

# NEUROCARDIOLOGY: CURRENT PRACTICES IN THE STROKE MANAGEMENT

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## DISCLOSURES

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## CURRENT PRACTICES IN NEUROCARDIOLOGY

### Outline

- Atrial fibrillation (AF) as a stroke risk factor
  - Available devices to detect AF after stroke
  - Left atrial appendage (LAA) closure for stroke prevention
- Patent foramen ovale (PFO) as a stroke risk factor
  - Benefit of PFO closure
- Heart-brain collaboration

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## CLINICAL CASE #1

77-years-old man with HTN, DM, CAD, smoker, OSA, presented with aphasia and right hemiparesis, found to have left MCA territory embolic infarct. CTA does not show significant vessel stenosis. TTE showed normal ejection fraction, moderate dilatation of left atrium and no significant valvular abnormality. ECG shows sinus rhythm

What is the stroke mechanism?

What are the next steps?

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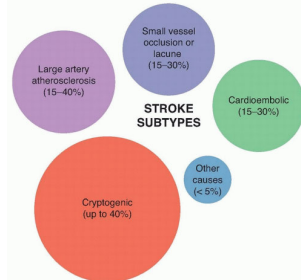
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## STROKE MECHANISMS

TOAST-Trial of Org 10172 in Acute Stroke Treatment




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## CRYPTOGENIC STROKE AND ESUS

"Cerebral infarction for which no probable cause is identified after adequate diagnostic evaluation"

Cryptogenic stroke according to TOAST:

- 1) Incomplete workup
- 2) More than one potential cause
- 3) **No determined etiology after complete investigation**

Embolic stroke of undetermined source (ESUS) -international working group 2014

"Non-lacunar infarct in the absence of: extracranial or intracranial atherosclerosis causing >50% luminal stenosis in the artery supplying the ischemic region, major cardioembolic sources permanent or paroxysmal atrial fibrillation (AF), sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumors, mitral stenosis, myocardial infarction within the past 4 weeks, left ventricular (LV) **ejection fraction <30%**, valvular vegetations or infective endocarditis, and no dissection, arteritis, migraine/vasospasm, drugs"

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## CARDIAC CAUSES OF THE STROKE

### Sources with high primary risk of ischemic stroke

Left atrial thrombus  
 Left ventricular thrombus  
 Atrial fibrillation  
 Paroxysmal atrial fibrillation  
 Sick sinus syndrome  
 Sustained atrial flutter  
 Recent myocardial infarction (within 1 month)  
 Mitral stenosis or rheumatic valve disease  
 Bioprosthetic and mechanical heart valves  
 Chronic myocardial infarction together with low ejection fraction <28%  
 Dilated cardiomyopathy  
 Non-bacterial thrombotic endocarditis  
 Infective endocarditis  
 Papillary fibroelastoma  
 Left atrial myxoma  
 Patent foramen ovale and concurrent systemic embolism

### Sources with low or uncertain primary risk of ischemic stroke

Mitral annular calcification  
 Patent foramen ovale  
 Atrial septal aneurysm  
 Left ventricular aneurysm without thrombus  
 Isolated left atrial stroke (no mitral stenosis or atrial fibrillation)  
 Complex atheroma in the ascending aorta or proximal arch  
 Symptomatic congestive heart failure with ejection fraction <30%  
 Wall motion abnormalities (hypokinesia, akinesia, dyskinesia)  
 Hypertrophic cardiomyopathy  
 Left ventricular hypertrophy  
 Left ventricular hypertrophy/non-compaction  
 Other rare sources (atrial or ventricular septal defect, preexcitation syndromes, left atrial dilation)

## ATRIAL FIBRILLATION (AF)

- Framingham Heart Study: in 37% after the age of 55 years
- Paroxysmal >2/3, 5-10%/y progress to persistent

