

PFO device closure for elderly patients  
with cryptogenic stroke:  
Is it really clinically relevant procedure?

Jae-Kwan Song, MD, PhD

Professor of Medicine

University of Ulsan College of Medicine

Asan Medical Center

Seoul, South Korea

Trial (Year)	F/U years	Age limitation	PFO	Comparator	Result
CLOSURE (2012)	2	Yes, ≤60 yrs	All	Antiplatelet or anticoagulation	Negative
PC (2013)	4.1	Yes, <60 yrs	All	Antiplatelet or anticoagulation	Negative
RESPECT (2013)	2.1	Yes, ≤60 yrs	All	Antiplatelet or anticoagulation	Negative
REDUCE (2017)	3.2	Yes, <60 yrs	All	Antiplatelet	Positive
CLOSE (2017)	5.3	Yes, ≤60 yrs	High risk	Antiplatelet	Positive
RESPECT (2017)	5.9	Yes, ≤60 yrs	All	Antiplatelet or anticoagulation	Positive
<b>DEFENSE -PFO (2018)</b>	<b>2.8</b>	<b>No</b>	<b>High risk</b>	<b>Antiplatelet or anticoagulation</b>	<b>Positive</b>

# Age Limitation in the Current Guidelines

COR	LOE	Recommendations
2a	B-R	2. In patients <u>18 to 60 years of age</u> with a nonlacunar ischemic stroke of undetermined cause despite a thorough evaluation and a PFO with high-risk anatomic features,* it is reasonable to choose closure with a transcatheter device and long-term antiplatelet therapy over antiplatelet therapy alone for preventing recurrent stroke. <sup>552-557</sup>

American Heart Association/American Stroke Association, Stroke 2021;52:e364

Population	Secondary prevention of stroke, TIA, or other left circulation thromboembolism
Intervention	Percutaneous closure of PFO
Comparison	Medical therapy
Main outcomes	Stroke, TIA, death, bleedings, atrial arrhythmias
<hr/>	
<b>TYPE OF STATEMENT</b>	Strong statement for the intervention
<b>POSITION STATEMENTS</b>	The position of our societies is to perform percutaneous closure of a PFO in carefully selected patients <u>aged from 18 to 65 years</u> with a confirmed cryptogenic stroke, TIA, or systemic embolism and an estimated high probability of a causal role of the PFO as assessed by clinical, anatomical and imaging features.

ESC Position Paper, Eur Heart J 2019;40:3182

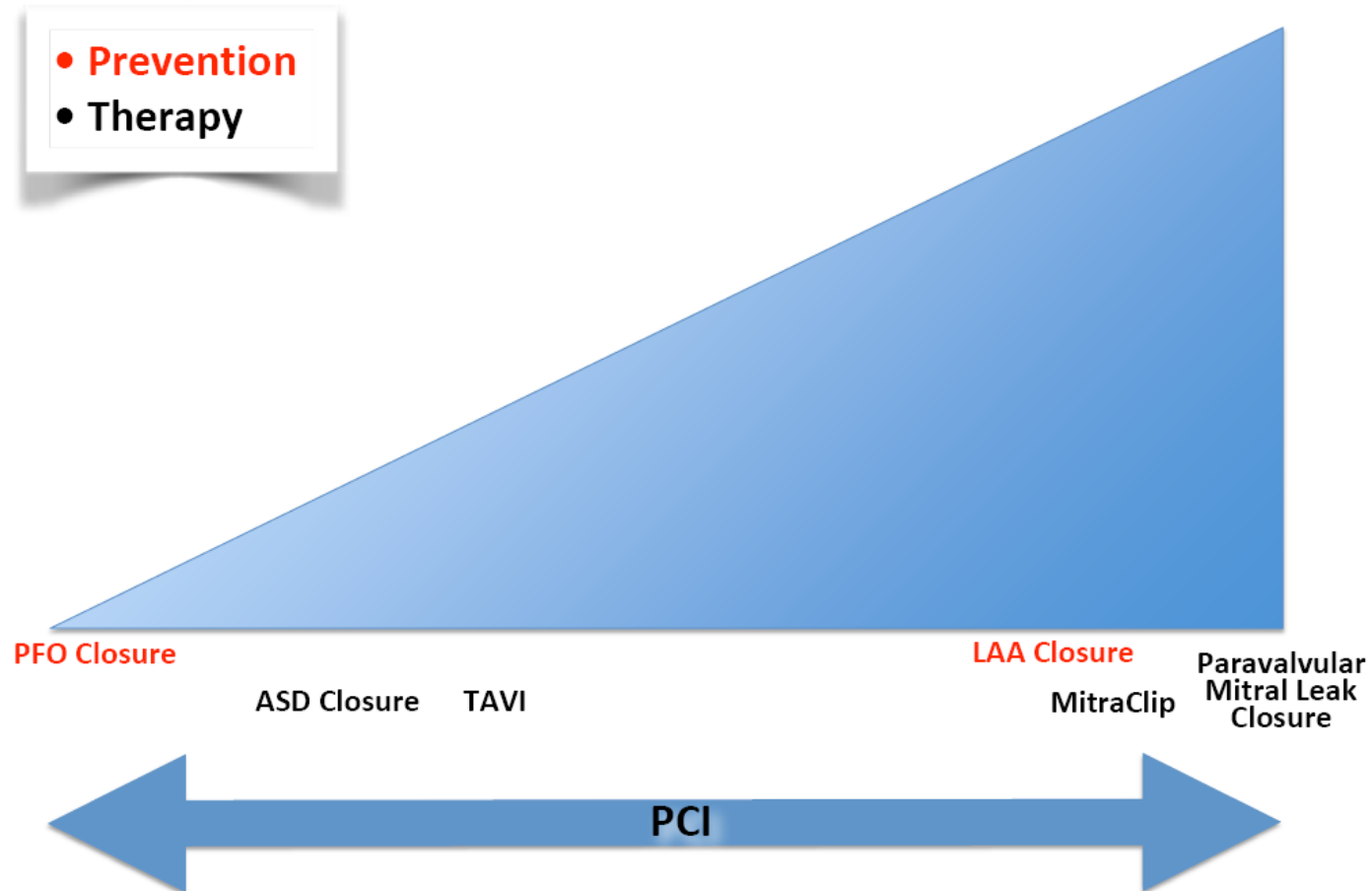
## *Statement 2a*

In patients younger than 60 years with a PFO and an embolic-appearing infarct and no other mechanism of stroke identified, clinicians may recommend closure following a discussion of potential benefits (reduction of stroke recurrence) and risks (procedural complication and atrial fibrillation) (level C).

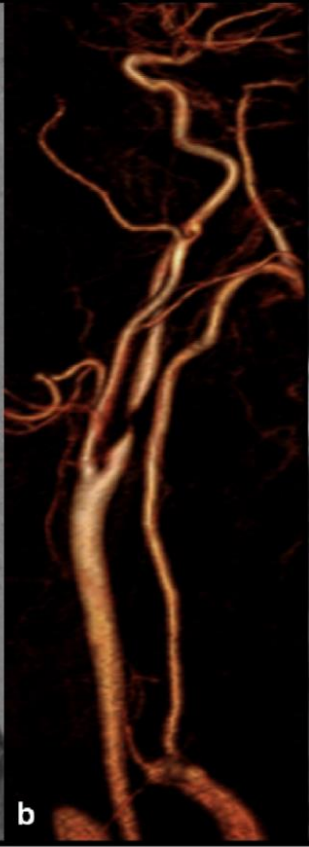
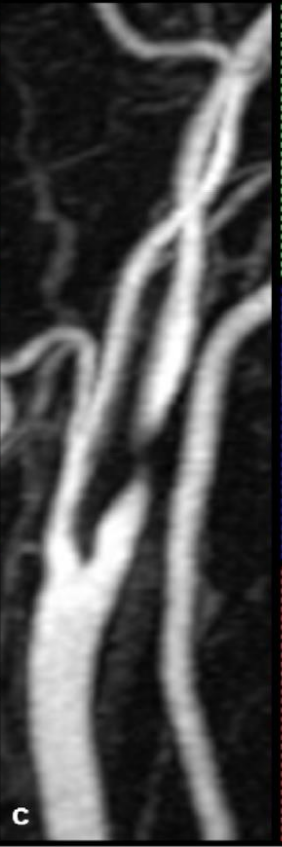
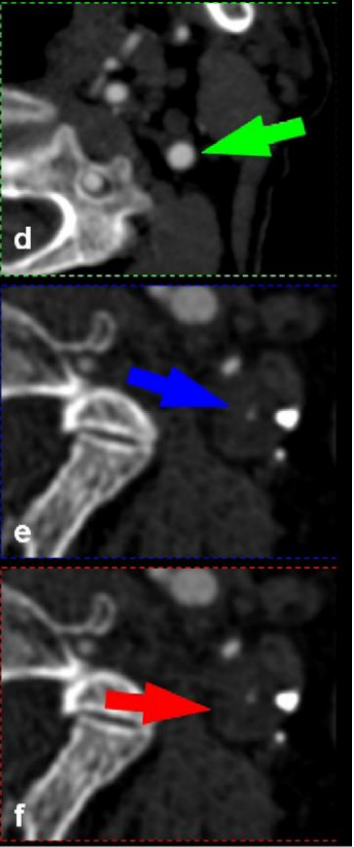
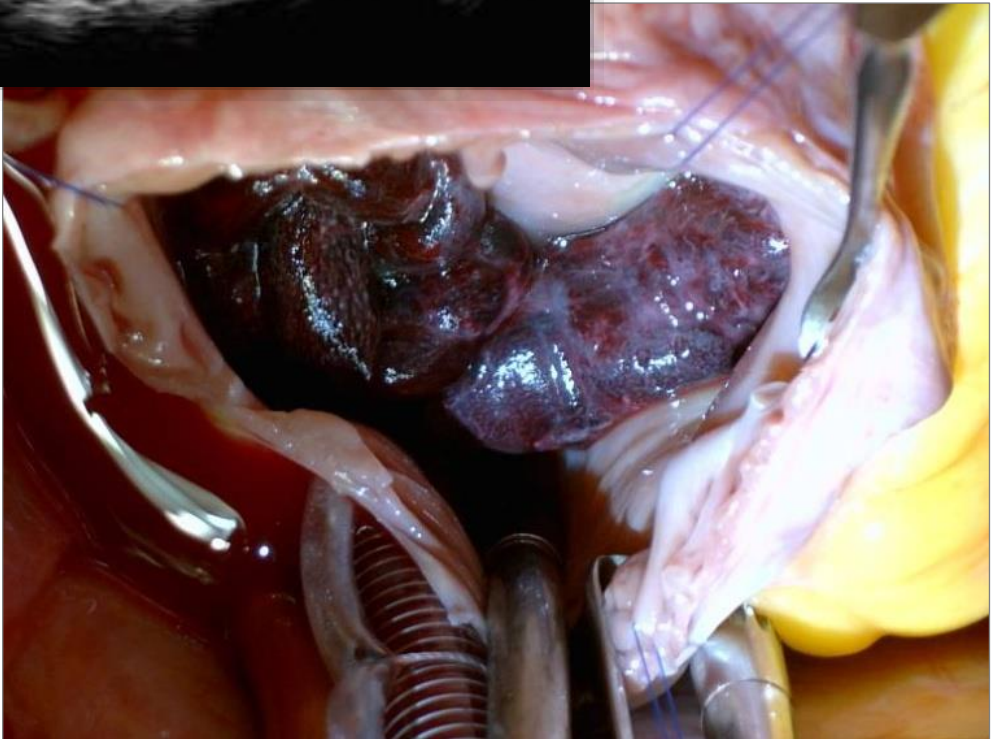
American Academy of Neurology, Neurology 2020;94:876

