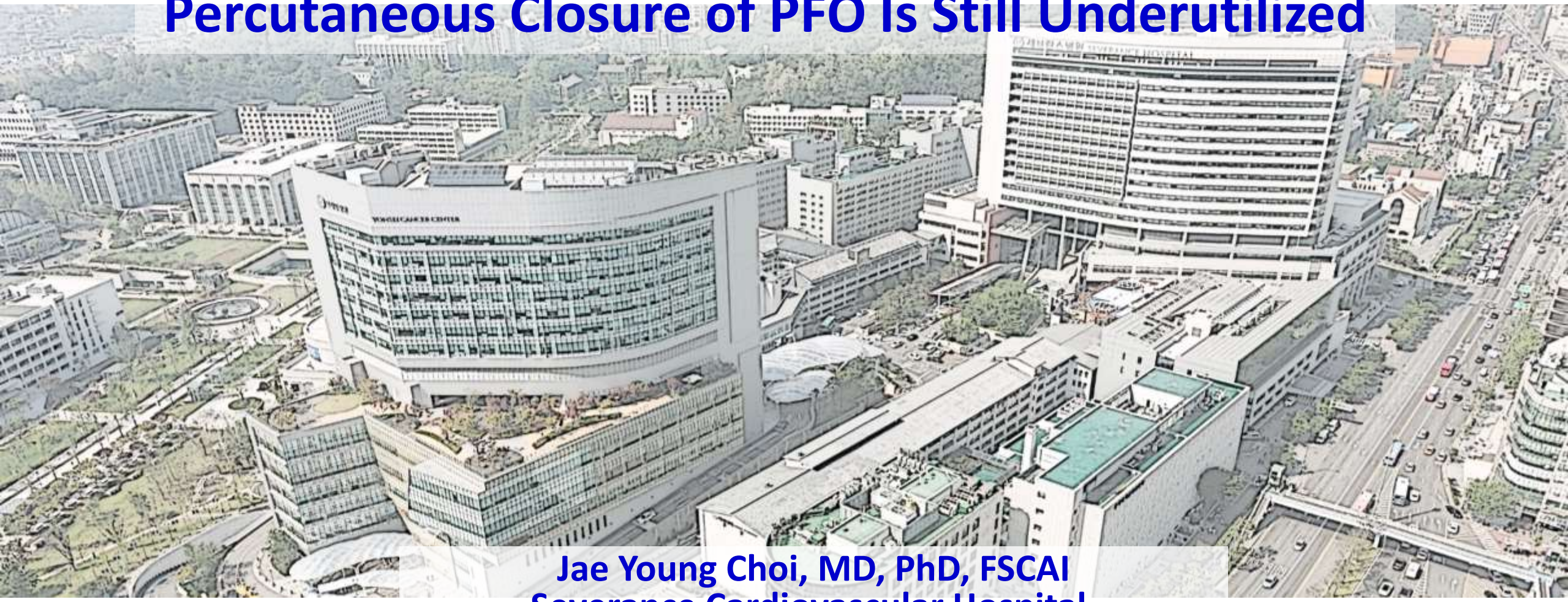
Debated 3: Patients with a Cryptogenic Stroke and No Other Known Sources of Stroke Besides a PFO

Percutaneous Closure of PFO Is Still Underutilized



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Yonsei University Health System, Seoul, Korea

Presenter Disclosure Information

I have no conflict of interest
in relation to this presentation.

