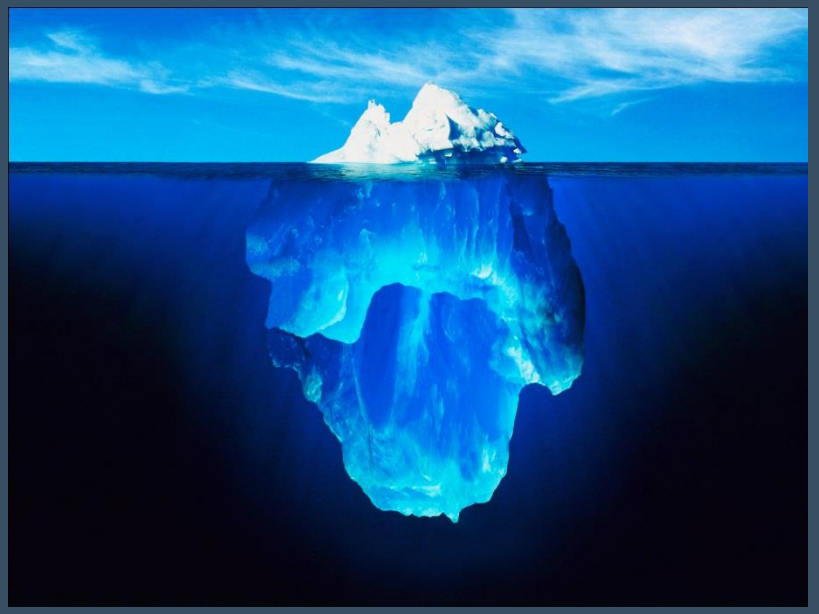
Serum biomarkers of cardiac dysfunction

Enlarged left atrium

P wave abnormalities on EKG

Genetic markers of atrial fibrillation

“Atrial cardiopathy” as a cause of stroke



Atrial fibrillation

- Chronic AF
- Paroxysmal AF
- Occult AF

Other arrhythmias