# Age Limitation: Why Do You Bother Me?

## Intricacy of Adult Interventional Cardiology Procedures



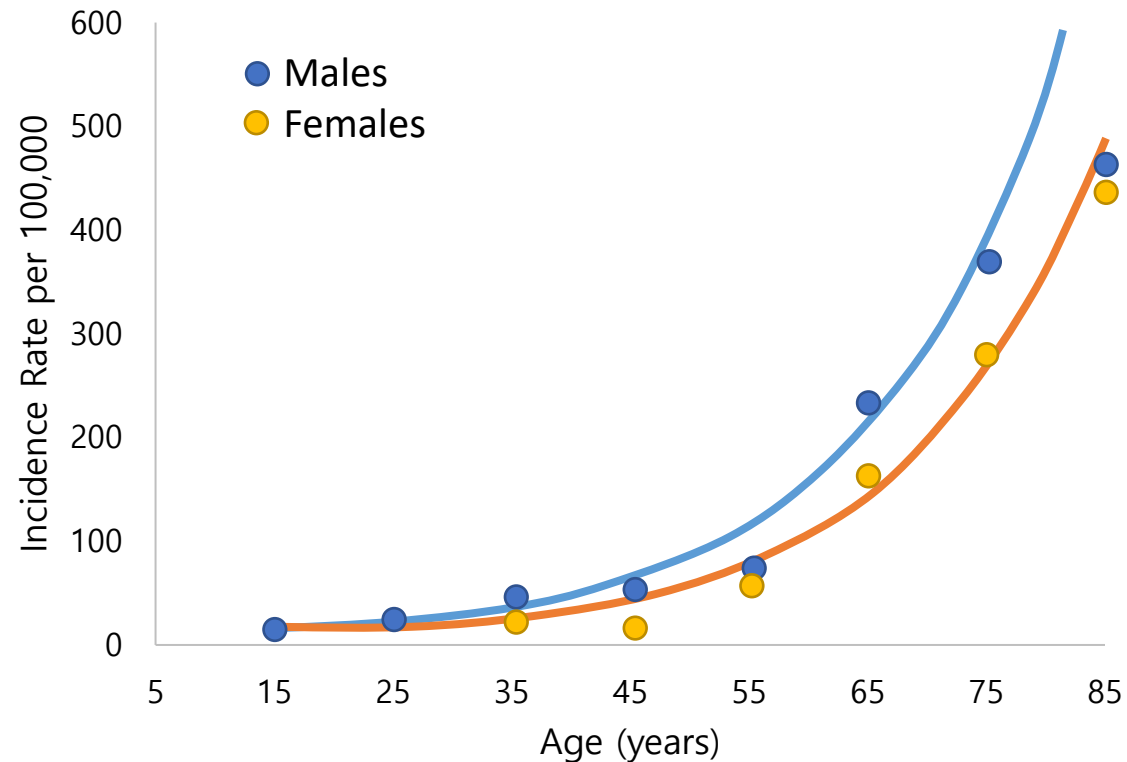
Courtesy of Dr. Bernhard Meier



# Unresolved Issues: Age Limitation

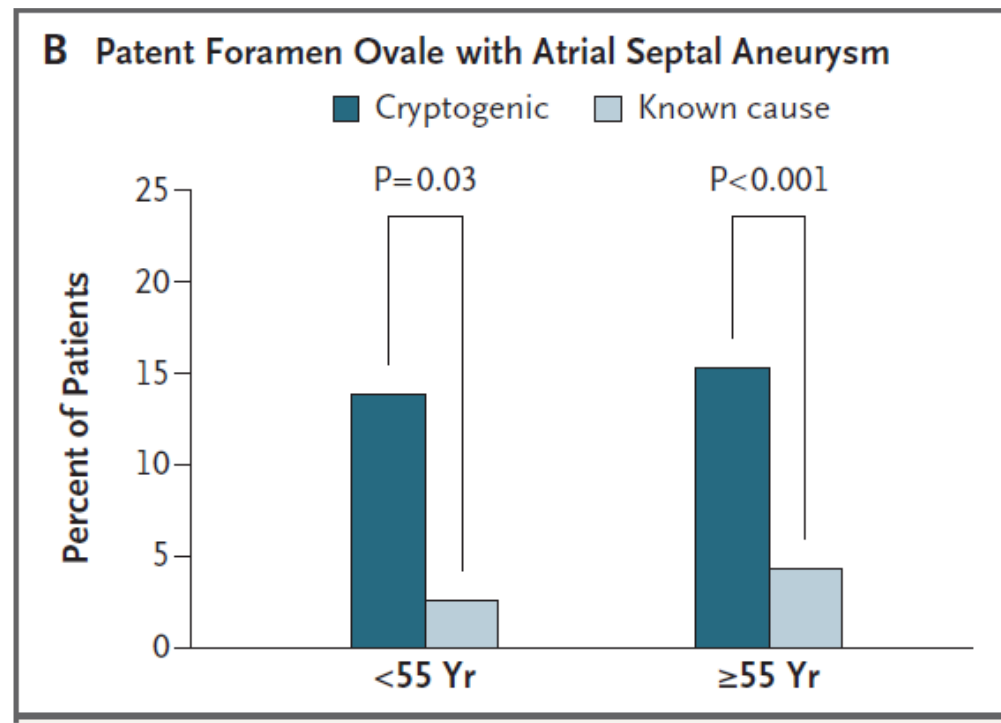
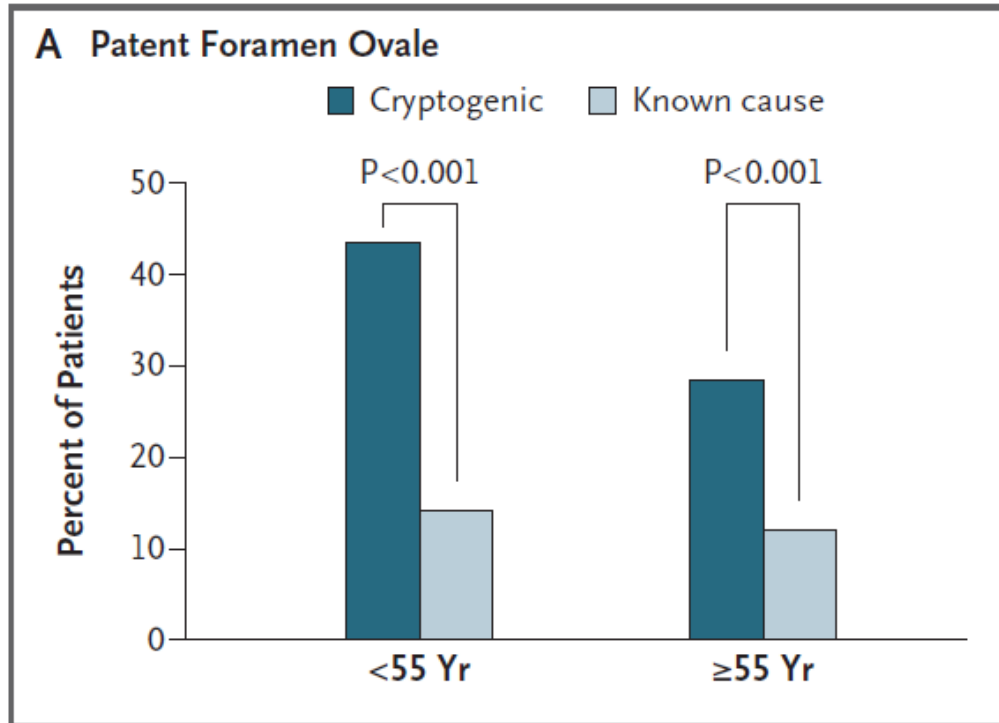
## Annual Incidence of Venous Thrombotic Events

(Population of Worcester, Massachusetts)



*Anderson FA, et al.  
Arch Intern Med. 1991;151:933-938*

# PFO and Cryptogenic Stroke in Older Patients (*NEJM* 2007;357:2262)

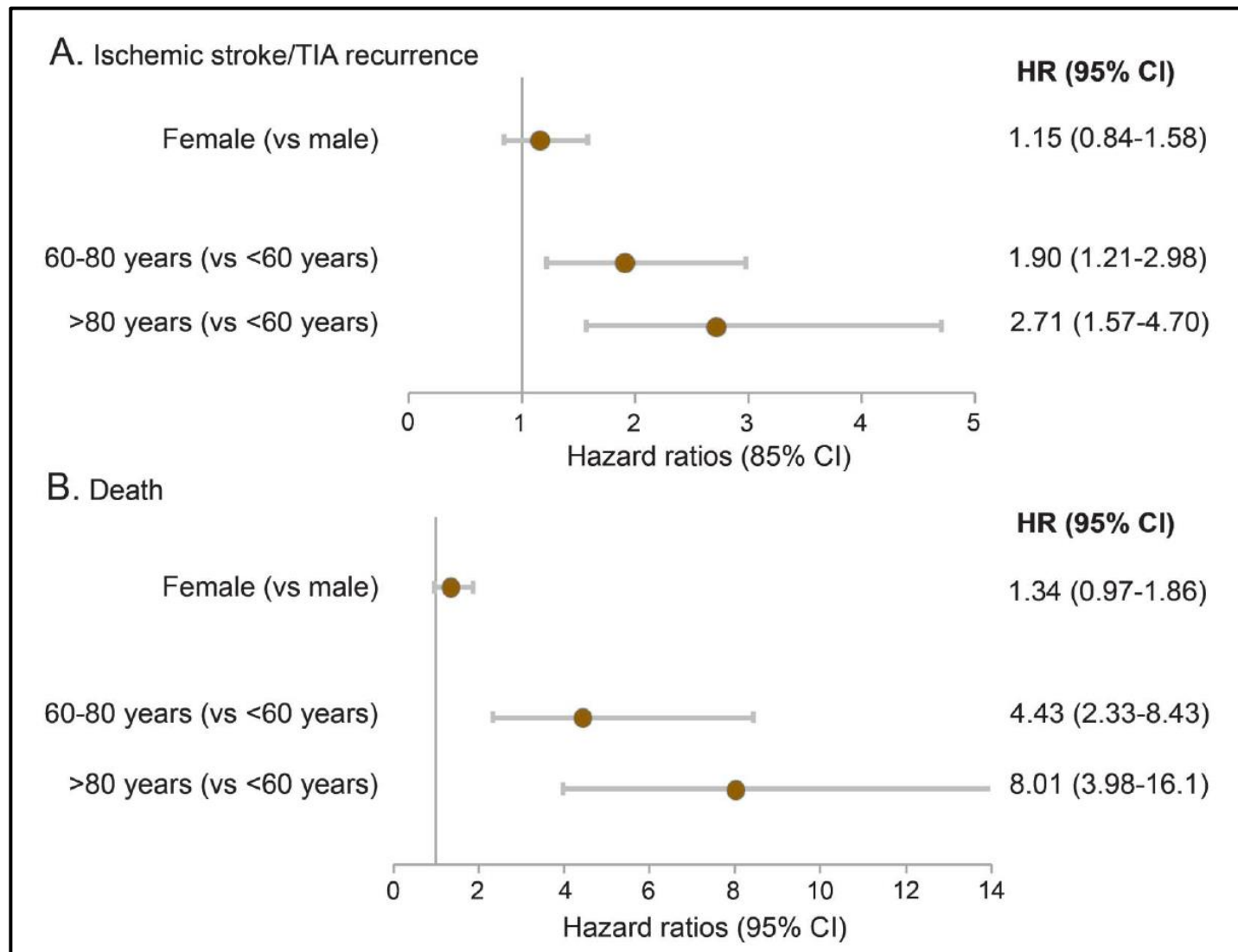
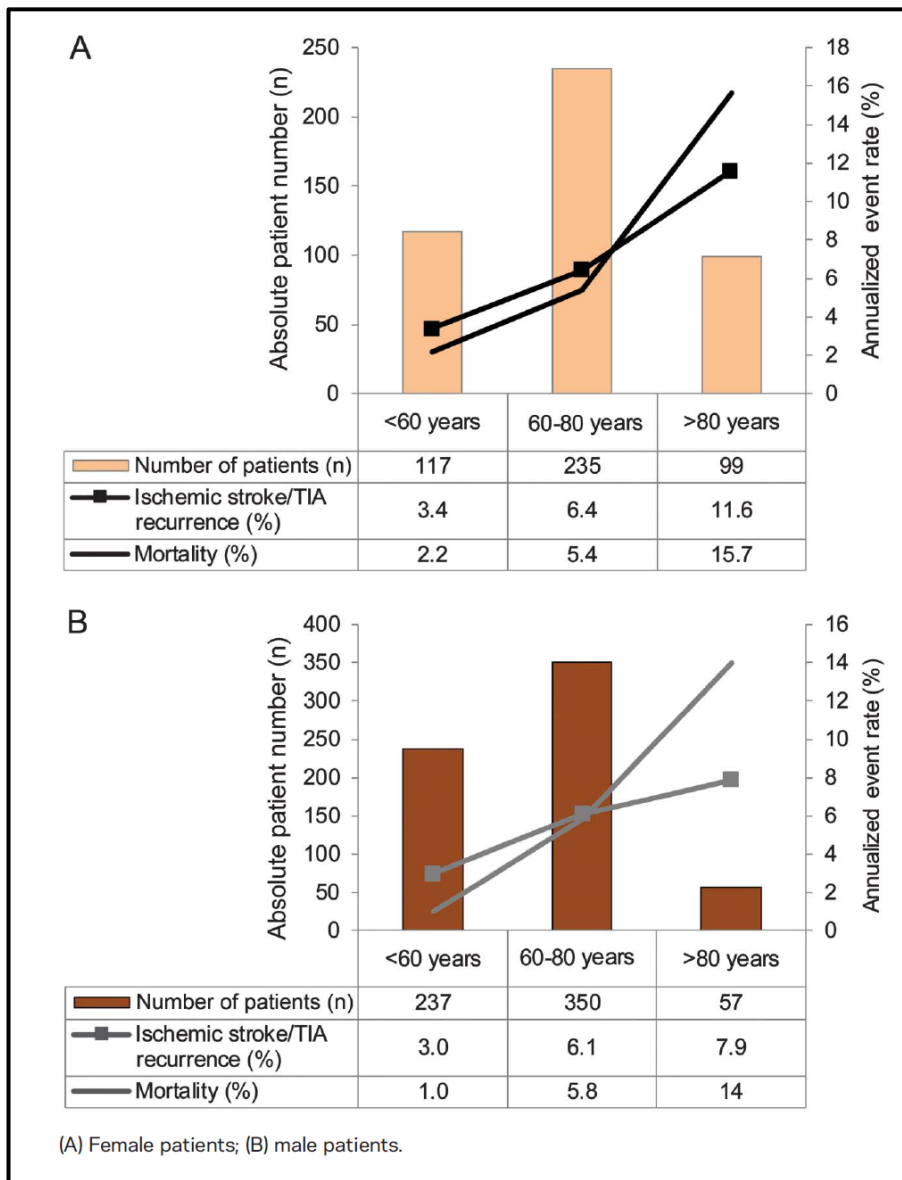