Debate *is a process that involves formal discussion on a particular topic.*

In a debate, opposing arguments are put forward to argue for opposing viewpoints.

https://en.wikipedia.org/wiki/Debate

Patients with a Cryptogenic stroke &
No other known sources of stroke besides a PFO

Percutaneous closure of PFO is still under-utilized ⟷ *debate* ⟷ **Percutaneous closure of PFO is over-utilized**

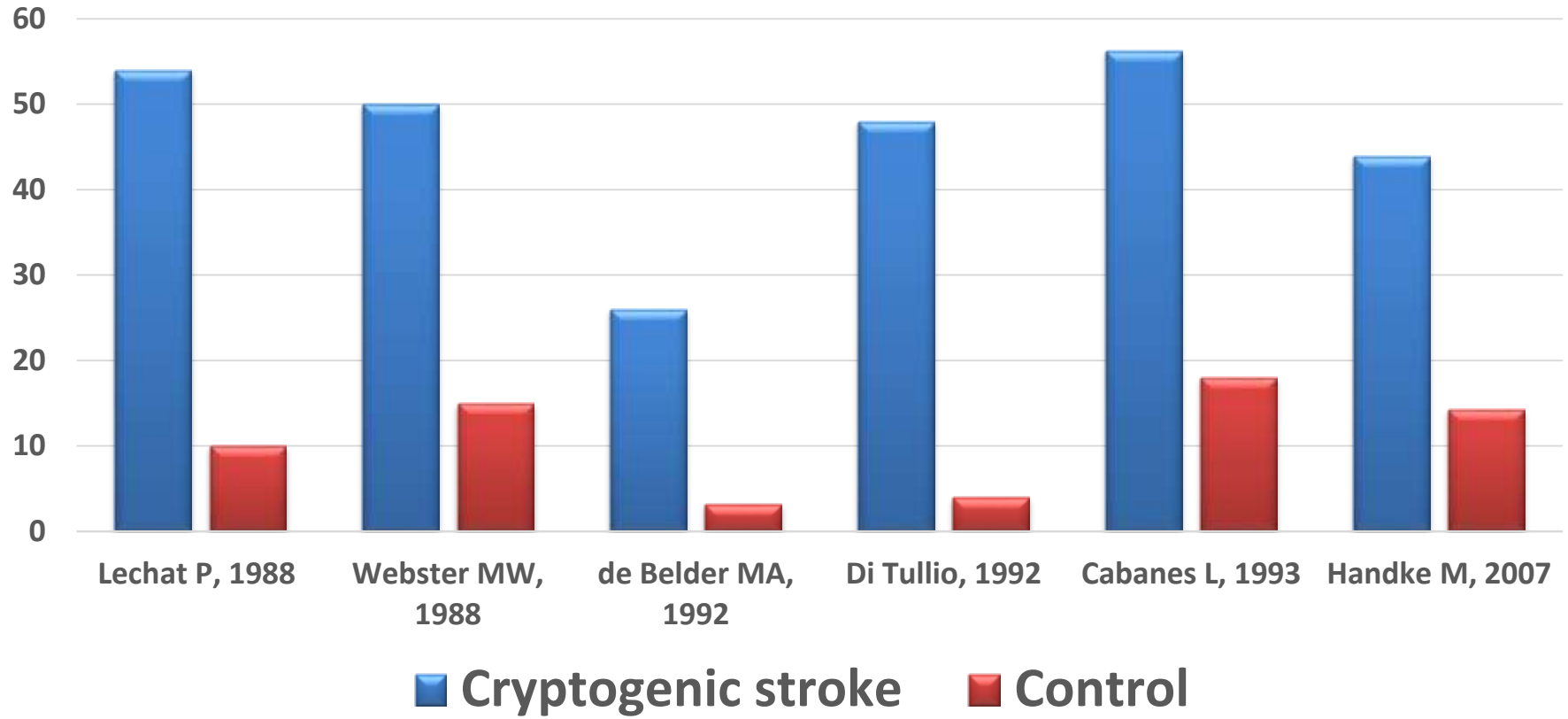
not necessarily debatable

PC Closure of PFO should be used in restricted patients ⟷ *debate* ⟷ **PC Closure of PFO should be used in most of the patients**

Prevalence of PFO is Higher in Cryptogenic Stroke!

