

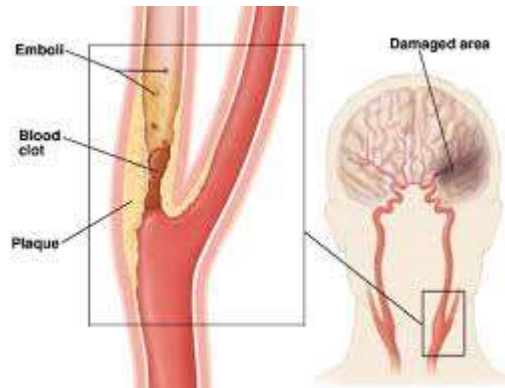
Neurologists' Perspective: Recent Data and the Best Practice for Managing patients



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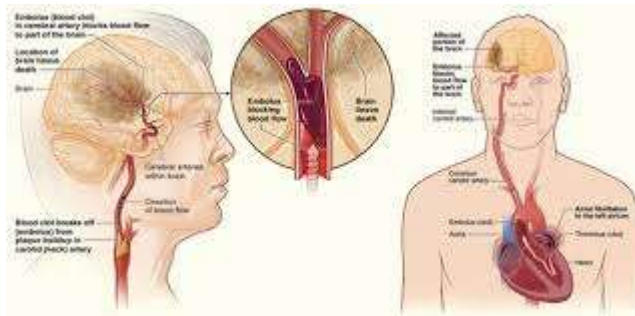
Stroke, An heterogeneous etiology

- Various mechanism of stroke

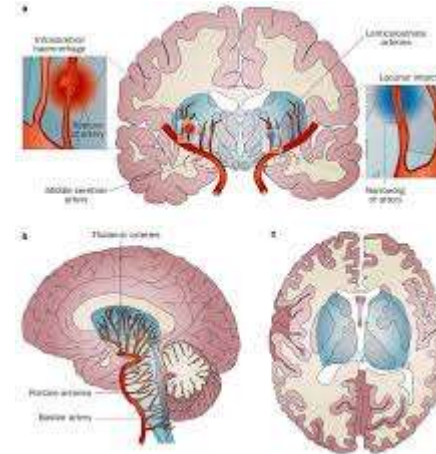


Large artery atherosclerosis

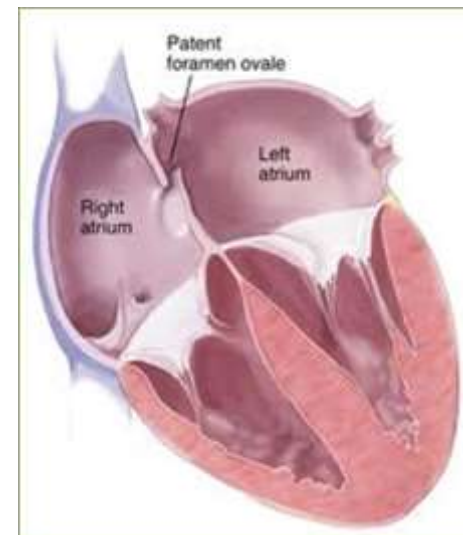
- A-A embolism
- In situ thrombosis
- hemodynamic



Cardioembolism



Small vessel disease



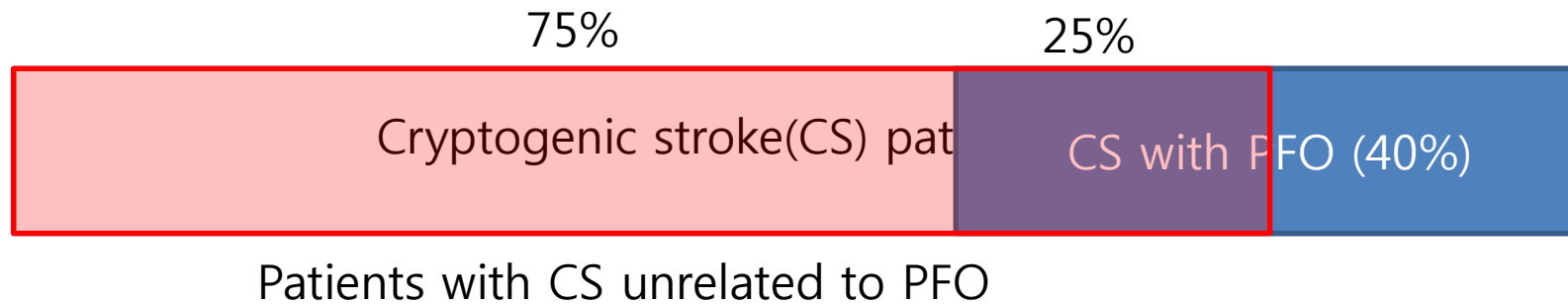
Patent foramen ovale
-right-to-left shunt

Mechanism based Stroke treatment

Culprit PFO

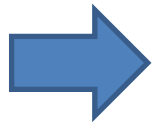
Incidence of PFO in cryptogenic stroke: 40%

Incidence of PFO in normal population: 25%



Assumptions

1. CS patients without a detected PFO is not caused by an undetected PFO
2. If not for those strokes attributable to PFO, PFO prevalence of CS = Control