Group	Cryptogenic Stroke (N=227)	Stroke of Known Cause (N=276)	Adjusted Odds Ratio (95% CI)
All patients	77/227	34/276	3.12 (1.98–5.10)
Patients <55 yr	36/82	7/49	3.70 (1.42–9.65)
Patients ≥55 yr	41/145	27/227	3.00 (1.73–5.23)

Negative Association      Positive Association

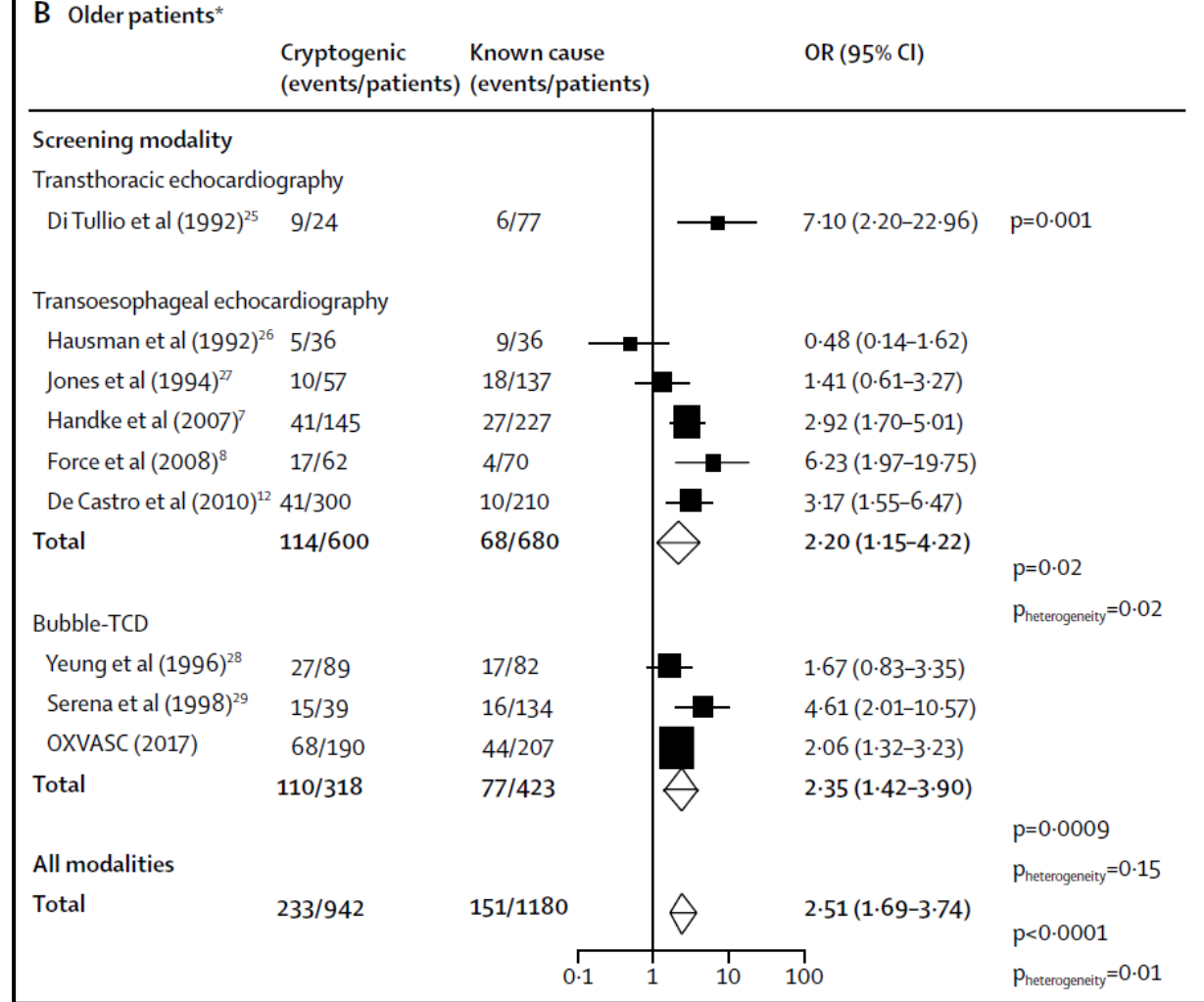
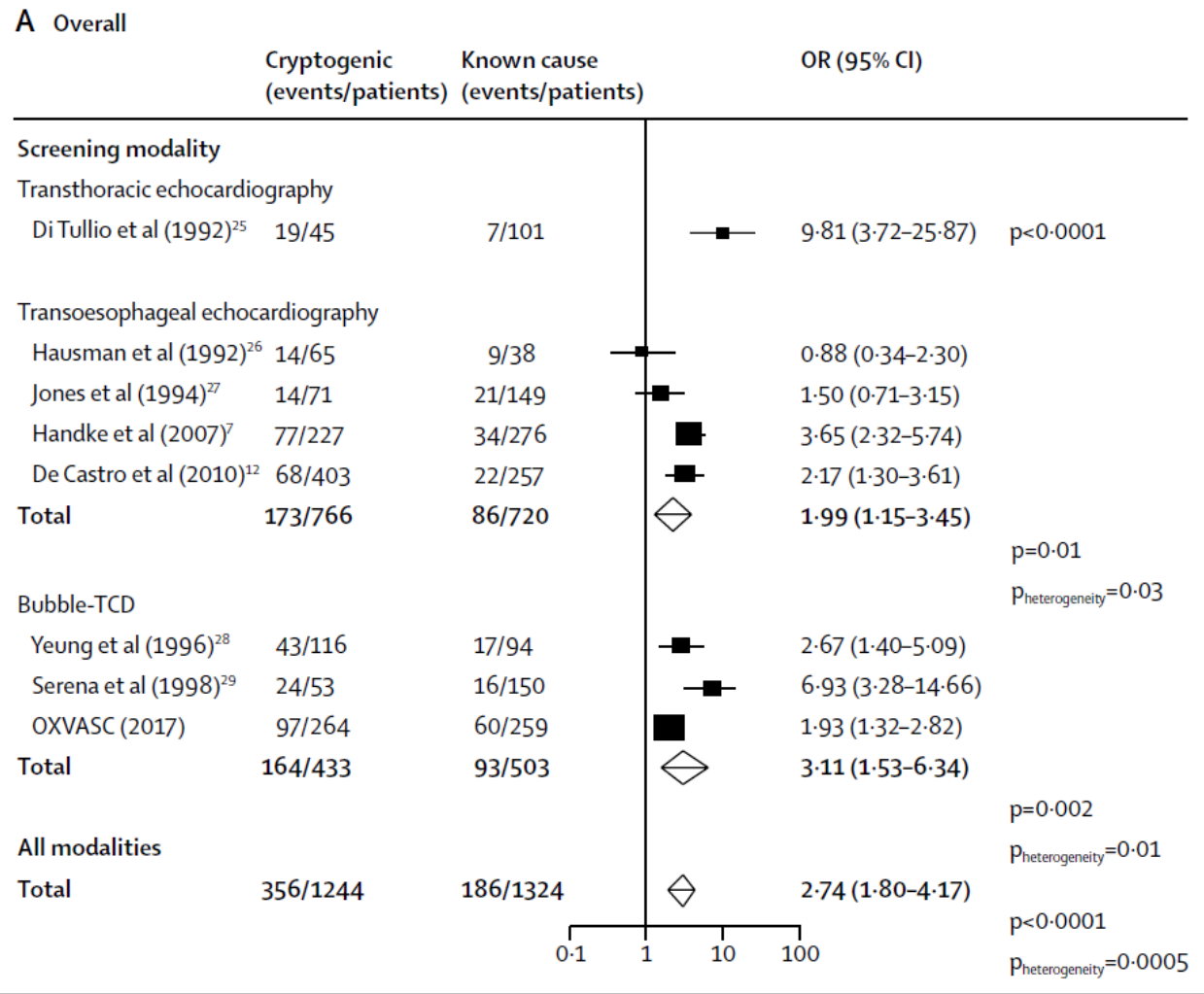
# Age- & Sex-specific Analysis of Patients with ESUS

## Pooled Data of 11 Stroke Registries (1,095 patients/68 years)





# PFO in Elderly Patients with Cryptogenic Stroke & TIA Population-based Study (Oxford Vascular Study, OXVASC)



# Prognosis of Cryptogenic Stroke with PFO at Older Ages (9 Trials & 14 Observational Studies)

Figure 2. Meta-Regression Analysis Between Recurrent Ischemic Stroke Risk and Mean Study Age