TABLE 1. Stroke risk stratified by CHA<sub>2</sub>DS<sub>2</sub>-VASc score<sup>a,b</sup>

CHA <sub>2</sub> DS <sub>2</sub>		CHA <sub>2</sub> DS <sub>2</sub> -VASc		CHA <sub>2</sub> DS <sub>2</sub> -VASc		Adjusted stroke rate (%/year)
Risk factor	Score	Risk factor	Score	score	score	
CHF	1	CHF/LV dysfunction	1	0	0	
HT	1	HT	1	1	1.3	
Age ≥75 years	1	Age ≥75 years	2	2	2.2	
DM	1	DM	1	3	3.2	
Prior stroke/TIA	2	Stroke/TIA/TE	2	4	4.0	
		Vascular disease (prior MI, PAD, or aortic plaque)	1	5	6.7	
		Age 65-74 years	1	6	9.8	
		Sex (female)	1	7	9.6	
				8	6.7	
Maximum score	6	Maximum score	9	9	15.2	

Abbreviations: CHF = congestive heart failure; DM = diabetes mellitus; HT = hypertension; LV = left ventricle; MI = myocardial infarction; PAD = peripheral arterial disease; TE = thromboembolism; TIA = transient ischemic attack.

### AF risk factors:

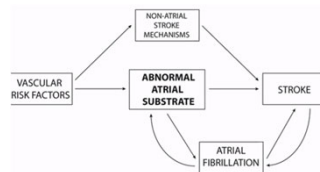
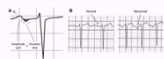
- Older age
- Male
- Obesity
- CAD
- HTN
- Smoking
- DM
- OSA
- Family
- h/o AF in a first-degree relative

## ATRIAL CARDIOPATHY

Fibrotic changes in the atrium might be a precursor of afib

Atrial cardiopathy:

- PTFV1 >5000mVs on 12-lead ECG
- Serum NT-proBNP >250pg/mL
- Left atrial enlargement



One third of patient with both AF and stroke do not manifest AF until after the stroke, despite many month of monitoring prior to stroke

## CLINICAL CASE #1

77-year-old man with HTN, DM, CAD, smoker, OSA, presented with aphasia and right hemiparesis, found to have left MCA territory embolic infarct. CTA does not show significant vessel stenosis. TTE showed normal ejection fraction, moderate dilatation of left atrium and no significant valvular abnormality. ECG shows sinus rhythm

What is the stroke mechanism?

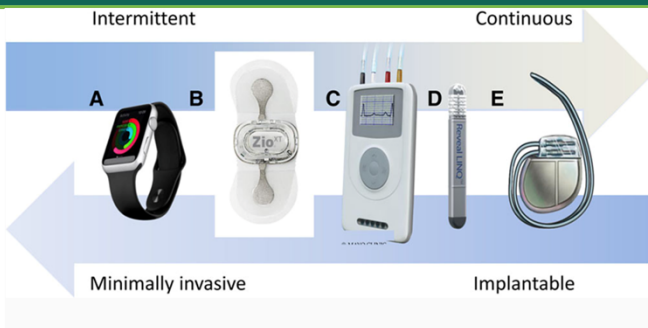
**Cryptogenic-ESUS**

What are the next steps?