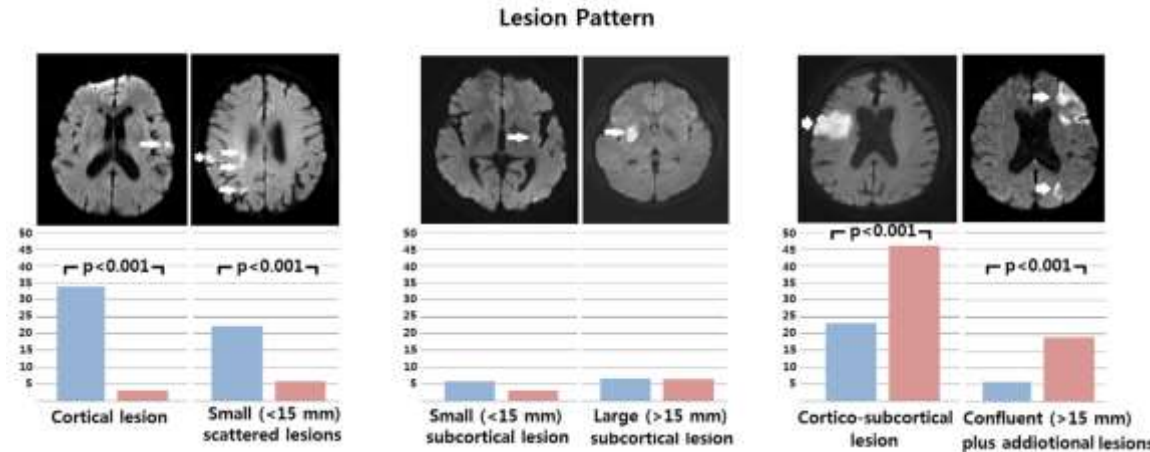
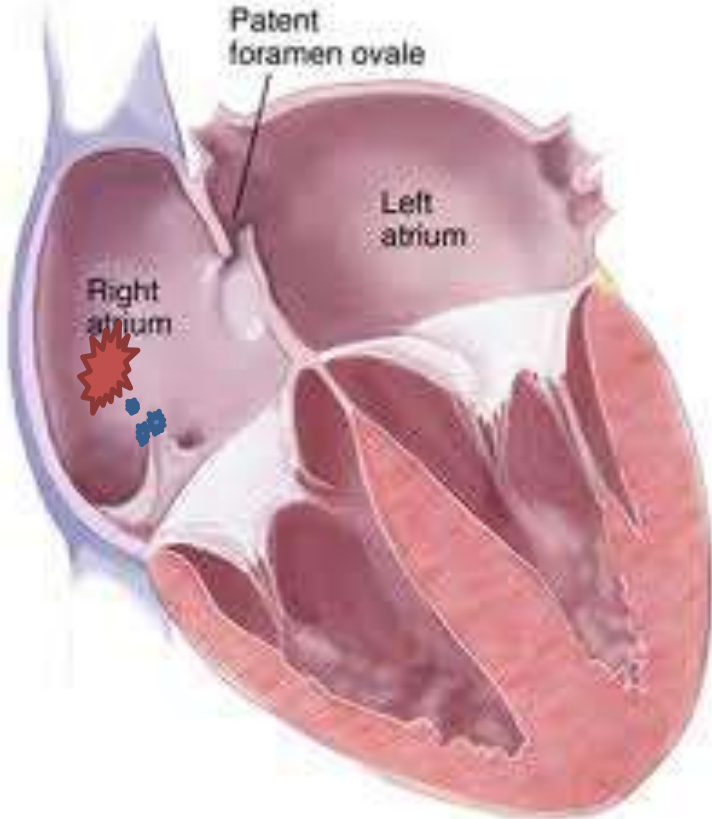
Of half of PFO culprit for Cryptogenic stroke