Prevalence of PFO in cryptogenic stroke ≈ 50%

PFO prevalence in general population ≈ 20~25%

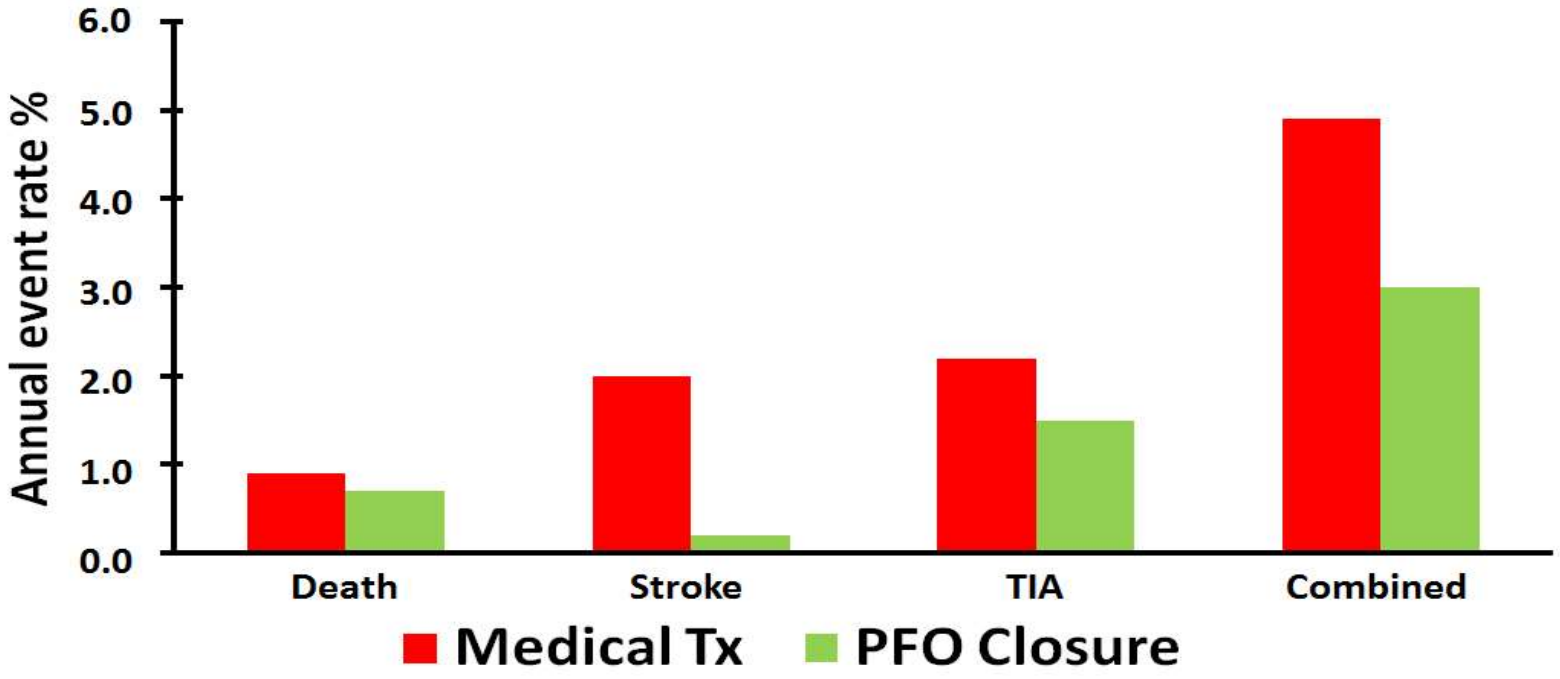


N Engl J Med 1988;318:1148, Lancet 1988;2:11, Am J Cardiol 1992;69:1316, Ann Intern Med 1992;117:461, Stroke 1993;24:1865, N Engl J Med 2007;357:2262