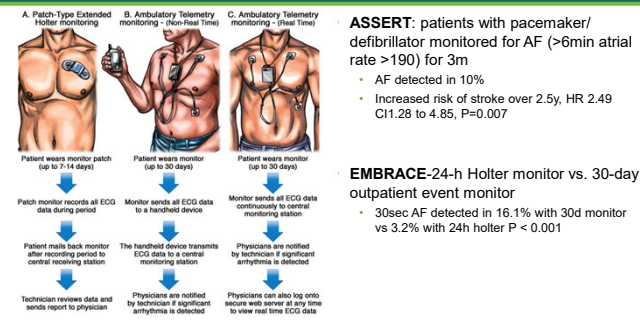
**Cardiac monitor**

**-Which device and how long?**

## SCREENING FOR AF-CLOSING THE LOOP



## EXTERNAL AMBULATORY ECG MONITORING



## REVEAL LINQ ICM

1. Reveal LINQ ICM



2. Procedure Tools



**CRYSTAL AF** – implantable long term monitor vs standard evaluation, 2min of AF

- 8.9% vs 1.4% AF detection at 6m in patients with REVEAL; HR=6.4 (95% CI, 1.9–21.7), P<0.001
- AF detected in 9% at 6m, 12% at 1y and 30% at 3y

3. Wireless Connectivity



4. MyCareLink Patient Home Monitor



5. Simplified Reports






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## APPLE HEART STUDY

- 419,297 US adults, 25000 ≥ 65
- 2160 (0.5%) notified for irregular heart rhythm; rate higher in ≥ 65yo (3.2%)
- 450/2160 (21%) returned wearable ECG patch
- AF confirmed in 153/450 (34%)

*Low AF rate concerning for poor accuracy;  
Unnecessary diagnostic test and treatment in patients who receive notification*




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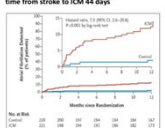
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## PREVALENCE OF AF IN NON EMBOLIC STROKE

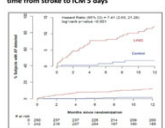
- Patients with ischemic stroke attributed to small or large vessel disease within 10d from stroke
- Age >60, or age 50-59y with one additional risk factors: congestive HF, HTN, DM, prior stroke within 90d prior MI, PAD, aortic plaque
- Medial CHA2-DS2-VASc score 5

**COMPARISON OF AF DETECTION IN TWO POPULATIONS**  
CRYSTAL AF (CRYPTOGENIC) VS. STROKE AF (SVO/LAA)  
INCIDENCE RATES OF AF THROUGH 12 MONTHS

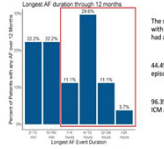
**CRYSTAL AF:** Mean age 61.5 ± 13.4 years; median time from stroke to ICM 44 days



**STROKE AF:** Mean age 67.1 ± 9.4 years; median time from stroke to ICM 5 days



**AF DURATION**



The majority (55.5%) of patients with AF detected in the ICM arm had an episode lasting <1 hour

44.4% of patients with AF had an episode lasting >1 hour

96.3% of first AF episodes in the ICM arm were asymptomatic

Median time to first detected AF was 99d  
Number needed to monitor for 1 AF case detected was 8 in ICM arm vs 56

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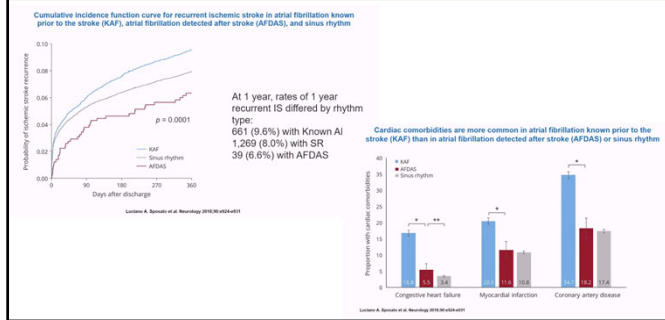
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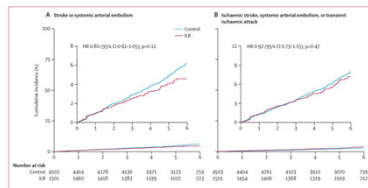
## AF BEFORE OR AFTER THE STROKE



## ARE ALL AF WORTH SCREENING FOR

### Loop study – Denmark

- 70-90yo with HTN or DM or HF or previous stroke
- ILR vs usual care; median CHA2DS2 VASc score 4
- ~17% with h/o stroke in both arms
- AF found in 31.8% in ILR group and vs 12.2% in control (HR 3.17, CI 2.81–3.59,  $p < 0.0001$ )