Characteristics of PFO-stroke

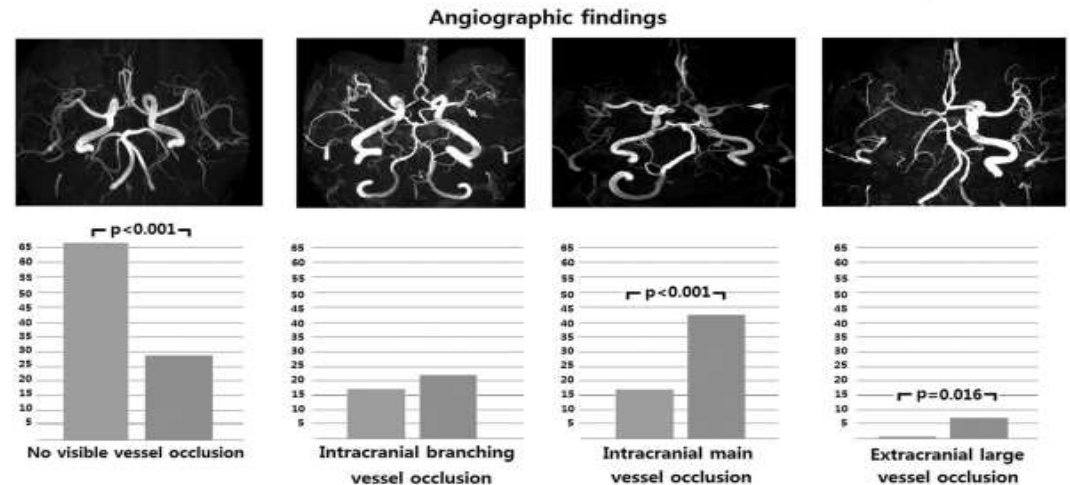
Paradoxical embolism

- Mainly embolic
- Needs to pass through PFO

Small size embolus easier to pass through PFO

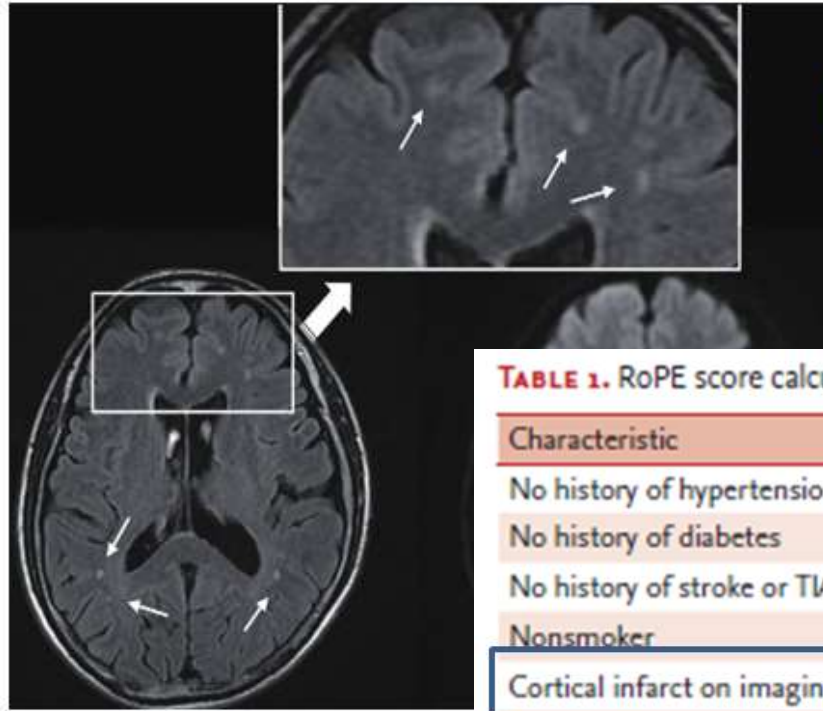


High prevalence of Small cortical or small scattered cortical lesion



Juxtacortical lesions in PFO-stroke

Juxtacortical spots of FLAIR image in cryptogenic TIA patients



	All patients (n=132)	p
	Adjusted OR (95% CI)	
RLS	3.802 (1.748-8.268)	0.001
Age	1.058 (1.018-1.100)	0.004
ABCD ₂ scores	0.989 (0.755-1.295)	0.936
DWI lesions	1.869 (0.764-4.572)	0.170

Table 3. Imaging characteristics according to RLS grade

TABLE 1. RoPE score calculator

Characteristic	Points
No history of hypertension	1
No history of diabetes	1
No history of stroke or TIA	1
Nonsmoker	1
Cortical infarct on imaging	1
Age, years	
18-29	5
30-39	4
40-49	3
50-59	2
60-69	1
≥70	0
Maximum score	10

	All subjects (n=132)			p
	Grade 1 (n=38)	Grade 2 (n=18)	Grade 3 (n=14)	
Grade 1	7 (18.4)	4 (22.2)	7 (50.0)	0.041
Grade 2	14 (36.8)	14 (77.8)	13 (92.9)	0.001
Grade 3	5 (13.2)	14 (77.8)	11 (78.6)	<0.001
Age	2.2	4.9±4.3	5.7±4.8	<0.001
Grade 1	2 (5.3)	2 (11.1)	1 (7.1)	0.284
Grade 2	2 (5.3)	2 (11.1)	2 (14.3)	0.890

➔ Juxtacortical with RLS

nts are associated

Kim DE et al. JCN 2013

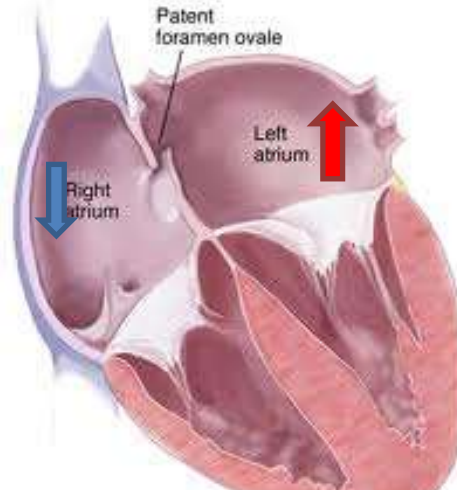
RoPE; risk of paradoxical embolism, TIA; transient ischemic attack.

Valsalva and PFO-stroke

- Right to left shunt aggravated by Valsalva maneuver

1. Initial pressure rise

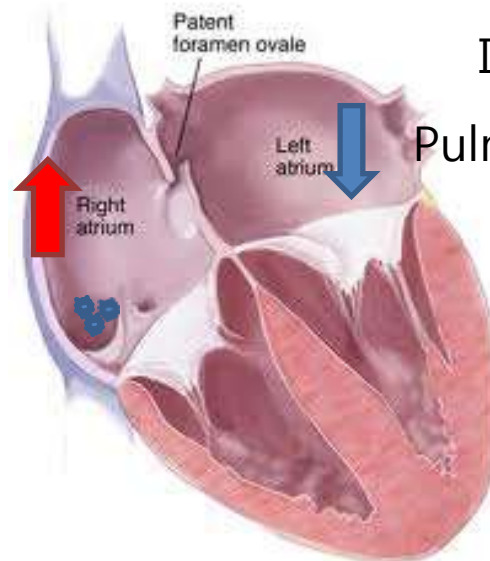
Systemic venous return ↓



Intra-thoracic pressure ↑

2. Pressure release

Systemic venous return ↑



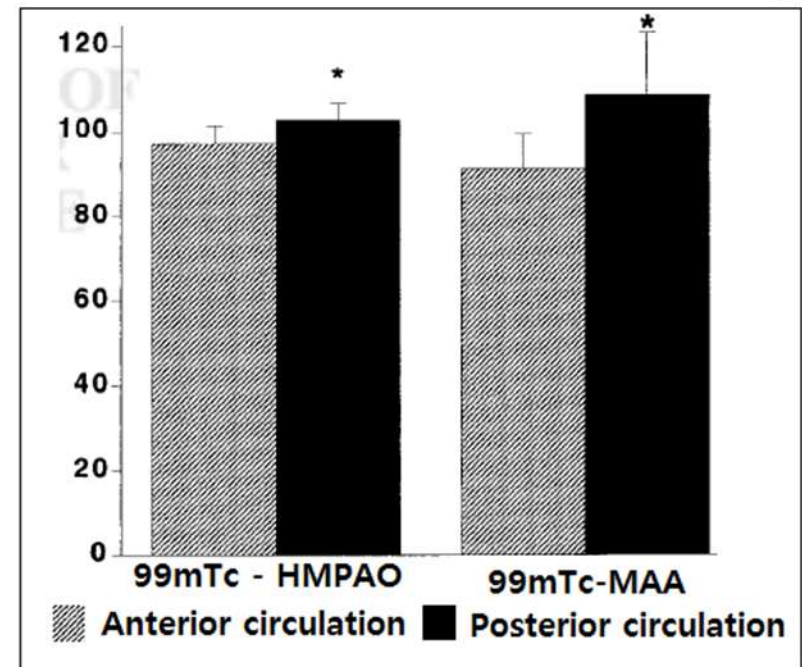
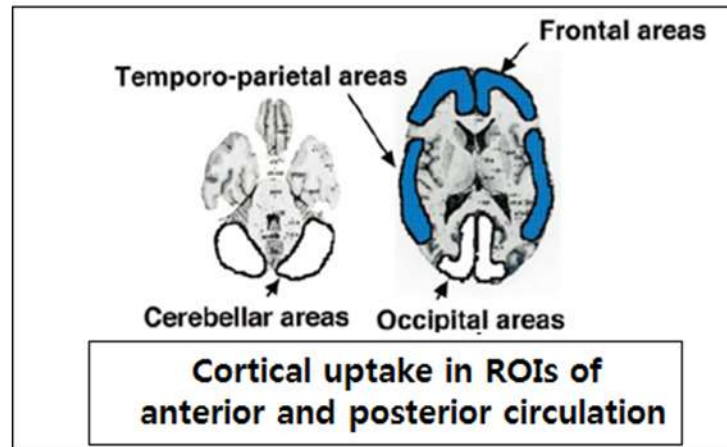
Intra-thoracic pressure ↓