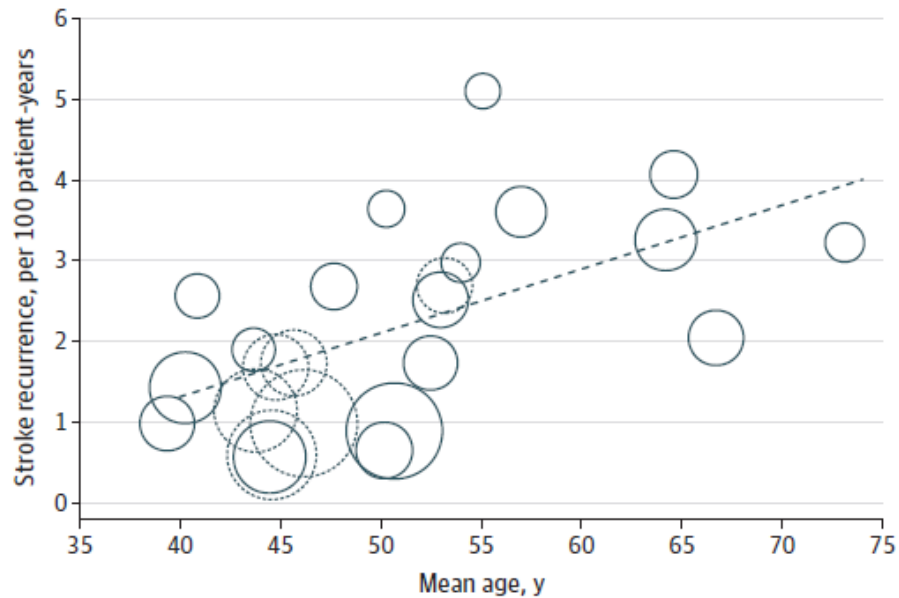
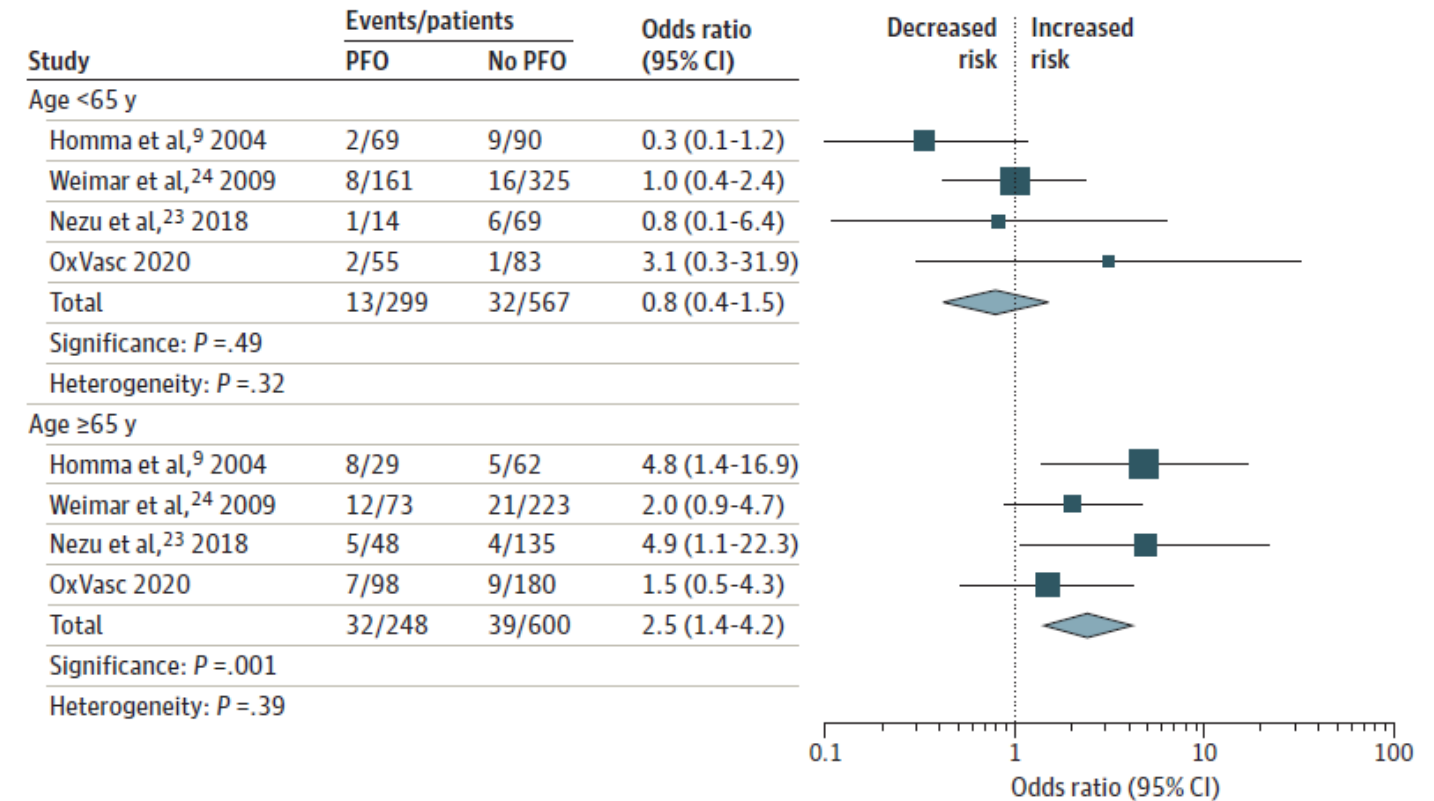
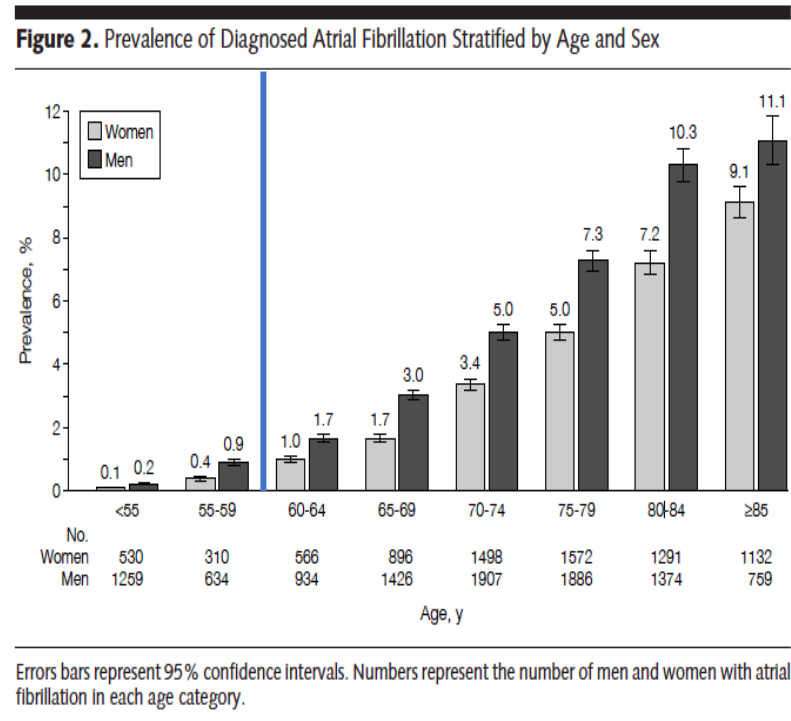


Figure 3. Risk of Ischemic Stroke Recurrence After Cryptogenic Transient Ischemic Attack/Stroke in Patients With Patent Foramen Ovale (PFO) vs Patients Without PFO



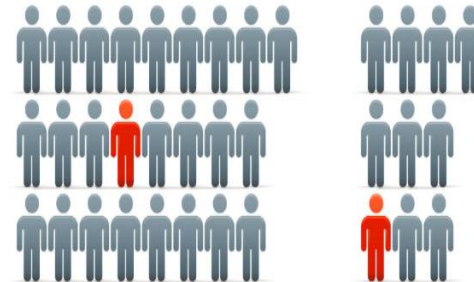
Age is a determinant of risk of ischemic stroke after cryptogenic TIA/stroke in patients with PFO!

# Atrial Fibrillation: a leading stroke risk in old patients



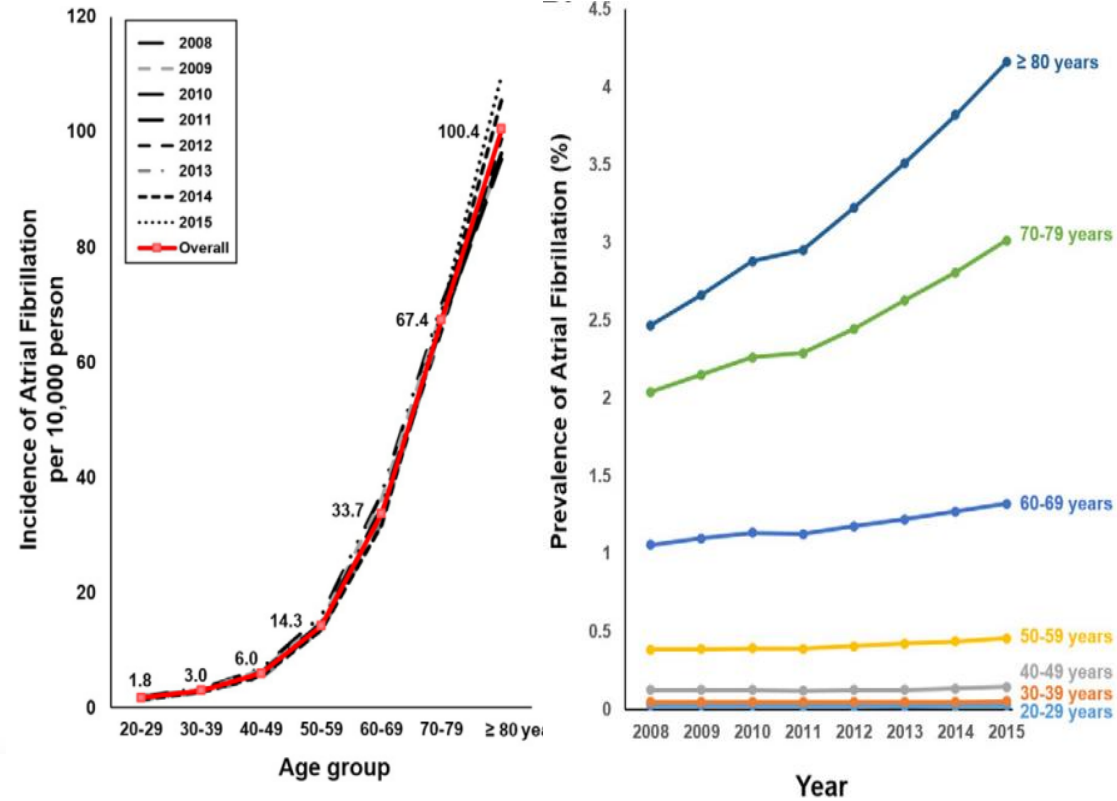
## AGING POPULATION

Age is a major risk factor and prevalence increases significantly as we grow older.



At age 60+,  
**1 in 25**  
Americans have AFib

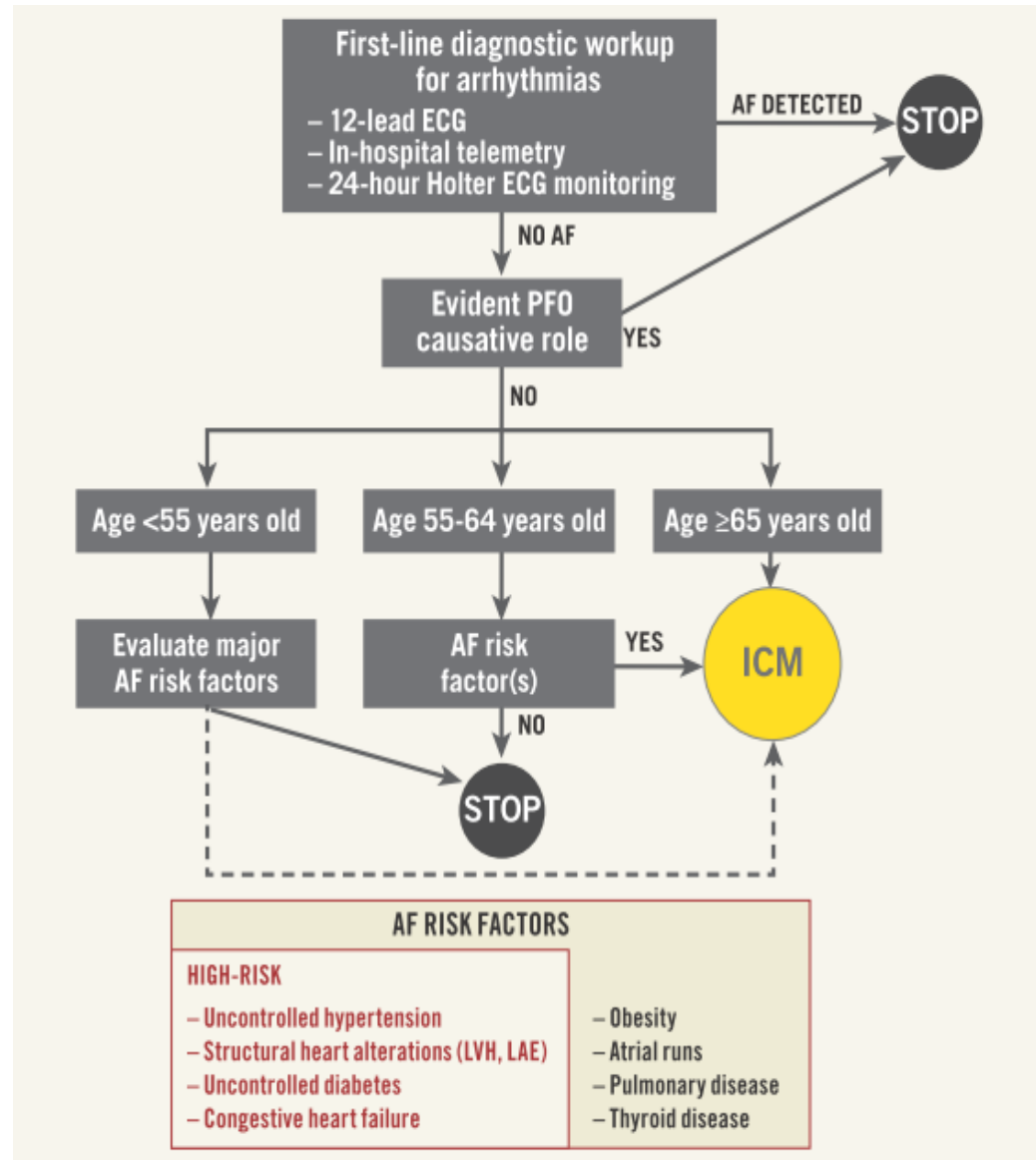
At age 80+, this increases to nearly  
**1 in 10**  
Americans have AFib (Go 2001)



Go et al. JAMA 2001;285:2370-2375.