Cryptogenic stroke may be prevented by PFO closure…

Meta-analysis of Event Rates in Patients with Cryptogenic Stroke

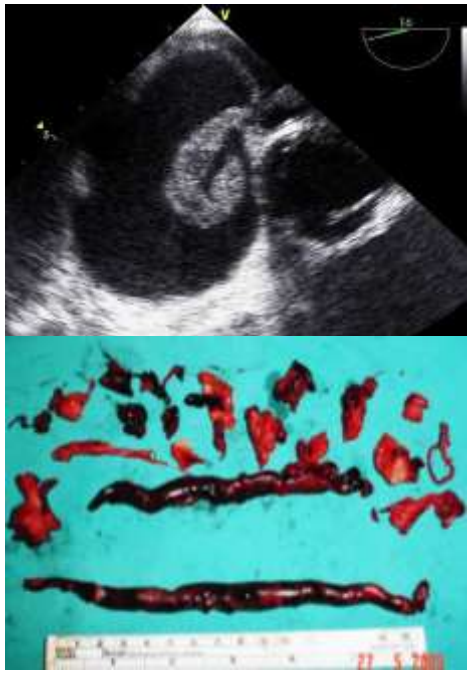
- 12 studies with 943 medically treated cryptogenic stroke patients (mean age 45 years, mean F/U 34 months)
- 12 studies with 1,430 stroke patients after PFO closure (mean age 46 years, mean F/U 18 months)



Homma S et al. Circulation 2005

Cryptogenic stroke (CS) & PFO closure

- ✓ *PFO cause stroke by means of "paradoxical embolism"*
  → recurrence may be prevented by PFO closure
- ✓ **Long journey to find the benefit of PFO closure for CS**
  - *→ HDE approval*
  - *→ "overuse"*
  - *→ Removal of HDE approval (2006)*
  - *→ Needs for RCTs*
  - *→ Ambiguous results from 1st round RCTs: "trials & errors"*
  - *→ 2nd-round RCTs & long-term F/U results*



RCTs : PFO closure vs. Medical Therapy

- ✓ **Closure I** *(Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale)*
- ✓ **PC Trial** *(Percutaneous Closure of Patent Foramen Ovale versus Medical Treatment in Patients with Cryptogenic Embolism)*
- ✓ **RESPECT** *(Randomized Evaluation of Recurrent Stroke comparing PFO Closure to Established Current Standard of Care Treament)*

✓ **REDUCE** *(Gore HELEX/Gore Septal Occluder and Antiplatelet Medical Management for Reduction of Recurrent Stroke or Imaging-Confirmed TIA in Patients with Patent Foramen Ovale)*	**- PFO closure + Antiplatelet > Antiplatelet alone** **- Subseq IS↓ Device Cx, Afib ↑**
✓ **CLOSE** *(Patent Foramen Ovale Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence)*	**- PFO (c ASA or large) + Antiplatelet > Antiplatelet alone** **- Recurrent IS↓, Afib ↑**
✓ **RESPECT-LT** *(Randomized Evaluation of Recurrent Stroke comparing PFO Closure to Established Current Standard of Care Treament - Long-term effects of PFO closure)*	**- PFO closure +/- Antiplatelet > diverse medical therapy** **- Recurrent IS↓, Device Cx, Afib ↑**
✓ **DEFENCE-PFO** *(Device Closure Versus Medical Therapy for Cryptogenic Stroke Patients With High-Risk Patent Foramen Ovale)*	**- PFO closure +/- medical Tx > antiplatelet or anticoagulation** **- PEP and Recurrent IS↓**

EDITORIAL COMMENT

PFO

"Please Figure Out," or Now "Potentially Figured Out?"*

Barry A. Love, MD,[a] Hans-Christoph Diener, MD, PhD[b]

The current meta-analysis calculated the number needed to treat (NNT) at 67 to prevent 1 stroke over 2.5 years, which really is too short a horizon to consider for this disease. For the average 45-year-old patient in the trials, the appropriate time frame to be considering benefit is 15 or 20 years, which would reduce the NNT to 11 and 8, respectively. This very reasonable number is far lower than the NNT used to justify many other invasive medical procedures, such as implantable defibrillators (NNT 15 to 20 for primary prevention) (5).