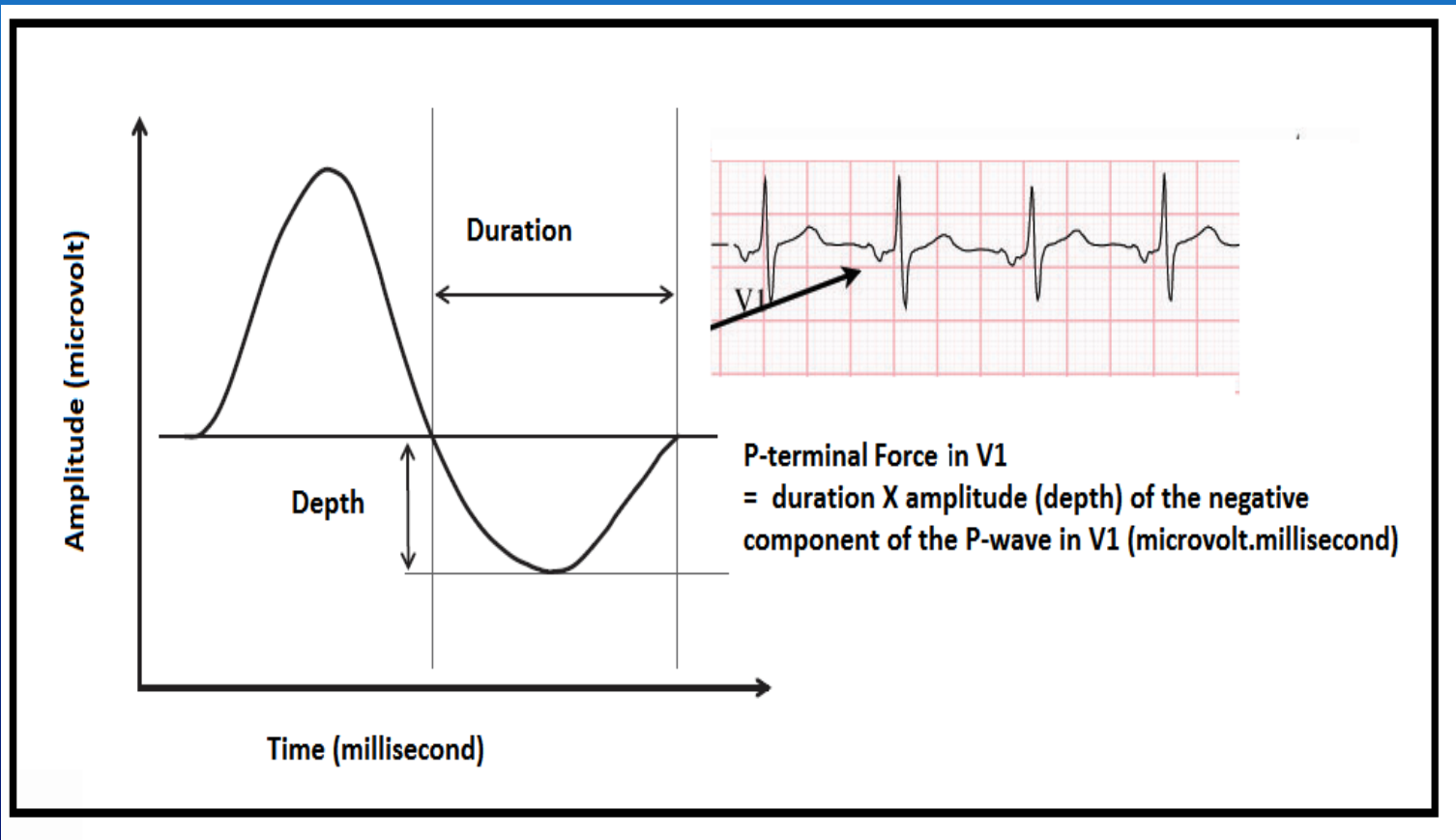
Serum biomarkers of cardiac dysfunction

Enlarged left atrium

P wave abnormalities on EKG

Genetic markers of atrial fibrillation

P wave abnormalities



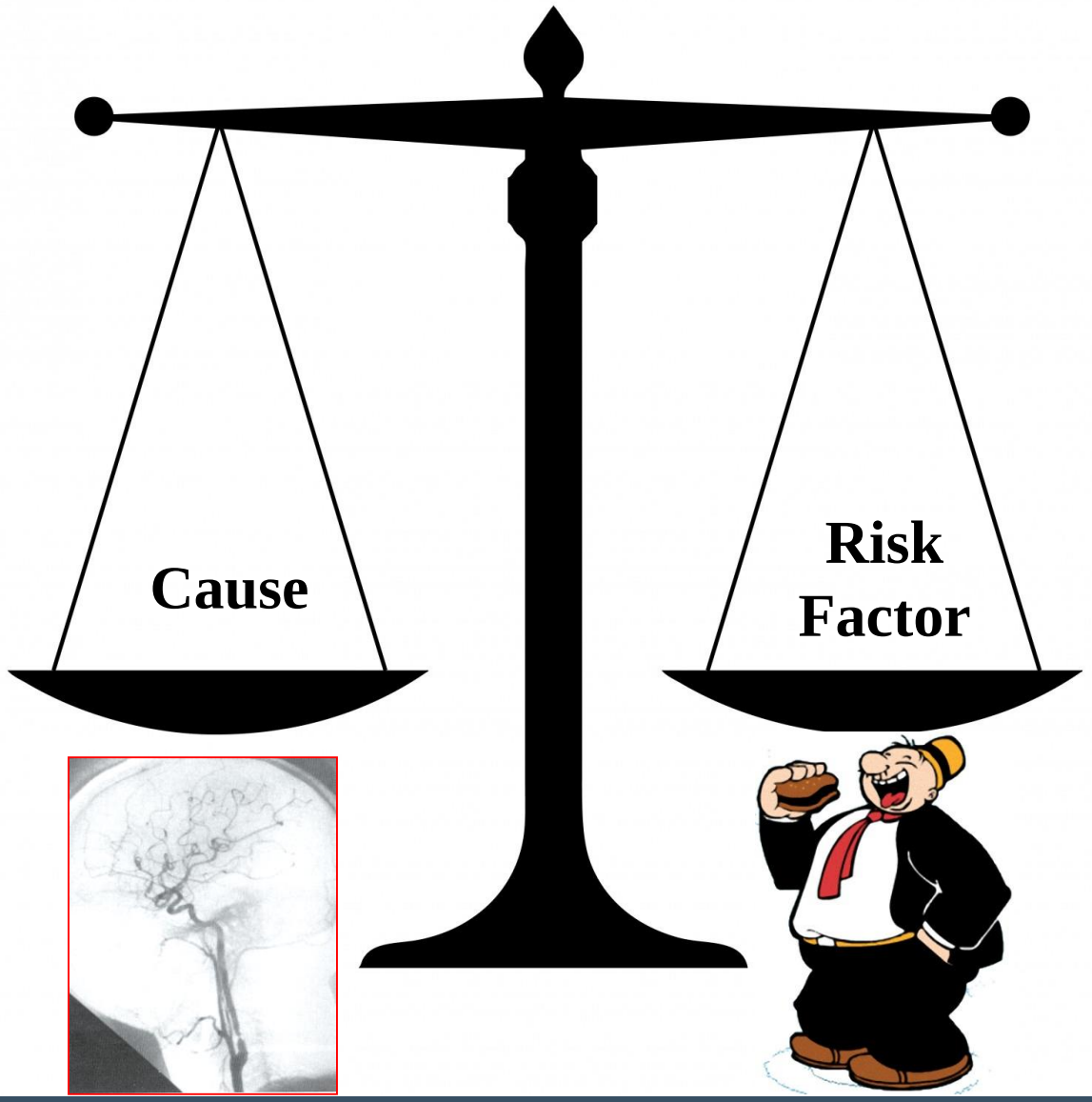
Reflects left atrial structure and function