Pulmonary vessel re-expand

Valsalva – posterior circulation

Valsalva and blood flow in posterior circulation

- Measurement of blood flow by SPECT after Valsalva maneuver



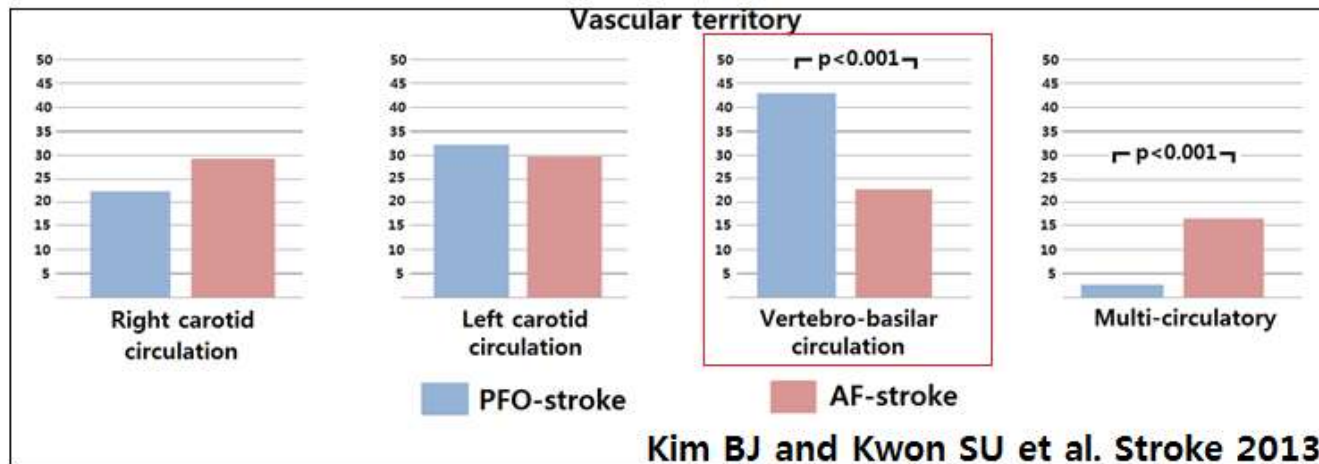
PFO-stroke and vascular territory

Vascular territory n (%)	PFO group n=25	Non-PFO group n=21	PFO vs. non-PFO p-Value
Middle cerebral artery	16 (64.0%)	13 (61.9%)	1.000
Anterior cerebral artery	0	3 (14.3%)	0.090
Anterior choroidal artery	0	1 (4.8%)	0.460
Posterior cerebral artery	9 (36.0%) ↑	0	0.002
Basilar artery	1 (4.0%)	2 (9.5%)	0.590
Inferior cerebellar artery	1 (4.0%)	3 (14.3%)	0.320
Middle cerebellar artery	0	0	
Superior cerebellar artery	4 (16.0%)	0	0.110

Boutet et al. Eur. J. Radiol. 2014

Brain imaging	Medium or Large PFO (n=14)		No or Small PFO (n=81)		P
	n	(%)	n	(%)	
Site					
Occipital/brainstem/cerebellar	8	(57) ↑	20	(27)	0.02
Hemispheric, not occipital	4	(29)	25	(31)	
Basal ganglia, internal capsule, or thalamus	2	(14)	30	(37)	
Undetermined	0	(0)	6	(7)	
Vascular findings					
Large artery territory*	9	(64)	31	(38)	0.05
Posterior circulation	9	(64) ↑	27	(33)	0.05