J Am Coll Cardiol. 2016;67:918-20

Number Needed to Treat in 5 years

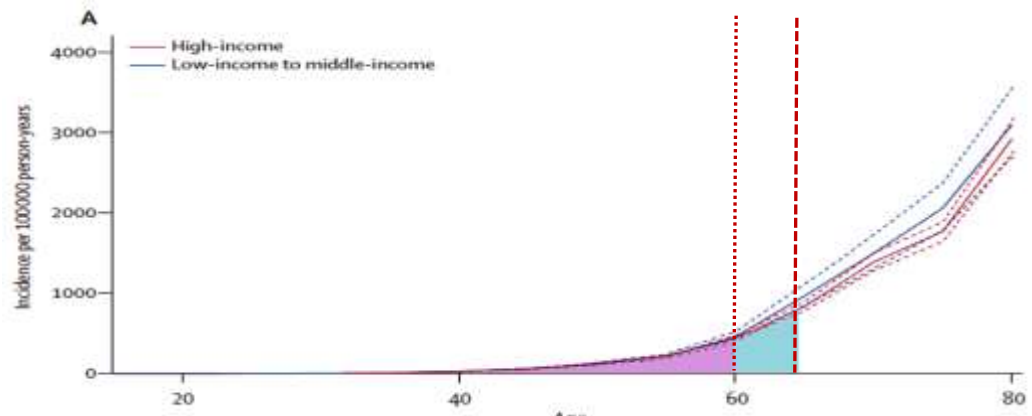
Trial	RESPECT-LT	REDUCE	CLOSE
Primary end point (all recurrent ischemic strokes)			
No. of patients with events/randomized patients	Device arm: 18/499 Medical arm: 28/481	Device arm: 6/441 Medical arm: 12/223	Device arm: 0/238 Medical arm: 14/235
Event rates per 100 patient-years	Device arm: 0.58 Medical arm: 1.07	Device arm: NA Medical arm: NA	Device arm: NA Medical arm: NA
Recurrent stroke risk reduction, %	45	77	97
HR (95% CI) *P* value	0.55 (0.31–0.999) *P*=0.046	0.23 (0.09–0.62) *P*=0.001	0.03 (0–0.25) *P*<0.001
Recurrent stroke rate at 5 y	Device arm: 2.6% Medical arm: 5.0%	Device arm: 1.4% Medical arm: 5.4%	Device arm: 0% Medical arm: 5.0%
Number needed to treat in 5 y	42	25	20
→ Number needed to treat in 15~20yrs	10~14	6~8	5~7

Wiktor DM, Carroll JD. Circ Cardiovasc Interv 2018;11:e004152

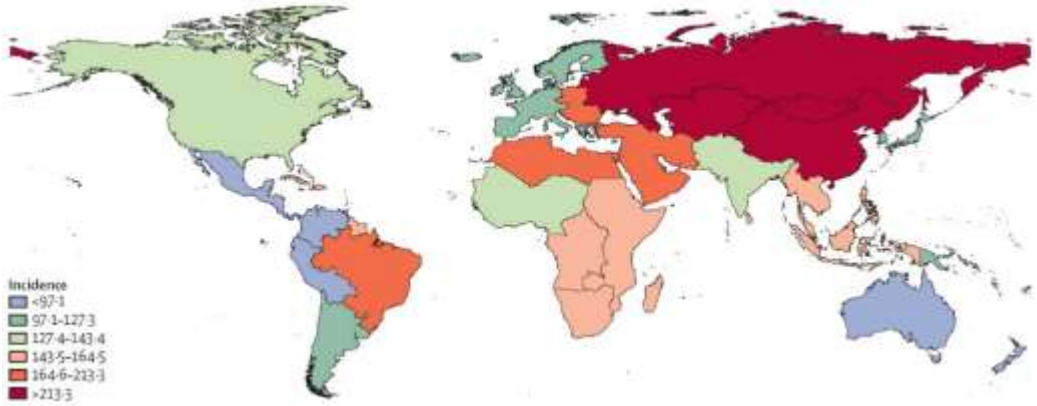
Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010