## CLINICAL CASE #1

77-year-old man with HTN, DM, CAD, smoker, OSA, presented with aphasia and right hemiparesis, found to have left MCA territory embolic infarct. CTA does not show significant vessel stenosis. TTE showed normal ejection fraction, moderate dilatation of left atrium and no significant valvular abnormality. ECG shows sinus rhythm

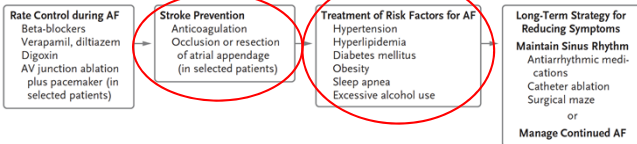
30d monitor – no AF

Implantable cardiac monitor- 7min of AF

What would you do next?

## AF TREATMENT

### C Considerations in Management of AF



No cardioversion unless AF is <48h old or TEE is negative for thrombus

## ANTICOAGULATION FOR AF

Warfarin or Direct Oral Anticoagulants  
62% risk reduction compared to placebo



### DOAC vs Warfarin

- Risk of stroke or systemic emboli 11% lower with DOAC vs warfarin
- Lower risk of ICH with DOACs vs Warfarin

Use Warfarin if: mechanical valve, valvular AF, APLS, LV thrombus

## DOACS FOR AF

**Table 1** The efficacy, safety, and special considerations for direct oral anticoagulants (DOAC)

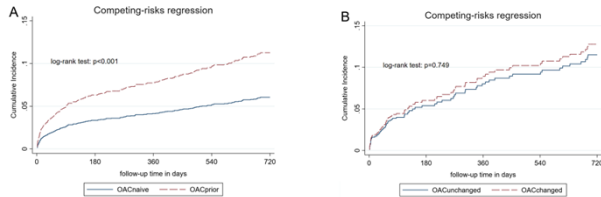
Study (DOAC)	Dosing	Mean age (±SD) Median (IQR)	Mean f/u yrs	Mean TTR	Mean CHA <sub>2</sub> DS <sub>2</sub> (±SD)	Ischemic stroke/100 patient-years vs. warf (95% CI)	Intercranial hemorrhage/100 patient-years HR vs. warf (95% CI)	Permanent Discontinuation
RE-LY (dabigatran) n = 18,113	150 mg b.i.d	71.5 ± 8.8	2	64%	2.1 ± 1.1	0.92 vs. 1.2% RR 0.76 (0.60-0.98) p = 0.03	0.39 vs. 0.79% RR 0.40 (0.27-0.60) P < 0.001	Dabigatran 21.2% Warfarin 16.6%
ARISTOTLE (apixaban) n = 18,201	5 mg b.i.d 70 (63-76)		1.8	62%	2.1 ± 1.1	0.97 vs. 1.09% HR 0.92 (0.74-1.13) p = 0.42	0.33 vs. 0.80% HR 0.42 (0.30-0.58) p < 0.001	Apixaban 25.3% Warfarin 27.5%
ENGAGE-AF (edoxaban) n = 21,305	60 mg/day 72 (64-78)		2.8	66%	2.8 ± 1.0	1.23 vs. 1.25% HR 1.03 (0.83-1.19) p = 0.97	0.39 vs. 0.85% HR 0.47 (0.34-0.63) P < 0.001	Edoxaban 34.4% Warfarin 34.5%
ROCKET-AF (rivaroxaban) n = 14,264	20 mg/day 73 (65-78)		1.94	55%	3.5 ± 1	1.34 vs. 1.42% HR 0.94 (0.75-1.17) p < 0.581	0.5 vs. 0.7% HR 0.67 (0.47-0.93) p = 0.02	Rivaroxaban 23.7% Warfarin 22.2%

None of the trials enrolled patients with h/o bleeding or at risk for high bleeding

## STROKE WHILE TAKING ANTICOAGULATION

Patients who have stroke on oral anticoagulation are at higher risk of recurrent stroke?