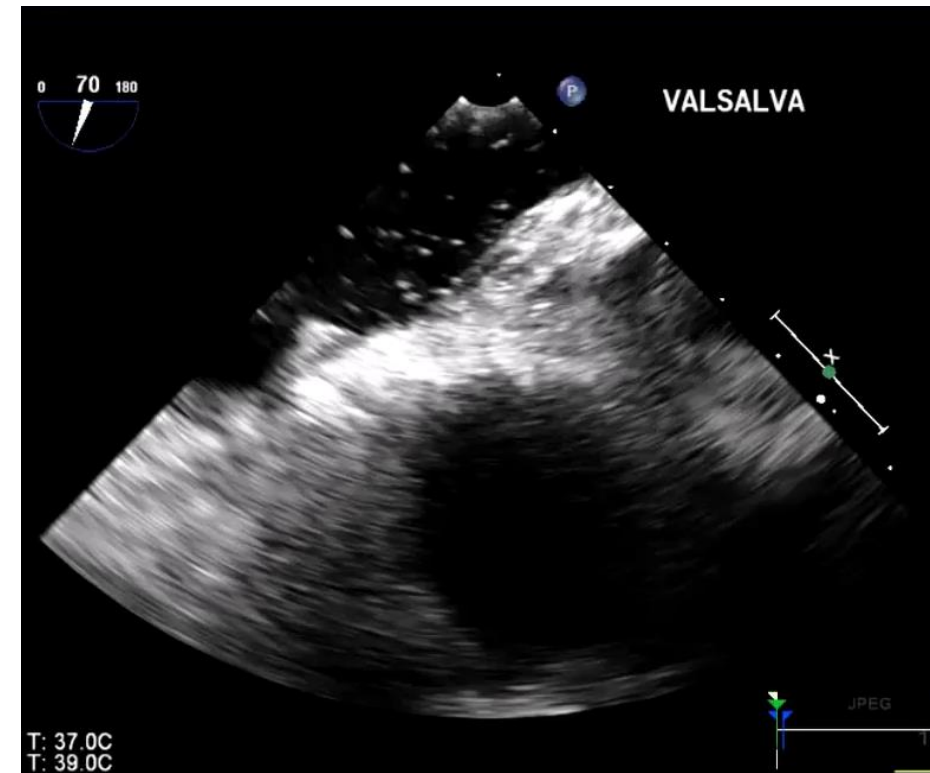
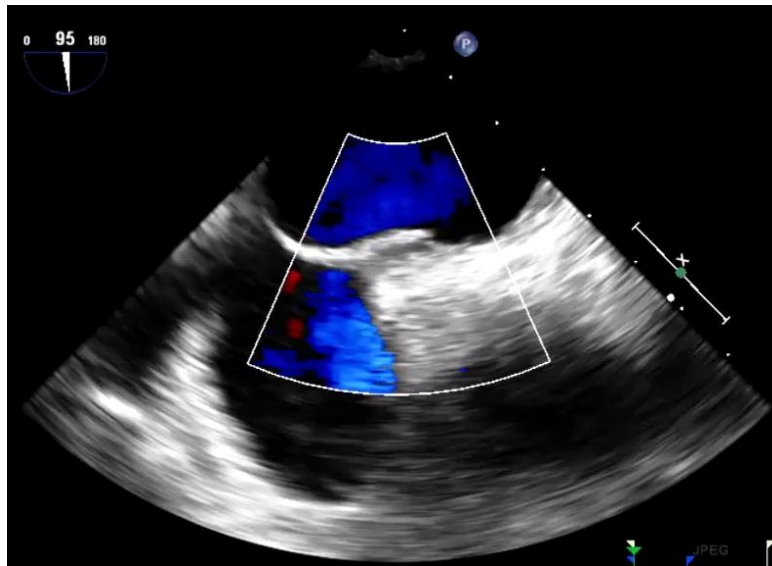
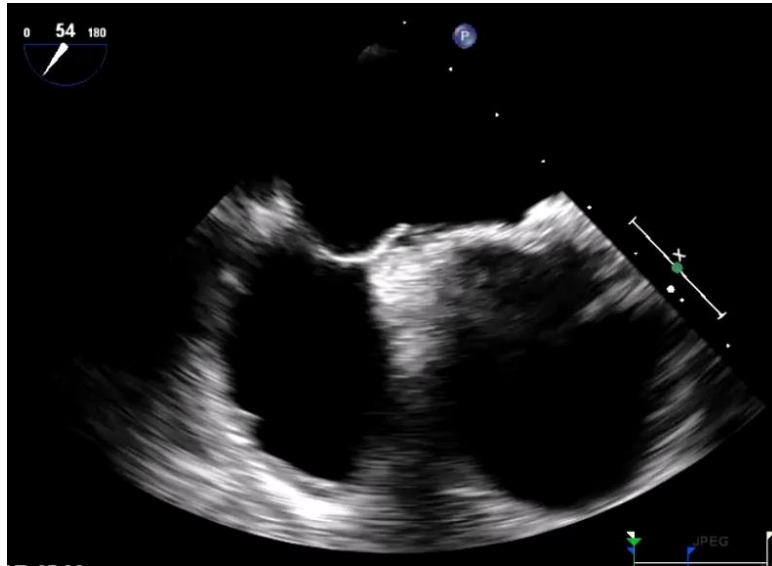
Lee SR et al. Int J Cardiol. 2017;236:226-231.

# Extended Monitoring for AF in Elderly Patients



ICM (insertable cardiac monitors) = implantable loop recorder

# Clinical Case (1): F/67, TEE for cardiac source of embolism

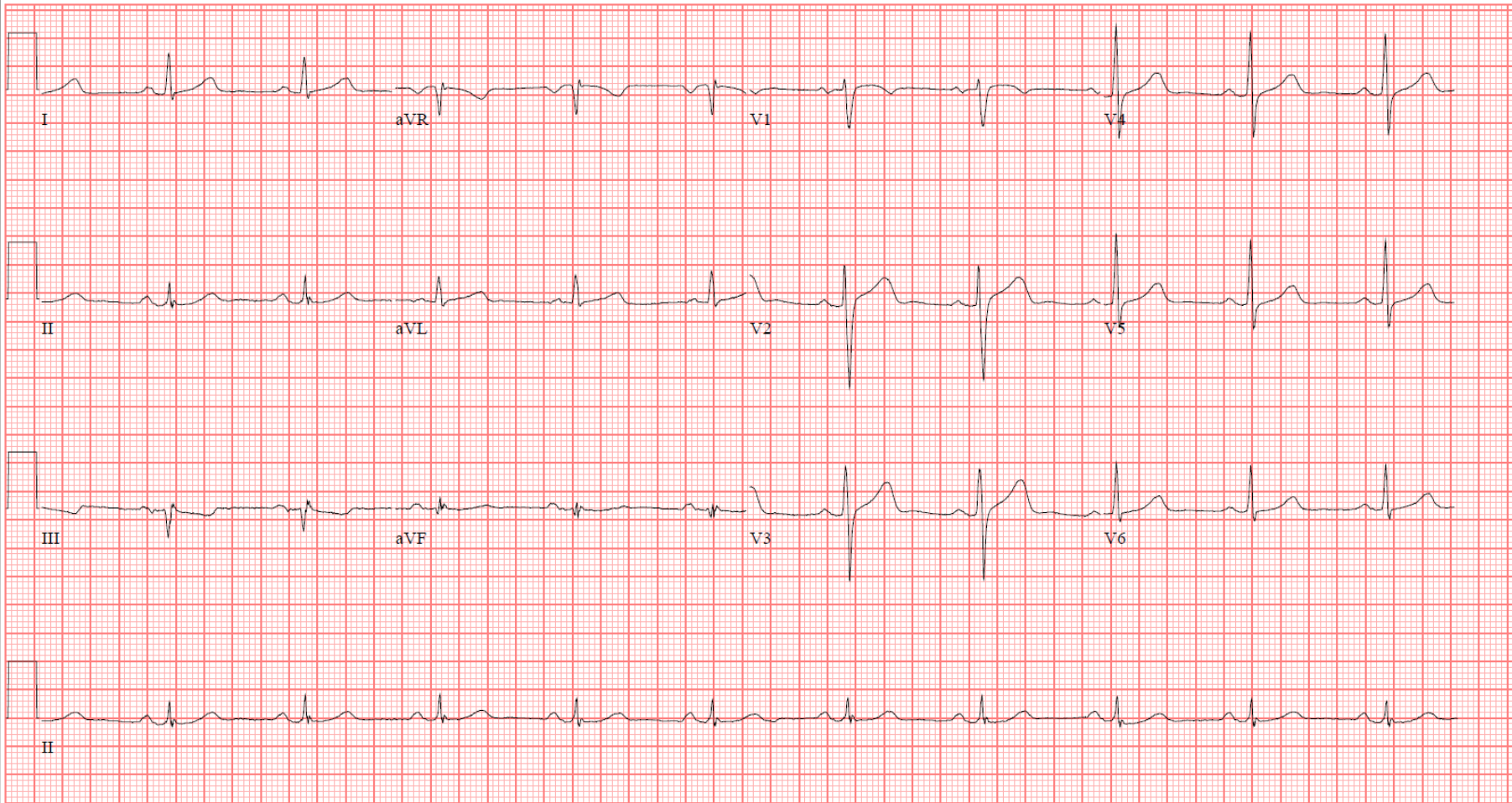


67 yr	Vent. rate	63	BPM	Normal sinus rhythm
Male	PR interval	172	ms	Inferior infarct , age undetermined
	QRS duration	100	ms	Abnormal ECG
Room:	QT/QTc	430/440	ms	
Loc:114	P-R-T axes	45 0 5		

Technician: PMK  
Test ind:324975

Referred by: CV

Confirmed By: GI BYOUNG NAM



24hr Holter monitoring:  
Non-specific finding

# Insertable Cardiac Monitor (Implantable Loop Recorder)



## Episode List

Device: REVEAL LINQ LNQ11

Serial Number: RLA156633G

Date of Visit: 14-Apr-2020 15:16:30

Patient: .

Physician: CHO, MIN SOO - - -

**Arrhythmia Episode List:** 13-Jan-2020 15:45:11 to 14-Apr-2020 15:16:30

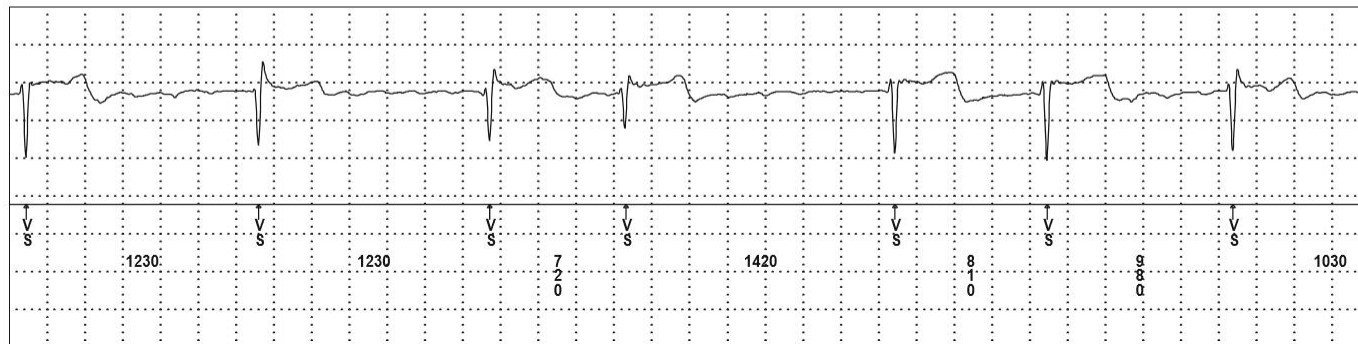
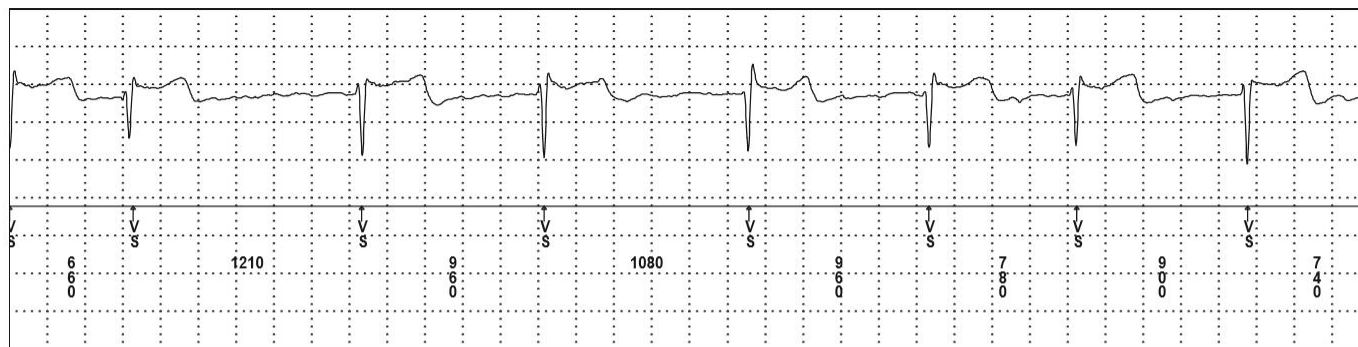
All collected episodes.