Rita V Krishnamurthi, Valery L Feigin, Mohammad H Forouzanfar, George A Mensah, Myles Connor, Derrick A Bennett, Andrew E Moran, Ralph L Sacco, Laurie M Anderson, Thomas Truelsen, Martin O'Donnell, Narayanaswamy Venketasubramanian, Suzanne Barker-Collo, Carlene M M Lawes, Wenzhi Wang, Yukito Shinohara, Emma Witt, Majid Ezzati, Mohsen Naghavi, Christopher Murray, on behalf of the Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) and the GBD Stroke Experts Group*

Krishnamurthi RV et al. Lancet Glob Health 2013;1:e259-81



Incidence for ischaemic stroke, by age and country income level (2010)

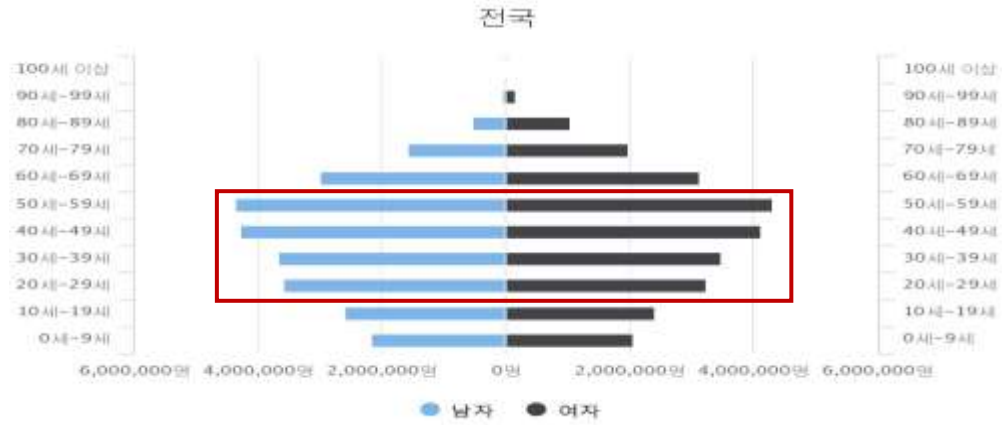


Age-standardized incidence of ischemic stroke/100,000 person-years (2010)

- **Incidence of first-ever ischemic stroke in high-income countries by age**
  <20yrs: 2.11, **≥20-64yrs: 93.82**, *65-74yrs: 1104.11, ≥75yrs: 2344.00*
- **Korean population 20~60yrs (2019) - 31,200,000**
  (61% of total, 20~64≈34,000,000)

→ ***32,000 ischemic stroke in 20-64yrs of population***

Population statistics of the Ministry of Public Administration & Security (2019)



- **Acute increase of stroke incidence > 60yrs**
  Proportion of population in btw 60~64yrs