PTV1 in NOMAS: Case-cohort analysis

Associations between P-Wave Terminal Force in Electrocardiogram Lead V_1 and Incident Ischemic Stroke Subtypes (n=1107)		
Outcome	**Unadj**	**Adj**
Any ischemic stroke	1.24 (1.07-1.42)	1.20 (1.03-1.39)
Ischemic stroke subtypes		
Cryptogenic or cardioembolic	1.31 (1.10-1.55)	1.31 (1.08-1.58)
Cryptogenic	1.29 (0.99-1.68)	1.29 (0.96-1.72)
Cardioembolic	1.32 (1.07-1.62)	1.23 (0.97-1.56)
Non-cardioembolic	1.14 (0.94-1.40)	1.14 (0.92-1.40)

Results are reported as the hazard ratio (95% CI) for each 1-standard deviation increase in PWV1.
Adjusted model includes age, sex, race, education, smoking status, diabetes, hypertension, lipid levels, atrial fibrillation, and heart failure.

Kamel H et al. Stroke 2015.


Cause
Risk
Factor

INTERSTROKE 2010

90% OF THE ATTRIBUTABLE RISK OF STROKE EXPLAINED BY 10 RISK FACTORS

3000 cases/3000 controls; 84 centers; 22 countries

Hypertension	52%	80%
Physical inactivity	29%	
Abdominal obesity	27%	
Hyperlipidemia	25%	
Diet	19%	
Current smoking	19%	
Cardiac disease	7%	
Diabetes	5%	
Psychosocial stress/depression	5%	
Alcohol consumption	4%	

O'Donnell MJ et al. (INTERSTROKE) Lancet 2010 376:112-23.c

Cryptogenic Stroke: Explaining the Unexplained

1. **Cryptogenic Stroke Is Common**

2. **What You See Is What You Get:**
   - **Diagnosis of Cryptogenic Stroke is a Diagnosis of Exclusion (Exclude the Known Knowns)**

3. **An Absence of Evidence is Not Always Evidence of Absence:**
   - **Exclusion Depends on How Hard One Looks for Other Causes (the Known Unknowns)**

4. **It Is…Until It Isn't:**
   - **Once a Cause Is Found, the Stroke Is No Longer Unexplained**

5. **"There Are Things We Don't Know We Don't Know":**
   - **Methods to Detect Causes of Stroke Continue to Improve (Unknown Unknowns)**

6. **Why We Care:**
   - **Identifying the Cause is the Best Way to Prevent Recurrence**


Thanks for your attention!