Steiner et al. Stroke 1998



PFO-stroke more often observed from posterior circulation

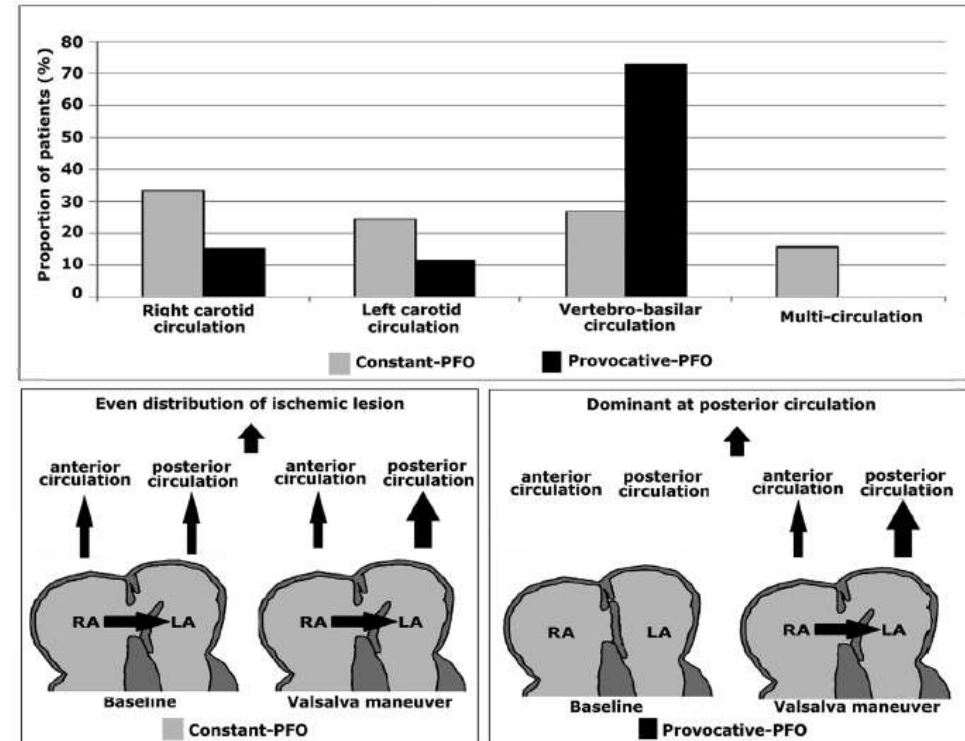
Valsalva and posterior PFO-stroke

Table 1. Comparison of the Constant RLS and Provoked RLS Groups

	Constant RLS (n=50)	Provoked RLS (n=26)	P Value
Age	57.2±13.4	49.5±14.6	0.03
Male	32 (64.0)	20 (76.9)	0.25
Hypertension	25 (50.0)	9 (34.6)	0.20
Diabetes mellitus	15 (30.0)	4 (15.4)	0.16
Hyperlipidemia	9 (18.0)	6 (23.1)	0.60
Smoking	12 (24.0)	10 (38.5)	0.19
Previous stroke	5 (10.0)	0 (0.0)	0.10
RoPE score	6.5±1.8	7.4±1.8	0.03
Microbubble at rest	50.7±85.4	0 (0.0)	<0.001
Microbubble after Valsalva maneuver	106.6±108.7	47.6±75.3	0.002
Lesion pattern			
Cortico-subcortical	9 (18.0)	5 (19.2)	0.11
Cortical	16 (32.0)	8 (30.8)	
Subcortical <1.5 mm	3 (6.0)	2 (7.7)	
Subcortical >1.5 mm	0 (0)	3 (11.5)	
Confluent plus additional	5 (10.0)	2 (7.7)	
Small scattered	9 (18.0)	6 (23.1)	
Multiterritorial	8 (16.0)	0 (0.0)	
Vascular territory			
Right-carotid circulatory	16 (32.0)	4 (15.4)	0.004
Left-carotid circulatory	12 (24.0)	3 (11.5)	
Vertebro-basilar circulatory	14 (28.0)	19 (73.1)	
Multicirculatory	8 (16.0)	0 (0.0)	
Moderate to high-risk PFO	27 (54.0)	12 (44.4)	0.42

The results are expressed as number (%) or mean±SD.

PFO indicates patent foramen ovale; and RLS, right-to-left shunt.



Valsalva maneuver may associate with the high prevalence of posterior circulation infarction in PFO-stroke

Characteristics of PFO-stroke

TABLE 5. Clinical and imaging clues suggesting PFO-associated stroke

Clinical clues^{26,40}

- Young patient without other cause
- Valsalva maneuver preceding the neurological symptoms
- Recent prolonged travel
- History of migraine
- Dyspnea, tachycardia at onset

Neuroimaging clues^{13,15}

- Small cortical infarction
- Multiple small scattered lesions
- Posterior circulation

Echocardiographic clues^{21-23,41,42}

- Large PFO
- Large amount of shunt
- Presence of shunt at rest
- Presence of atrial septal aneurysm
- Long-tunneled PFO (≥ 1 cm)

PFO; patent foramen ovale.

Recent study results

TABLE 4. Results of clinical trials of PFO closure

	CLOSURE I ²⁹	PC ³¹	RESPECT ^{34,38}	CLOSE ³⁶	Gore REDUCE ³⁷	DEFENSE-PFO ³⁹
Patients	909	414	980	663	664	120
Mean age, years	45.9	44.5	45.9	43.3	45.2	51.8
Mean follow-up time, years	3.7	4.1	5.9	5.3	3.2	2.8
ASA, %	36.6	23.7	35.6	32.8	20.4	10.8
Medical therapy	Aspirin, warfarin or both	Antiplatelet, warfarin or both	Antiplatelet or warfarin	Antiplatelet or warfarin	Antiplatelet	Antiplatelet or warfarin
Closure device	STARFlex	Amplatzer	Amplatzer	Any approved PFO closure device	GORE_ CARDIO-FORM Septal Occluder or GORE_ HELEX_ Septal Occluder	Amplatzer
Effective closure, %	86.1	95.9	93.5	93.0	75.6	100
Primary endpoint (HR [95% CI]), medical vs. closure	0.78 (0.45-1.35), (5.5% vs. 6.8%)	0.63 (0.24-1.62), (3.4% vs. 5.2%)	0.55 (0.31-0.999), (5.8% vs. 3.6%)	0.03 (0.00-0.26), (6% vs. 0%)	0.23 (0.09-0.62), (5.4% vs. 1.4%)	Unavailable, (12.9% vs. 0%)
AF (medical vs. closure)	0.7% vs. 5.8%	1.0% vs. 3.0%	1.5% vs. 3.1%	0.9% vs. 4.6%	0.4% vs. 6.6 %	0.0% vs. 3.3 %

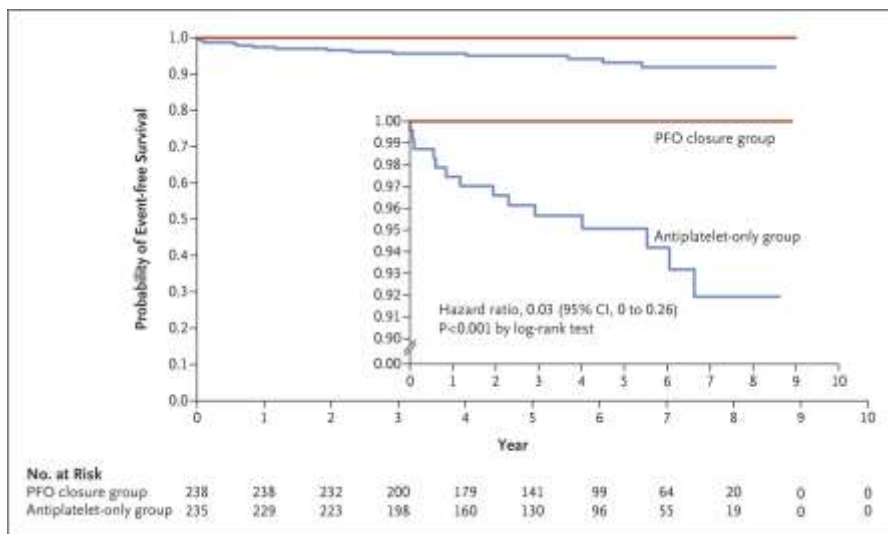
PFO; patent foramen ovale, ASA; atrial septal aneurysm, HR; hazard ratio, AF; atrial fibrillation.