ID#	Type	Date	Time hh:mm	Duration hh:mm:ss	Max V. Rate	Median V. Rate
16	AF	12-Apr-2020	16:48	:04:00	158 bpm (380 ms)	105 bpm (570 ms)
15	AF	12-Apr-2020	15:48		162 bpm (370 ms)	146 bpm (410 ms)
14	AF	07-Apr-2020	01:44	01:22:00	95 bpm (630 ms)	63 bpm (950 ms)
13	AF	26-Mar-2020	01:12	01:44:00	133 bpm (450 ms)	59 bpm (1020 ms)
12	AF	26-Mar-2020	00:52	:12:00	86 bpm (700 ms)	55 bpm (1100 ms)
11	AF	23-Mar-2020	22:08	:02:00	76 bpm (790 ms)	67 bpm (900 ms)
10	AF	13-Mar-2020	06:12	01:10:00	154 bpm (390 ms)	49 bpm (1230 ms)
9	Tachy	01-Mar-2020	07:15	:02:24	162 bpm (370 ms)	154 bpm (390 ms)
8	AF	13-Feb-2020	22:52	01:24:00	140 bpm (430 ms)	73 bpm (820 ms)
7	AF	27-Jan-2020	03:28	:44:00	125 bpm (480 ms)	67 bpm (890 ms)
6	AF	14-Jan-2020	04:24	03:54:00	154 bpm (390 ms)	87 bpm (690 ms)

----- Last Programmer Session 13-Jan-2020 -----

----- Last Medtronic CareLink Monitor Session 17-Dec-2019 -----

(Data prior to last session has not been interrogated.)





# How Often is Occult AF Causally-Related to Cryptogenic Ischemic Stroke

## OCCULT AF CAUSES

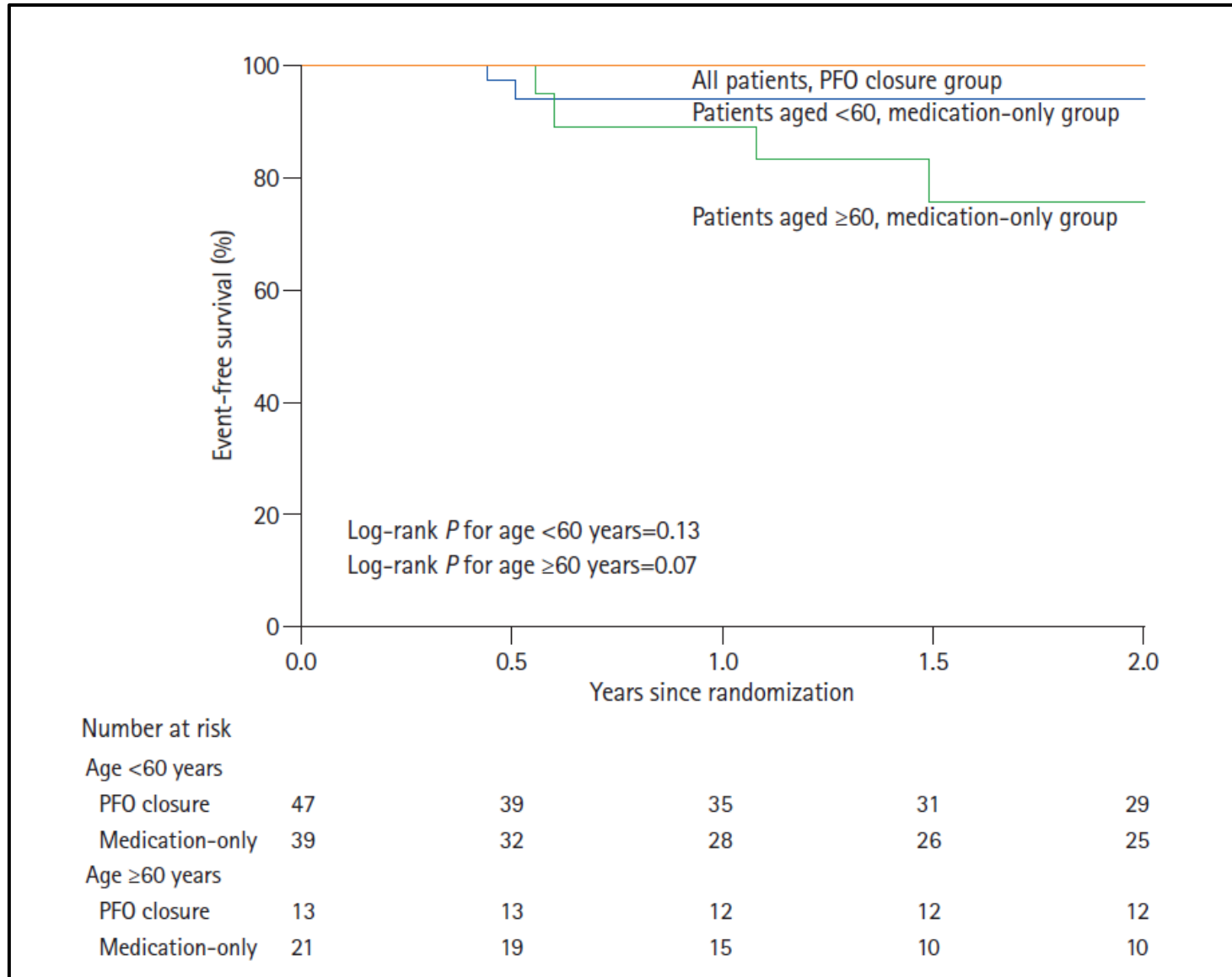
- ~ 6% of cryptogenic ischemic stroke in young+middle-aged adults
- ~ 6% of all cryptogenic ischemic stroke in older adults
- ~ 1% of all ischemic stroke

## PFOs CAUSE

- ~ 38% of cryptogenic ischemic stroke in young+middle-aged adults
- ~ 14% of cryptogenic ischemic stroke in older adults
- ~ 5% of all ischemic stroke



# Unresolved Issues: Age Limitation

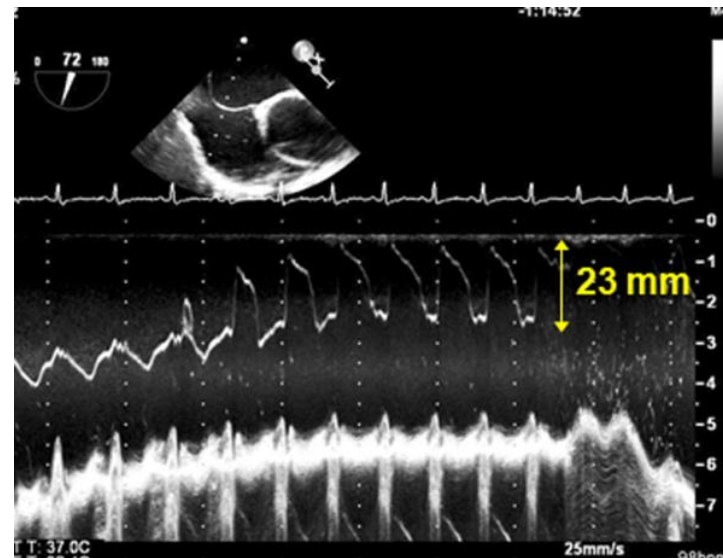
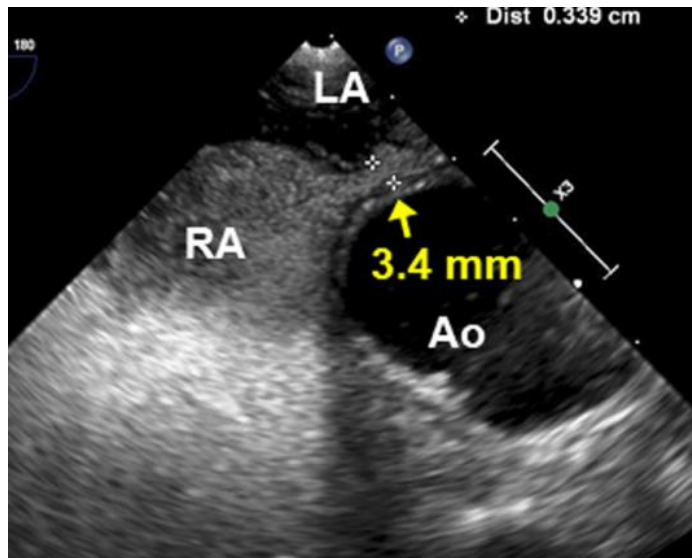
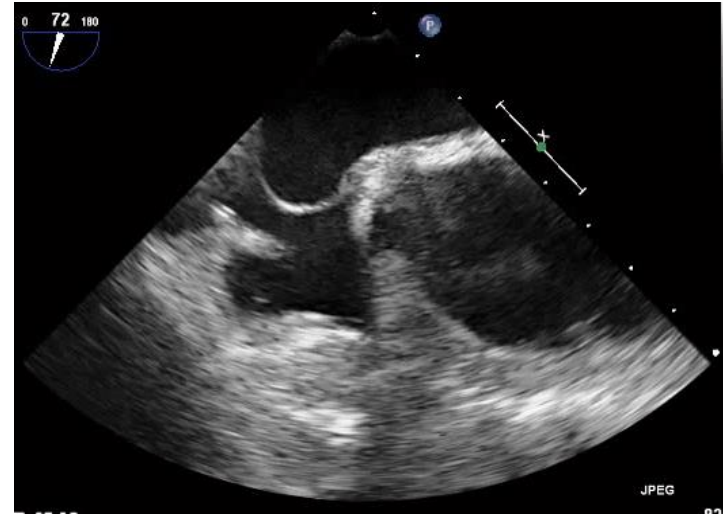