Changing the type of oral anticoagulant is not associated with reduced risk of stroke



## CLINICAL CASE #1

77-year-old man with HTN, DM, CAD, smoker, OSA, presented with aphasia and right hemiparesis, found to have left MCA territory embolic infarct. CTA does not show significant vessel stenosis. TTE showed normal ejection fraction, moderate dilatation of left atrium and no significant valvular abnormality. ECG shows sinus rhythm

30d monitor – no AF

Implantable cardiac monitor- 7min of AF

Started Apixaban

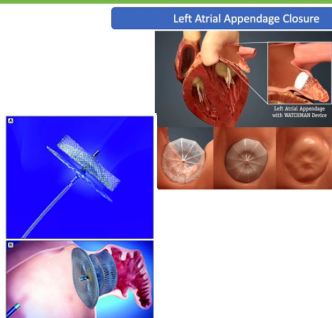
15 months later patient developed intracerebral hemorrhage

What would you do next?

## ALTERNATIVE TO ANTICOAGULATION

Increased risk of bleeding

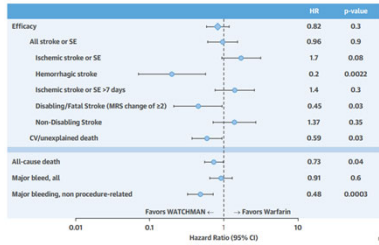
- Thrombocytopenia
- Recurrent bleeding
- Prior severe bleeding
- High risk of falling
- Strong indication for combined use of dual antiplatelet and anticoagulant
- Poor compliance





## LAA CLOSURE VS WARFARIN

LLA closure vs Warfarin- PROTECT AF & PREVAIL

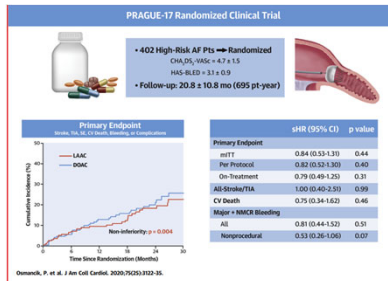


**Anticoagulation Regimen**

- Implant to 6 weeks
  - Warfarin
  - Aspirin
- 6 weeks to 6 months
  - Clopidogrel
  - Aspirin
- After 6 months
  - Aspirin

## LAA CLOSURE VS DOAC

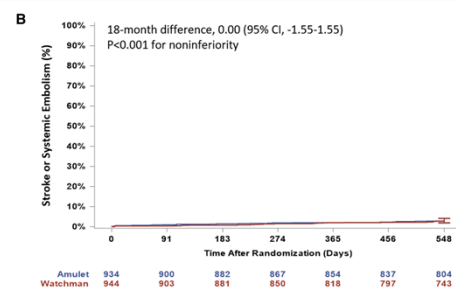
### PRAGUE 17 trial



Non valvular AF +

- h/o bleeding requiring intervention or hospitalization or
- h/o cardioembolic event while taking oral anticoagulation or

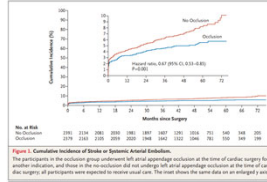
## WATCHMAN AND AMULET DEVICES



## LAA CLOSURE FOR PRIMARY PREVENTION

### LAAOS III trial

- Included: AF and CHA2 DS2 -VAsC  $\geq 2$  undergoing cardiac surgery for another reason
- Primary outcome: stroke or systemic emboli



Primary outcome in 4.8% in occlusion group vs 7.0% (HR 0.67, CI 0.53 to 0.85; P=0.001)