- PFO closure effective for those with PFO-stroke
- Better technique, Better indications

CLOSE

- 663 patients with recent PFO-stroke with ASA or Large shunt
 - Randomized to (1:1:1) → f/u 5.3 years
 - PFO + antiplatelet treatment (DAPT 3month -> SAPT)
 - Antiplatelet treatment alone (aspirin 86.7%, DAPT 1.3%)
 - Anticoagulation (Warfarin, No data on TTR)

Outcome	Randomization Groups 1 and 2			P Value	Randomization Groups 1 and 3		
	PFO Closure Group (N=238)	Antiplatelet-Only Group (N=235)	Hazard Ratio (95% CI) [†]		Anticoagulant Group (N=187)	Antiplatelet-Only Group (N=174)	Hazard Ratio (95% CI) [‡]
Primary efficacy outcome							
Stroke in the intention-to-treat population — no. of patients	0	14§ 6%	0.03 (0.00–0.26)	<0.001	3¶	7§	0.44 (0.11–1.48)
Stroke in the per-protocol population — no./total no. of patients	0/217	14/223§	0.04 (0.00–0.27)	<0.001	2/143¶	7/164§	0.37 (0.07–1.38)



10 month later: 93% had no or minimal residual shunt (<10 bubbles)

4.6% with atrial fibrillation or flutter occurring within 1 month after the procedure as compared with 0.9% in the antiplatelet-only group (P=0.02)

GORE REDUCE

- 664 patients PFO-stroke (81% moderate or large shunt)
 - Randomized to (2:1) → f/u 3.2 years
 - PFO closure + antiplatelet treatment (SAPT)
 - Antiplatelet treatment (SAPT)
 - Co-primary endpoint
 - Clinical ischemic stroke
 - New brain infarction (24 month f/u MRI)

End Point	PFO Closure Group	Antiplatelet-Only Group	Effect Size	P Value
	<i>no. of patients/total no. (%)</i>			
Clinical ischemic stroke†	6/441 (1.4)	12/223 (5.4)	0.23 (0.09–0.62)‡	0.002§
New brain infarction¶	22/383 (5.7)	20/177 (11.3)	0.51 (0.29–0.91)	0.04**
Recurrent clinical ischemic stroke	5/383 (1.3)	12/177 (6.8)	0.19 (0.07–0.54)	0.005**
Silent brain infarction only	17/383 (4.4)	8/177 (4.5)	0.98 (0.43–2.23)	0.97**

DEFENSE PFO

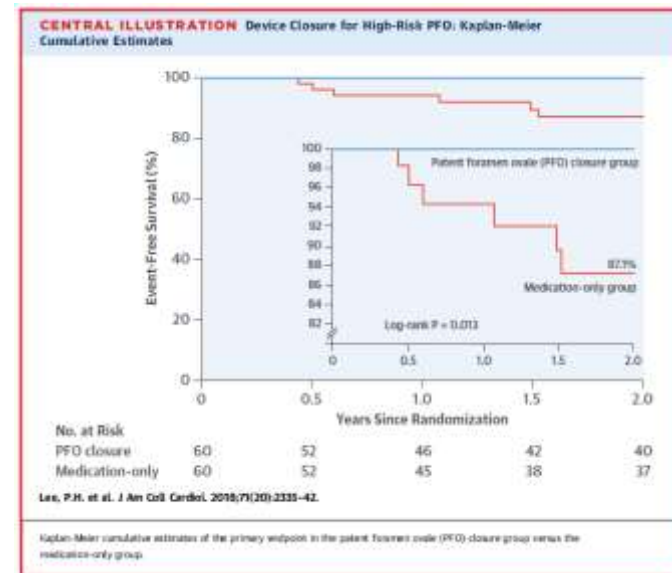
- 120 patients with PFO-stroke (High risk; ASA, hypermobile atrium, >2mm)
 - Randomized to
 - PFO closure + antiplatelet treatment (DAPT 6month -)
 - Medical treatment (SAPT, DAPT, warfarin)
 - Primary endpoint: MACE

TABLE 3 Clinical Outcomes

2-Yr Outcome	PFO Closure Group (n = 60)	Medication-Only Group (n = 60)	p Value
Primary endpoint	0 (0.0)	6 (12.9)	0.013
Secondary endpoint			
Ischemic stroke	0 (0.0)	5 (10.5)	0.023
Vascular death	0 (0.0)	0 (0.0)	NA
TIMI-defined major bleeding	0 (0.0)	2 (4.9)	0.15
Hemorrhagic stroke	0 (0.0)	1 (2.5)	0.30
Transient ischemic attack	0 (0.0)	1 (2.0)	0.32
Systemic embolism	0 (0.0)	0 (0.0)	NA
New ischemic lesion on MRI	3/34 (8.8)	7/38 (18.4)	0.24

Values are n (%) (Kaplan-Meier estimates) or n/N (%).

MRI = magnetic resonance imaging; NA = not applicable; PFO = patent foramen ovale; TIMI = Thrombolysis In Myocardial Infarction.



Can we implicate the result directly?