→ ***≈ 20,000 ischemic stroke in 20-60yrs (??)***

JoS

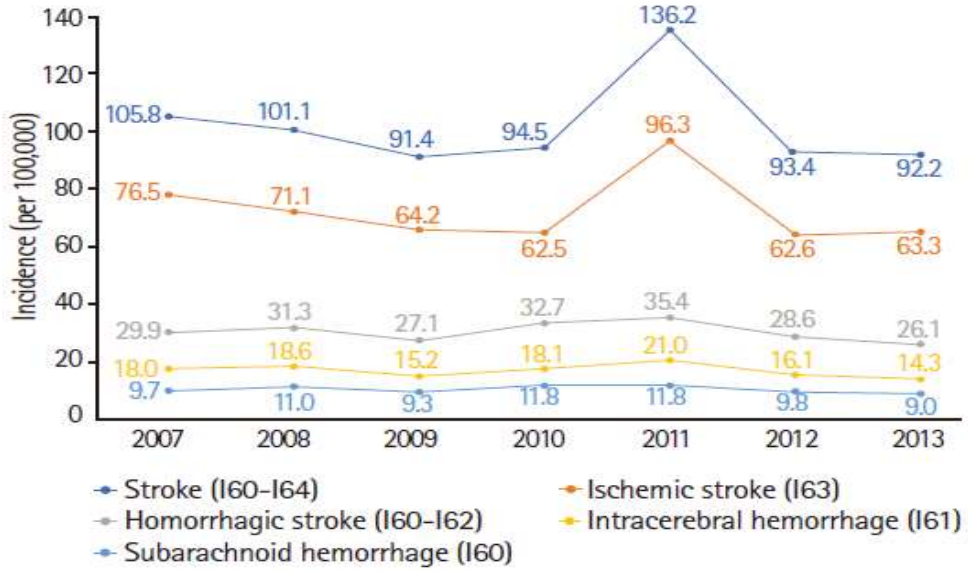
Review

Executive Summary of Stroke Statistics in Korea 2018: A Report from the Epidemiology Research Council of the Korean Stroke Society

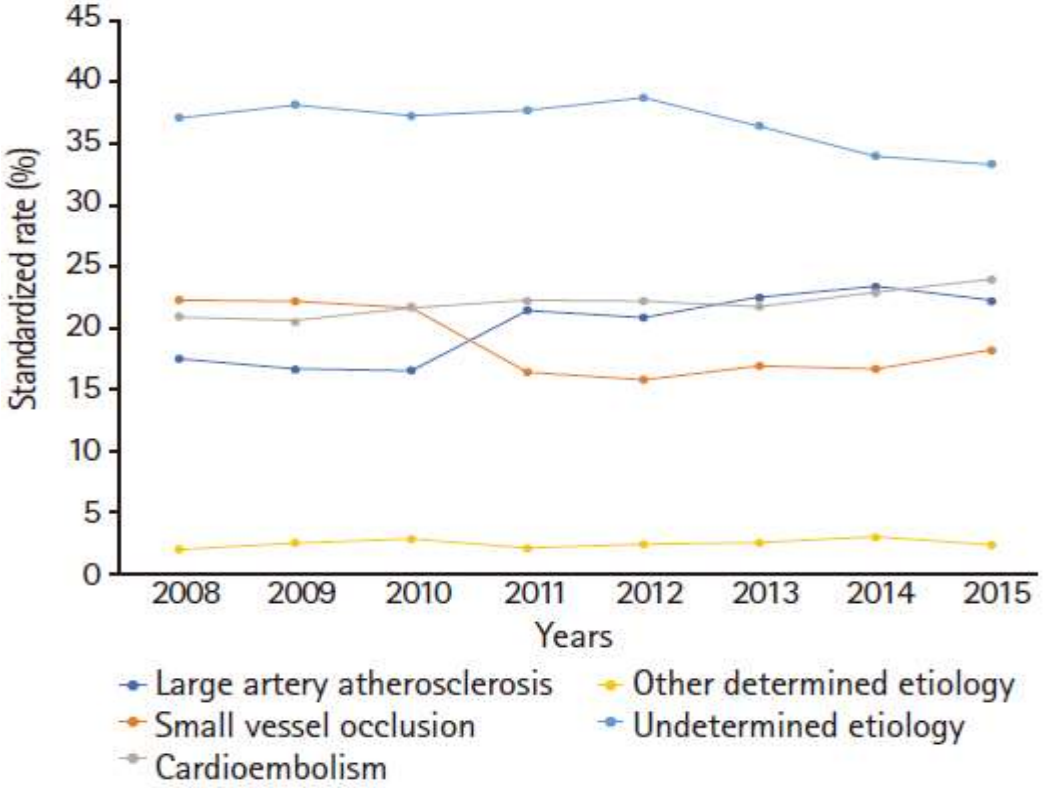
Kim JY et al. J Stroke 2019;21:42-59

Age-standardized incidence of first-ever stroke: 92.2/100,000 person-yrs ***(2013, NHIS-NSC database)***