## PATENT FORAMEN OVALE (PFO)

### CLINICAL CASE #2

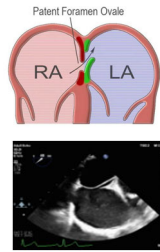
37-year-old woman with no medical history, on OCP, was admitted with mild right hemiparesis and aphasia. MRI showed scattered left MCA territory cortical infarcts. CTA head and neck, TTE, UDS, blood work is unremarkable. TEE showed moderate size PFO with ~25 bubbles crossing from right to left atrium. She also has atrial septal aneurysm. Hypercoagulable panel was negative and 30day cardiac monitor did not reveal atrial fibrillation or other significant arrhythmia. Leg doppler did not show DVT

- A) Antiplatelet until PFO closure
- B) Anticoagulation DOAC until PFO closure
- C) Antiplatelet only, no need for PFO closure
- D) Anticoagulation only, no need for PFO closure
- E) PFO closure and lifelong anticoagulation

## PFO-BACK DOOR TO THE BRAIN

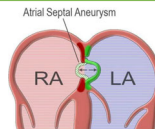
Interatrial slit-like channel or tunnel with a mean diameter ~5mm

- PFO is one of the most common congenital cardiac findings
- ~25% in general population
- Linked to stroke, systemic and coronary embolization, OSA, migraine with aura
- PFO is present in ~50% of cryptogenic stroke patients



## STROKE MECHANISMS IN PFO

- Paradoxical embolus**
- Direct in-situ thrombus formation
- Arrhythmia



**Atrial septal "aneurysm" (ASA)** 0.2 to 10%

- Focal outpouching of the hypermobile interatrial septum
- Increases stroke risk 6-fold when present with PFO



## DIAGNOSTIC MODALITIES FOR PFO DETECTION

	PFO shunt	Advantage	Disadvantage
<b>TTE</b>	Sensitivity 50-80% R to L shunt within 3 cardiac cycles Trace: <5 bubbles Moderate: 6-20 particles Severe: >20 particles	-Easily available -Allows for a better Valsalva maneuver with agitated saline contrast -Low cost	-Limited anatomic assessment of intraatrial septum -Limited by technical factors -Not reliable for small shunts
<b>TEE</b>	Sensitivity ~90-100% R to L shunt within 3 cardiac cycles Trace: <5 bubbles Moderate: 6-20 particles Severe: >20 particles	-Gold standard for visualization of the foramen ovale and associated anatomy -Surgical planning	-Invasive -Requires anesthesia -Local pharyngeal trauma, patient discomfort -Requires dedicated physician operator -Costly
<b>TCD</b>	Mild-moderate Spencer grade I, II  Moderate-severe Spencer grade III-V	Highly sensitive for identifying -R to L shunt -Determining shunt magnitude -Predicting post device residual shunting	-Cannot determine the location of the shunt or anatomy -Baseline positivity in patients with no anatomic shunt

TCD can detect small shunt missed by TEE due to better Valvula

## IS PFO INCIDENTAL OR RELATED TO THE STROKE

### RoPE score

Characteristic	Points	RoPE score
No history of hypertension	1	
No history of diabetes	1	
No history of stroke or TIA	1	
Non smoker	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 score (sum of individual points)		
Maximum score (a patient <30 y with no hypertension, no diabetes, no history of stroke or TIA, non smoker, and cortical infarct)	10	
Minimum score (a patient >70 y with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct)	0	

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## ROPE SCORE

Patients more likely to have stroke related to PFO have lower recurrence risk

CS patients with PFO (n = 1,324)		
RoPE score	No. of CS patients with PFO*	Estimated 2-y stroke/TIA recurrence rate (Kaplan-Meier), % (95% CI)
0-3	108	20 (1.2-28)
4	148	12 (6-18)
5	186	7 (3-11)
6	236	8 (4-12)
7	263	6 (2-10)
8	233	6 (2-10)
9-10	150	2 (0-4)