DEFENSE-PFO subgroup analysis

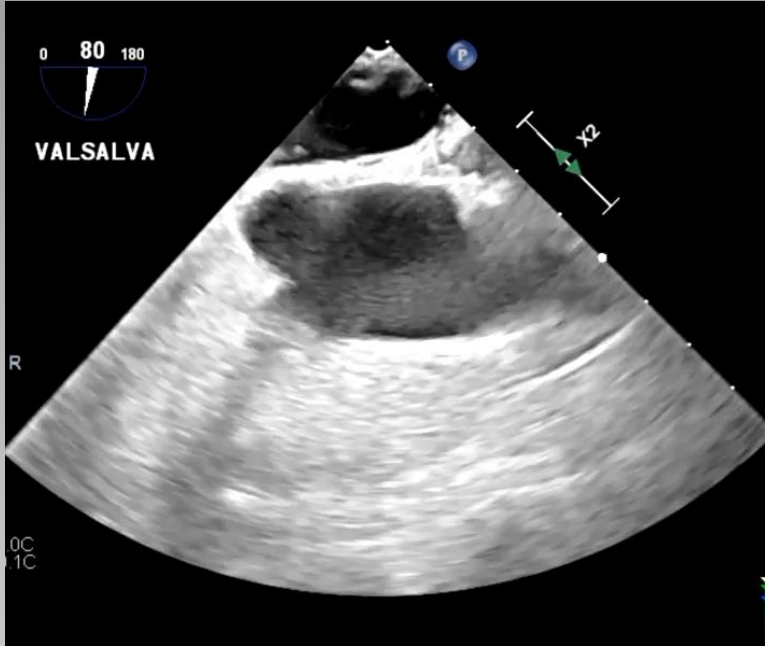
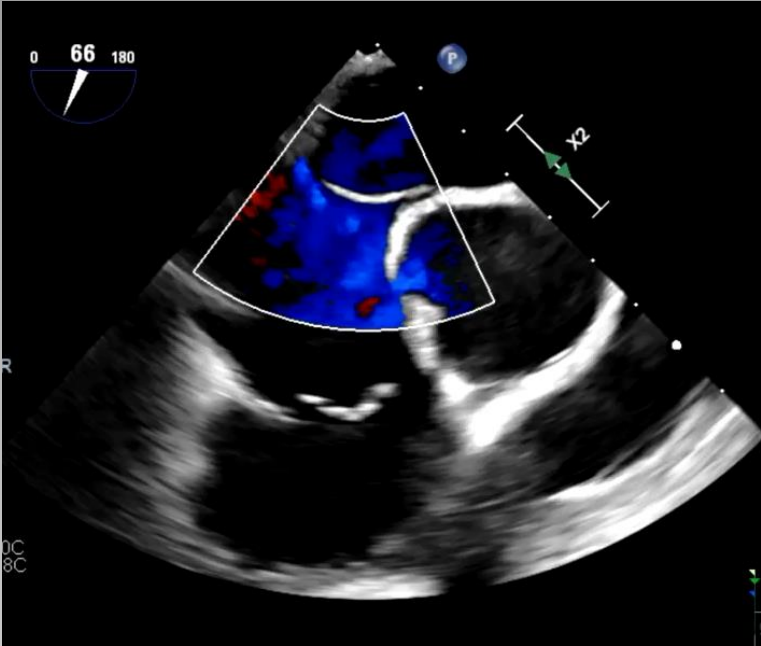
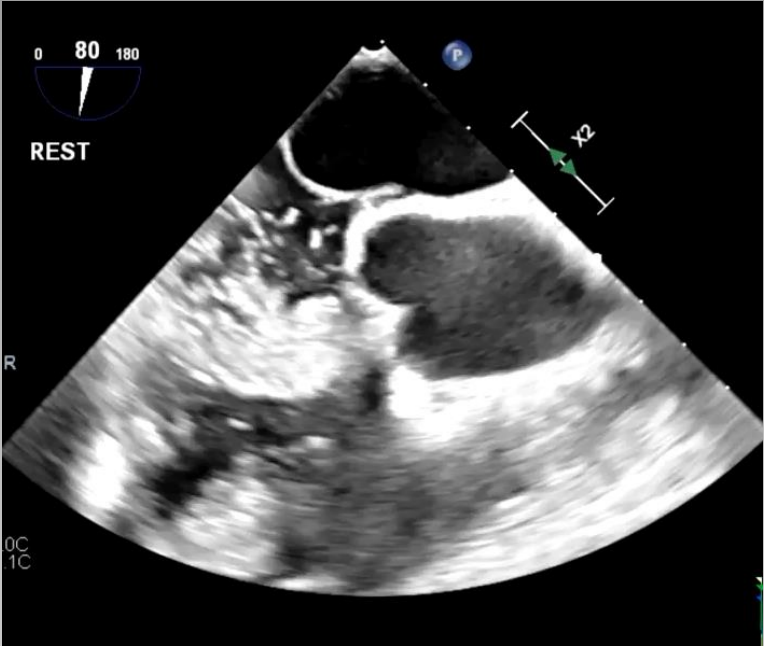
*J Stroke* 2021

# High- vs Low-risk PFO:

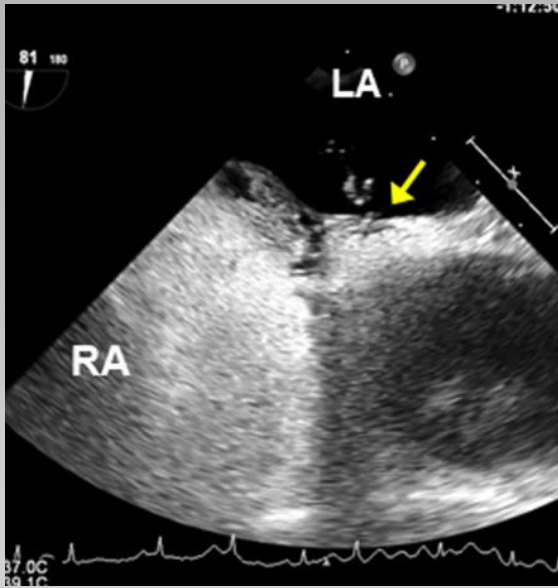
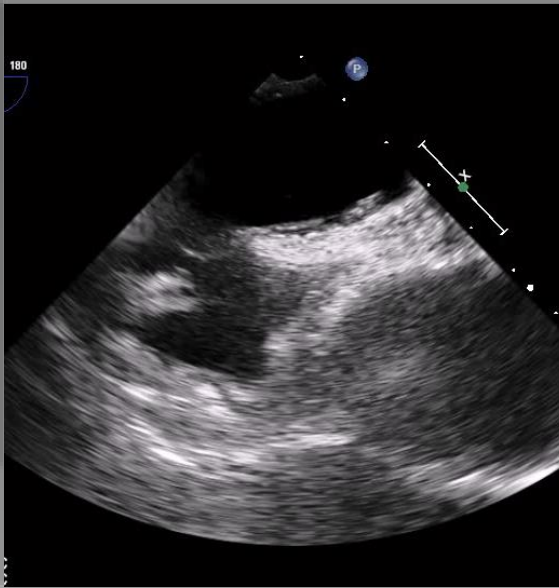
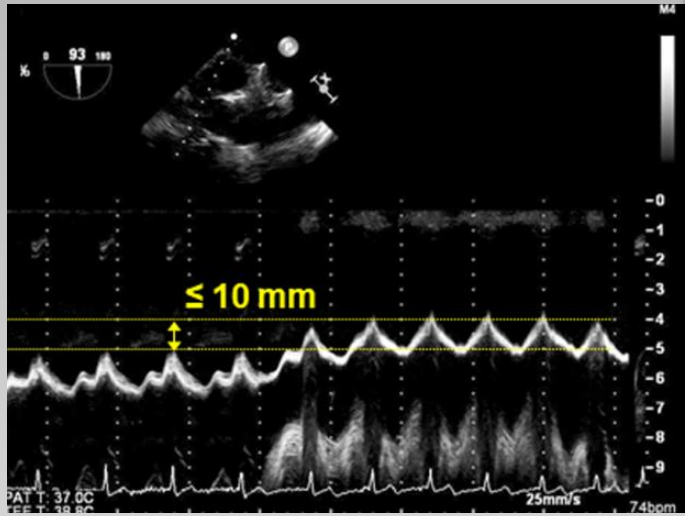
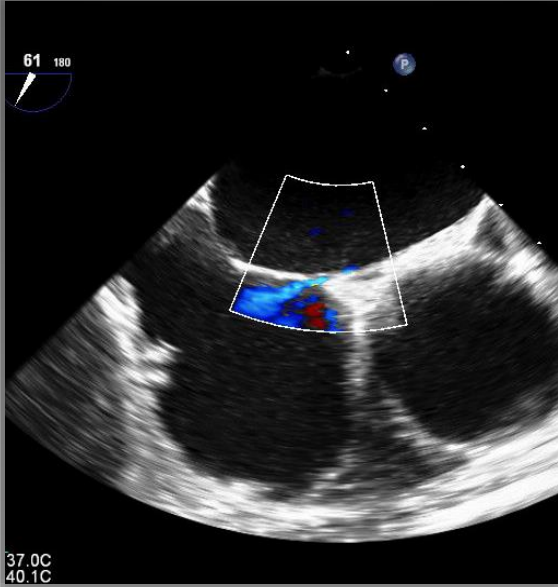
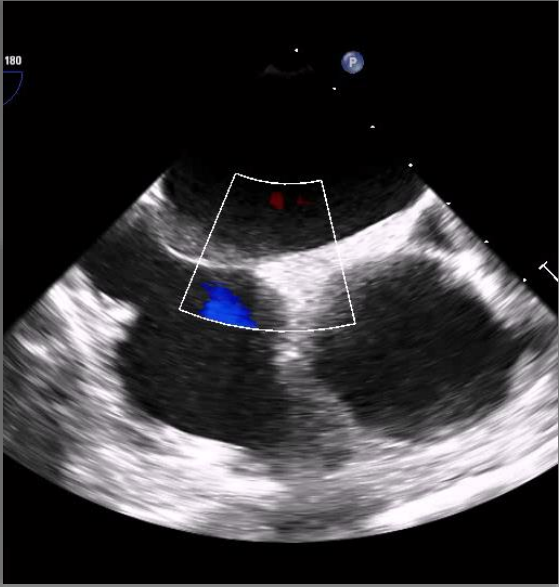
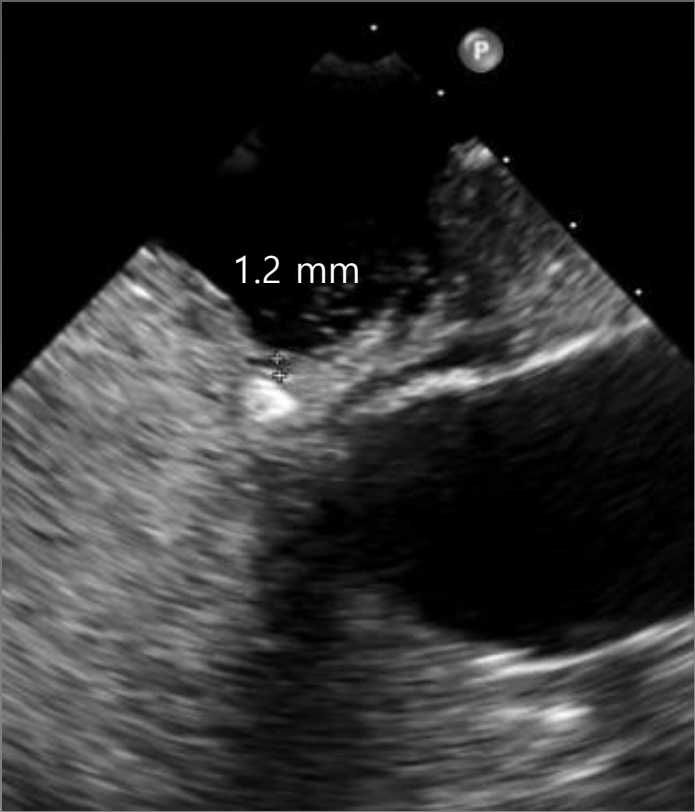
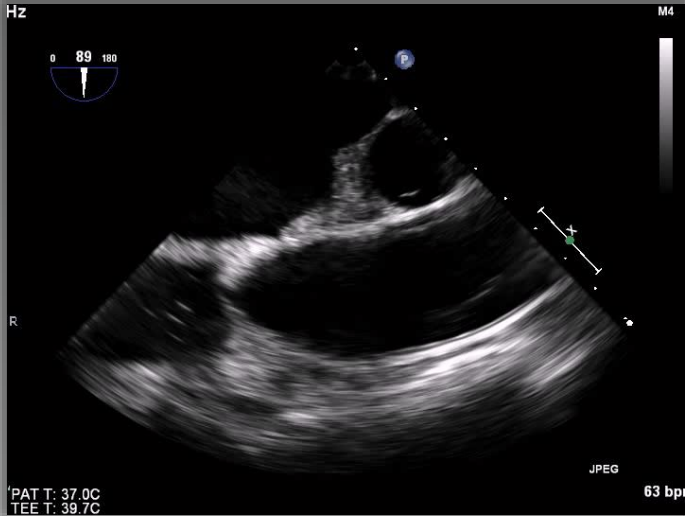
PFO size ( $>2$  mm), Atrial septal aneurysm or hypermobility ( $>10$  mm)