- No representative player



Antiplatelet treatment vs. anticoagulation

PFO in Cryptogenic Stroke Study

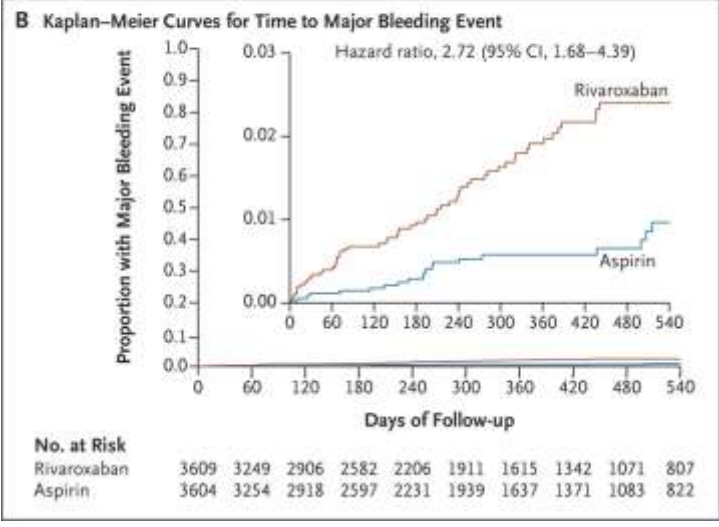
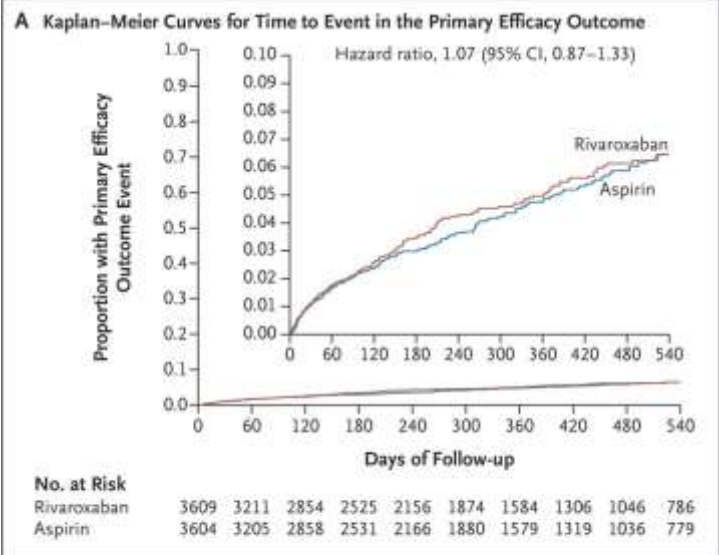
- Warfarin-Aspirin Recurrent Stroke Study의 하위 연구
- N=630 patients with TEE
- Study duration: 24 month follow-up
- 203 of 630 patients had PFO, 98 patients had Cryptogenic stroke

TABLE 3. Two-Year Rates of Recurrent Stroke or Death* in Patients With and Without PFO Assigned to Warfarin or Aspirin

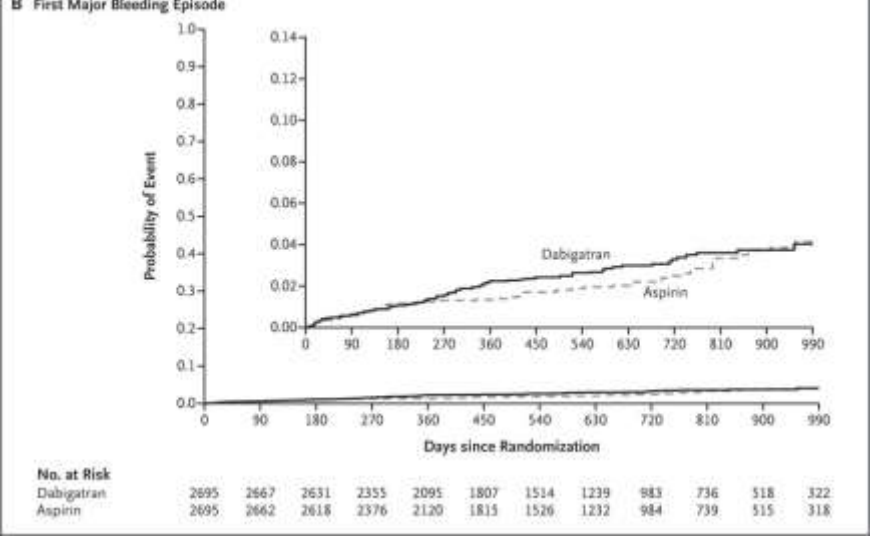
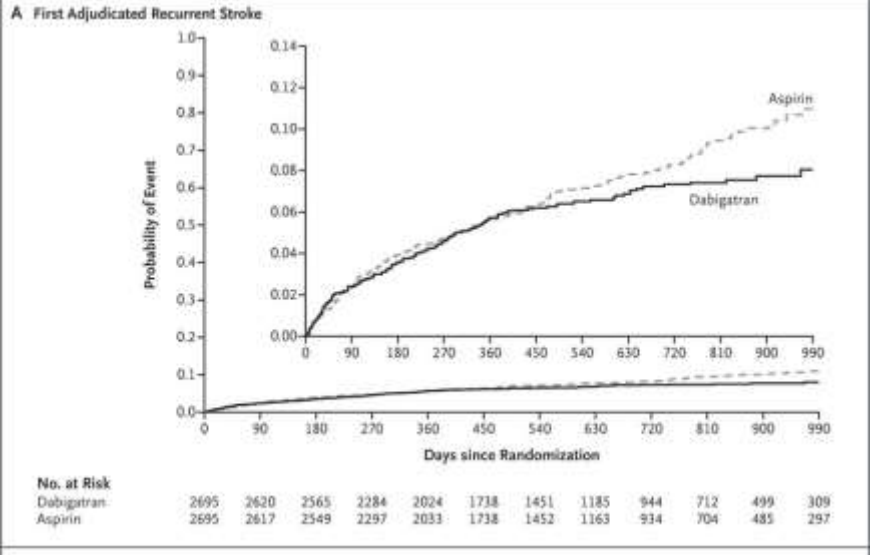
	Warfarin	Aspirin	Hazard Ratio (95% CI)	P
Entire PICSS cohort				
With PFO (n=203)	16.5% (n=97)	13.2% (n=106)	1.29 (0.63–2.64)	0.49
No PFO (n=398)	13.4% (n=195)	17.4% (n=203)	0.80 (0.49–1.33)	0.40
Cryptogenic cohort				
With PFO (n=98)	9.5% (n=42)	17.9% (n=56)	0.52 (0.16–1.67)	0.28
No PFO (n=152)	8.3% (n=72)	16.3% (n=80)	0.50 (0.19–1.31)	0.16

*From Kaplan-Meier curves.