Variables not included in RoPE study: hypercoagulable state, OCP, DVT/PE, prolonged travel/immobility, migraine, Valsalva at stroke onset, size of PFO/shunt or presence of ASA

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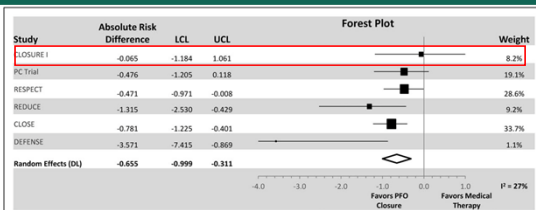
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## PFO CLOSURE VS MEDICAL THERAPY



Meta-analysis: absolute risk reduction of 3.4% over 5y; NNT 29 to prevent one stroke  
 -6 fold increase in AF in closure arm; ~3% major periprocedural complications

- ASA - NNT 13 over 5y
- Large shunt size - NNT 18

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## PFO CLOSURE DEVICES APPROVED IN USA

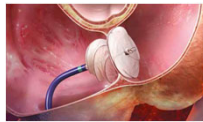
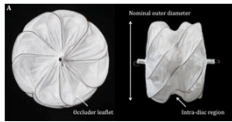
### The St. Jude Amplatzer PFO Occluder

Two asymmetric Nitinol wire mesh which traverses the PFO



### Gore Cardioform Septal Occluder

Two Nitinol discs which span the PFO



## SUBGROUPS TO CONSIDER

**Age:** most trials only included patients <60y

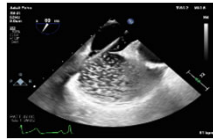
**Patients on anticoagulation: benefit of closure in unclear**

RESPECT: no benefit of PFO closure among anticoagulated patient (HR 1.32; CI 0.43–4.03; P, 0.63)

**Patients with thrombophilia:**

-All trials excluded patients with antiphospholipid antibodies

-Testing for inherited thrombophilia was sporadic in trials

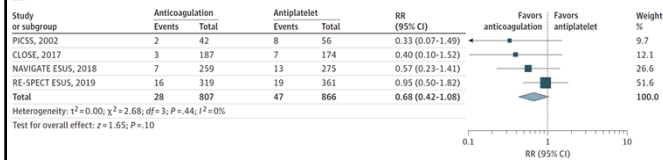


Trial	Women on OCPs	RESPECT-LT		REDUCE		CLOSE	
		Device Arm	Medical Arm	Device Arm	Medical Arm	Device Arm	Medical Arm

## ANTIPLATELET VS ANTICOAGULATION WITHOUT CLOSURE

Figure 1. Forest Plots Showing Study-Level Meta-analyses of Randomized Clinical Trials of Strategies to Prevent Recurrent Ischemic Stroke in Patients With Patent Foramen Ovale (PFO)

### A) Anticoagulation vs antiplatelet therapy



**No benefit of anticoagulation compared to antiplatelet therapy for recurrent stroke in patients with PFO**

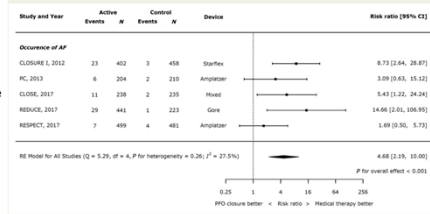
## AF AFTER PFO CLOSURE

5-fold increased risk of AF after closure compared to medical therapy (OR 5.3, CI 2.5–11.41,  $p < 0.001$ )

-Highest risk within first 45d

AF is higher in:

- Older patients
- Residual shunt after closure
- LA enlargement



## CLINICAL CASE #2

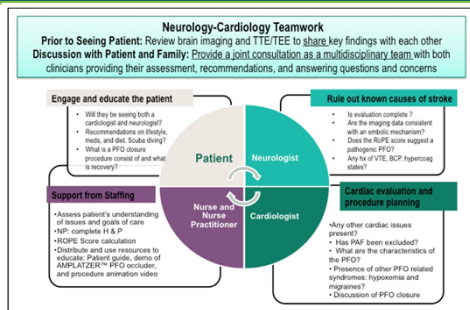
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In addition to stopping OCP what else would you recommend?