# Hypermobile atrial septum with a large PFO

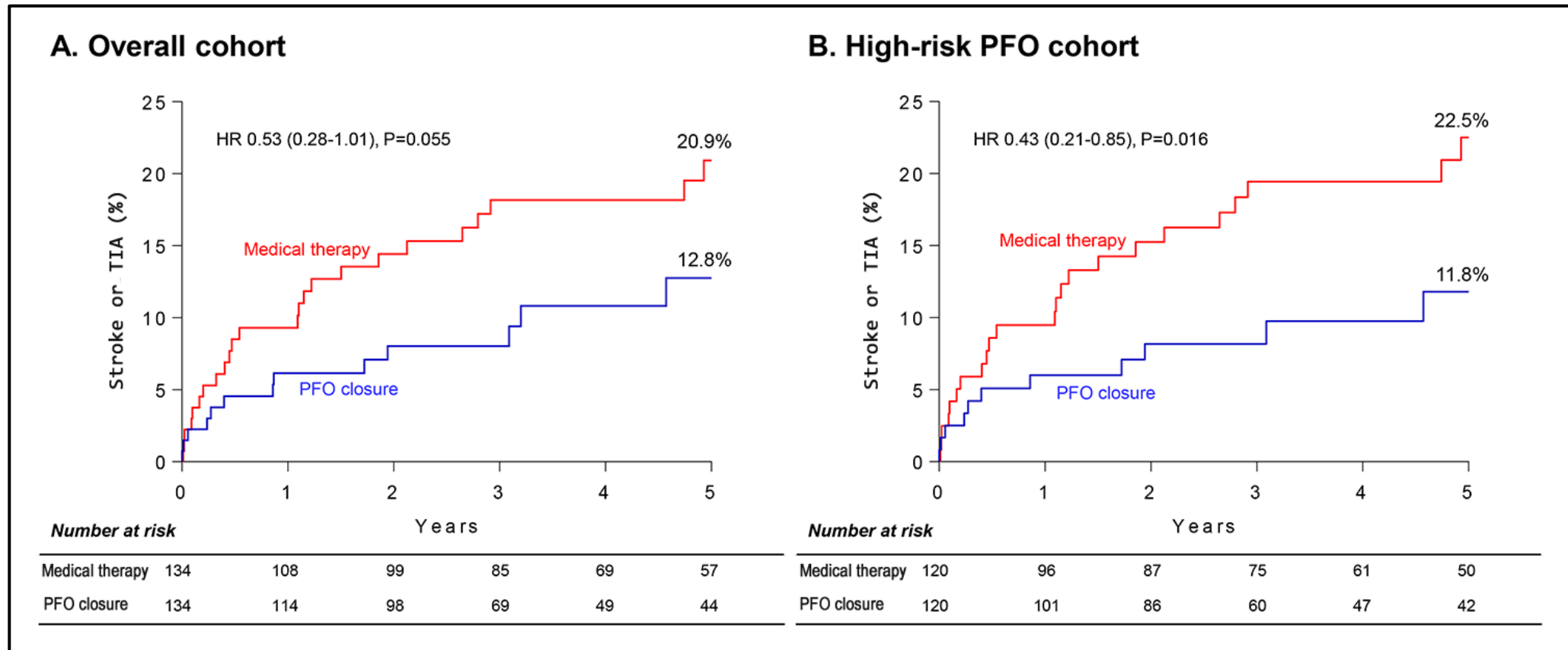


# Low-risk PFO



# Device Closure or Antithrombotic Therapy after Cryptogenic Stroke in Elderly Patients with a High-risk PFO

- 10 hospitals in South Korea – retrospective analysis
- 437 elderly patients with PFO-associated stroke (mean age, 68.1 years):
- 303 patients (69%) had a high-risk PFO: PFO closure was done in 161 patients (37%)
- Recurrent stroke or TIA in 64 patients (14.6%) during median F/U of 3.9 years



# Any RCTs?

NCT01018355

The Effect of Device Closure of **Patent Foramen Ovale** in Elderly Patients With Cryptogenic Stroke/TCl

ClinicalTrials.gov Identifier: NCT01018355

Recruitment Status ⓘ : Terminated (Dissatisfactory enrollment rate)

First Posted ⓘ : November 23, 2009

Last Update Posted ⓘ : May 6, 2010



Professor Jean-Louis Mas

PFO is associated with cryptogenic stroke

Risk of stroke recurrence in PFO-associated stroke:  
additive risk of atrial septal aneurysm

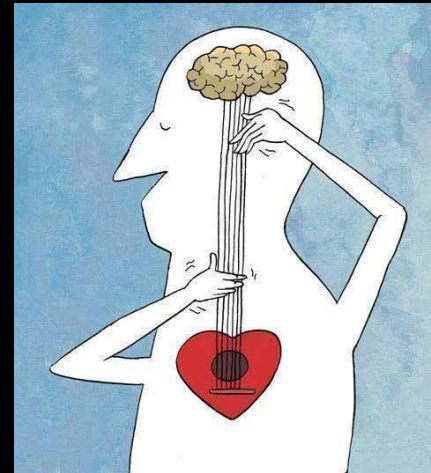
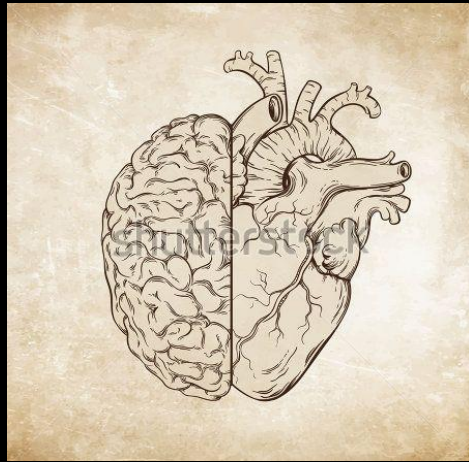
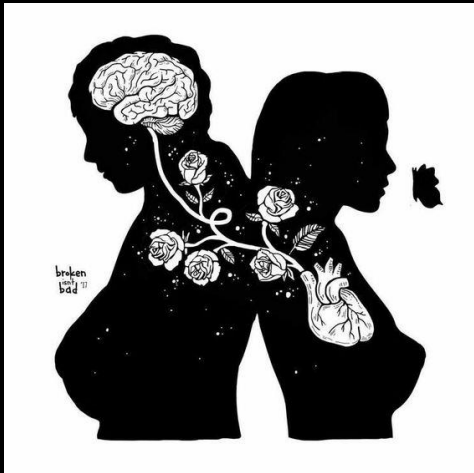
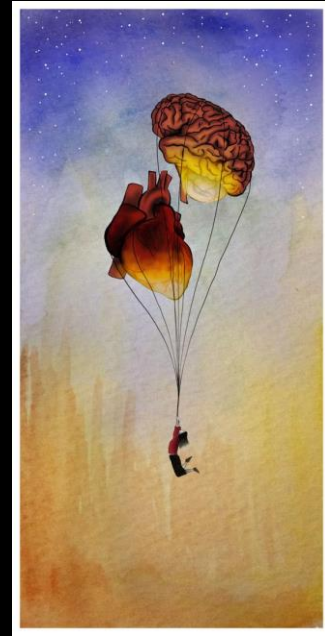
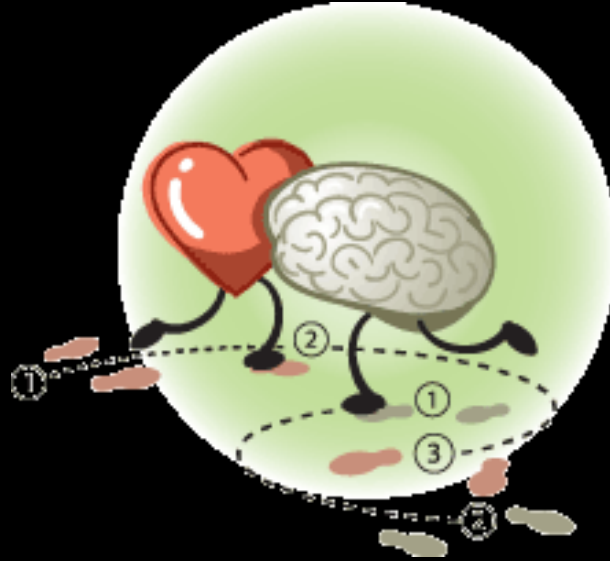
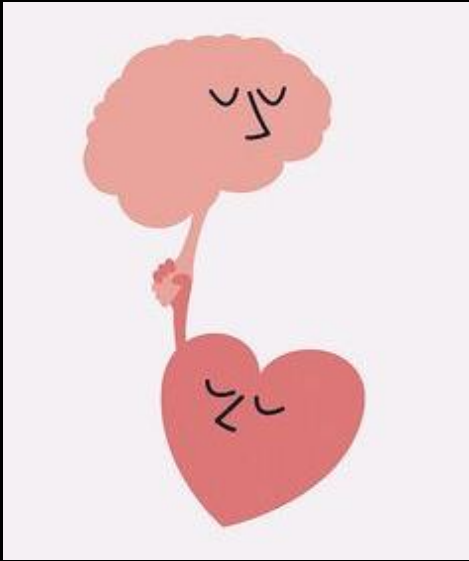
CLOSE trial – beneficial effect of device closure in  
patients with a high-risk PFO

CLOSE II trial for elderly cryptogenic stroke patients  
with a high-risk PFO

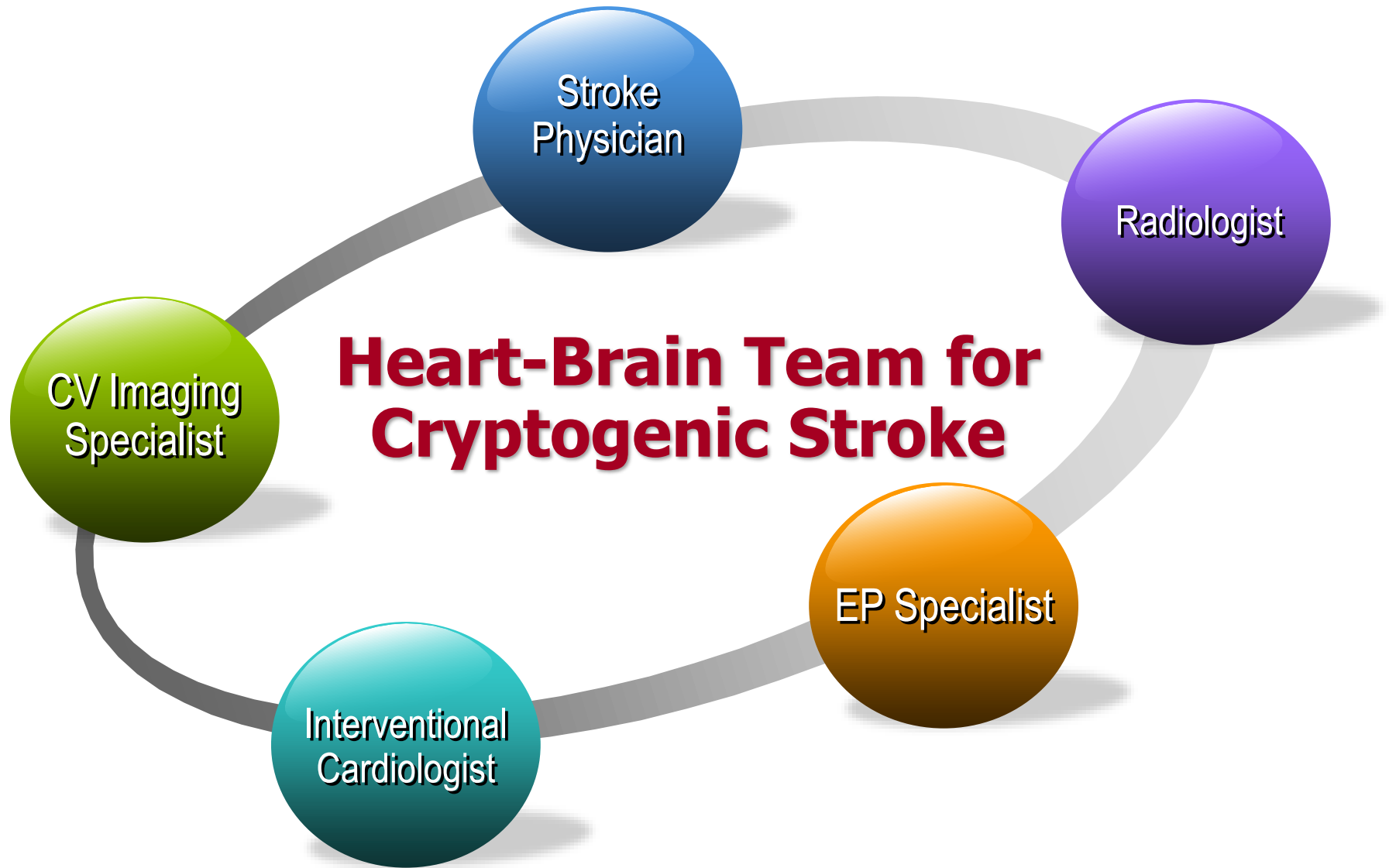


# Conclusion: PFO Closure in the Elderly Cryptogenic Stroke Patients with PFO

- Underestimated clinical significance of PFO in elderly cryptogenic stroke patients
- Retrospective analysis showed beneficial effect of device closure in elderly patients with a high-risk PFO
- RCT is ongoing – CLOSE II



Courtesy of Dr. Saver (UCLA Stroke Center)



Stroke  
Physician

Radiologist

## Heart-Brain Team for Cryptogenic Stroke

CV Imaging  
Specialist

EP Specialist

Interventional  
Cardiologist