Do we have evidence for NOAC?

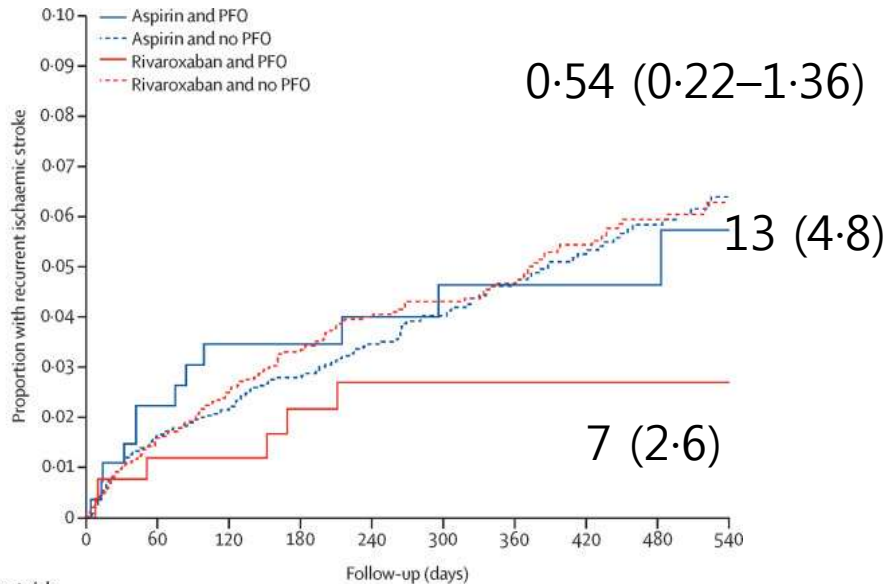


NAVIGATE ESUS



RESPECT ESUS

Anticoagulation and PFO



	Number at risk									
	0	60	120	180	240	300	360	420	480	540
Aspirin and PFO	275	248	223	194	169	150	132	110	87	65
Aspirin and no PFO	3327	2957	2637	2340	1999	1732	1449	1211	950	715
Rivaroxaban and PFO	259	234	213	194	171	150	131	112	92	75
Rivaroxaban and no PFO	3348	2978	2642	2334	1989	1729	1456	1194	955	711

Rivaroxaban group (n=3609)	Aspirin group (n=3604)		Hazard ratio (95% CI)*	Pinteraction*
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	Events (event Patients rate [†])	Events (event Patients rate [†])
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Size of PFO[‡]

Large	23	0 (0.0)	25	2 (9.4)	NA	..
Small	112	6 (4.5)	112	8 (6.6)	0.68 (0.24-1.97)	NA

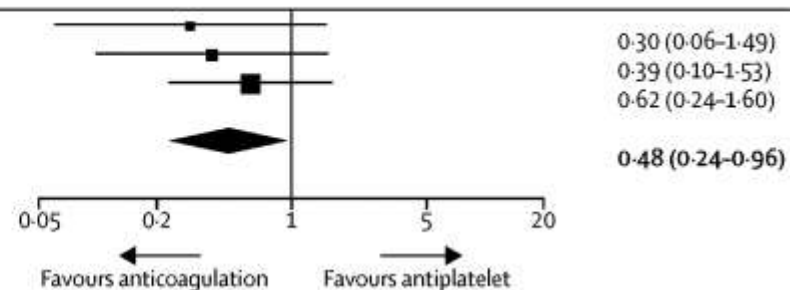
Arterial septal aneurysm reported[‡]

Yes	31	0 (0.0)	40	3 (6.7)	NA	..
No	151	7 (4.4)	157	9 (6.0)	0.75 (0.28-2.02)	NA

NAVIGATE ESUS

	Anticoagulation		Antiplatelet therapy		Weight (%)	OR (95% CI)
	Events	Total	Events	Total		
PICSS (2002)	2	42	8	56	19.2	0.30 (0.06-1.49)
CLOSE (2017)	3	187	7	174	26.4	0.39 (0.10-1.53)
NAVIGATE ESUS (2018)	7	182	12	197	54.3	0.62 (0.24-1.60)
Total (95% CI)		411		427	100	0.48 (0.24-0.96)
Total events	12		27			

Heterogeneity: $\tau^2=0.00$; $\chi^2=0.69$; $df=2$ ($p=0.71$); $I^2=0\%$
 Test for overall effect: $Z=2.07$ ($p=0.04$)



Anticoagulation may have potential benefit in those with High risk PFO

Best treatment?

We may say that **High risk PFO attributed to stroke** may be closed

But Gray zone may exist....

TABLE 2. PFO-attributable fraction and estimated 2-year risk of stroke/TIA by RoPE score

RoPE score	PFO-attributable fraction	Estimated 2-year stroke/TIA recurrence rate (Kaplan-Meier)
0-3	0 (0-4)	20 (12-28)
4	38 (25-48)	12 (6-18)
5	34 (21-45)	7 (3-11)
6	62 (54-68)	8 (4-12)
7	72 (66-76)	6 (2-10)
8	84 (79-87)	6 (2-10)
9-10	88 (83-91)	2 (0-4)

Values are presented as % (95% confidence interval).

PFO; patent foramen ovale, TIA; transient ischemic attack, RoPE; risk of paradoxical embolism.

Steps needed for Treatment decision...

- 1) Is stroke really associated with PFO ?
- 2) What is the risk of stroke for the patient with PFO
- 3) Risk and benefit of each treatment



Individualize treatment strategy for each patients