- ☒ A) Antiplatelet until PFO closure
- ☐ B) Anticoagulation with DOAC until PFO closure
- ☐ C) Antiplatelet only, no need for PFO closure
- ☐ D) Anticoagulation only, no need for PFO closure
- ☐ E) PFO closure and lifelong anticoagulation

## HEART-BRAIN CLINICS

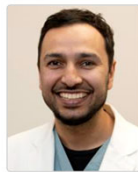
## HEART-BRAIN MULTIDISCIPLINARY TEAM



## HEART-BRAIN COLLABORATION AT UAB



Ekaterina Bakradze, MD



Mustafa Ahmed, MD

Referrals from across the state

Timely evaluation by interventional cardiology and stroke Neurology

Telemedicine evaluation during COVID pandemic

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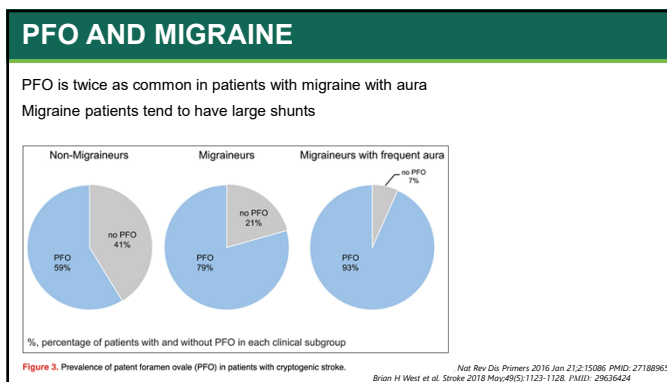
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## MIGRAINE AND PFO

### Percutaneous Closure of Patent Foramen Ovale in Patients with Migraine: A Meta-Analysis

The PREMIUM Trial

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**Background:** Observational studies have shown percutaneous patent foramen ovale (PFO) closure to be a safe means of reducing the frequency and duration of migraine. **Objective:** This study evaluated the efficacy and safety of PFO closure in patients with migraine using evidence-based medicine. **Methods:** The Pubmed (MEDLINE), Embase, and Cochrane Library databases were searched for randomized controlled trials (RCTs), cohort studies, and retrospective case series from January 1, 2001, to February 28, 2022. The Jaded scale and R 4.1.0 software were used to assess the quality of the literature and meta-analysis, respectively. **Results:** In total, three randomized controlled trials, one pooled study, and eight retrospective case series including 1,165 participants were included in the meta-analysis. Compared with control intervention in migraine, PFO closure could significantly reduce headache frequency (OR = 1.5698, 95% CI: 1.0465–2.3548,  $p = 0.0291$ ) and monthly migraine attacks and monthly migraine days (OR = 2.298, 95% CI: 1.6796–3.1496,  $p < 0.0001$ ). Subgroup analysis of patients who all completed PFO surgery showed resolution of migraine headache for migraines with aura (OR = 1.3858, 95% CI: 1.0665–2.3375,  $p = 0.0277$ ). **Conclusions:** Treatment with PFO closure could reduce the frequency of headaches and monthly migraine days and is an efficient treatment for migraine attacks with aura.

**nt foramen ovale in nized controlled trial**

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k Gawel<sup>1</sup>, Hartmut Gölbel<sup>1</sup>,  
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Hard Meier<sup>1</sup>

**Migraine Prospective, Multicenter, Randomized Controlled Trial**

Brain H West et al. Stroke 2018 May;49(5):1123-1128 PMID: 29636424

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