→ first-ever stroke in 46,495 pts, IS≈32,000 pts, ***ischemic stroke in 20~60yrs ≈ 19,000 pts/yr***



Age- and sex-standardized incidence of stroke (NHIS-NSC database, 2002~2013)



Secular trends in ischemic stroke subtypes evaluated using the CRCS-K database from 2008/04 to 2015/03. The MRI imaging-based diagnostic algorithm for acute ischemic stroke subtype classification (MAGIC) was applied.

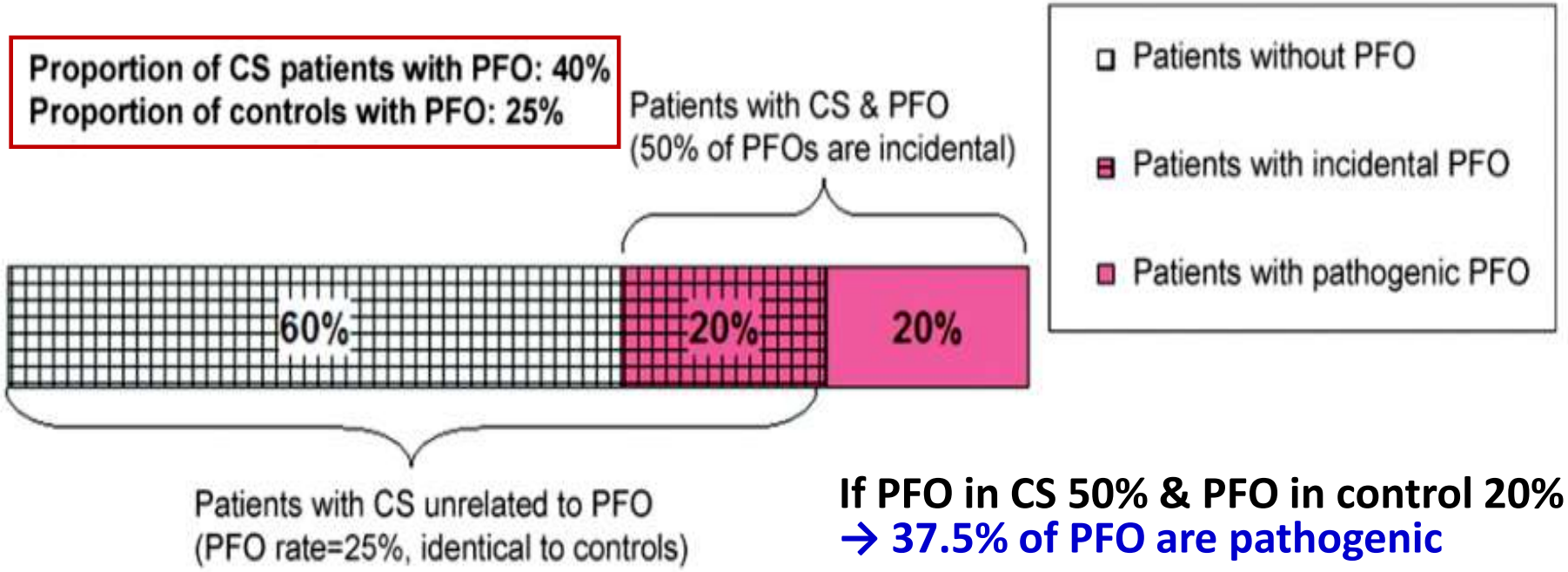
→ "cryptogenic stroke" in 20~60 yrs
: approximately 6000 pts/yr in Korea

- **PFO prevalence in cryptogenic stroke : 40~50%**
- **PFO prevalence in general population : 20~25%**

→ PFO is pathogenic in 20~37.5% of CS patients

→ Annual number of CS attributable to PFO

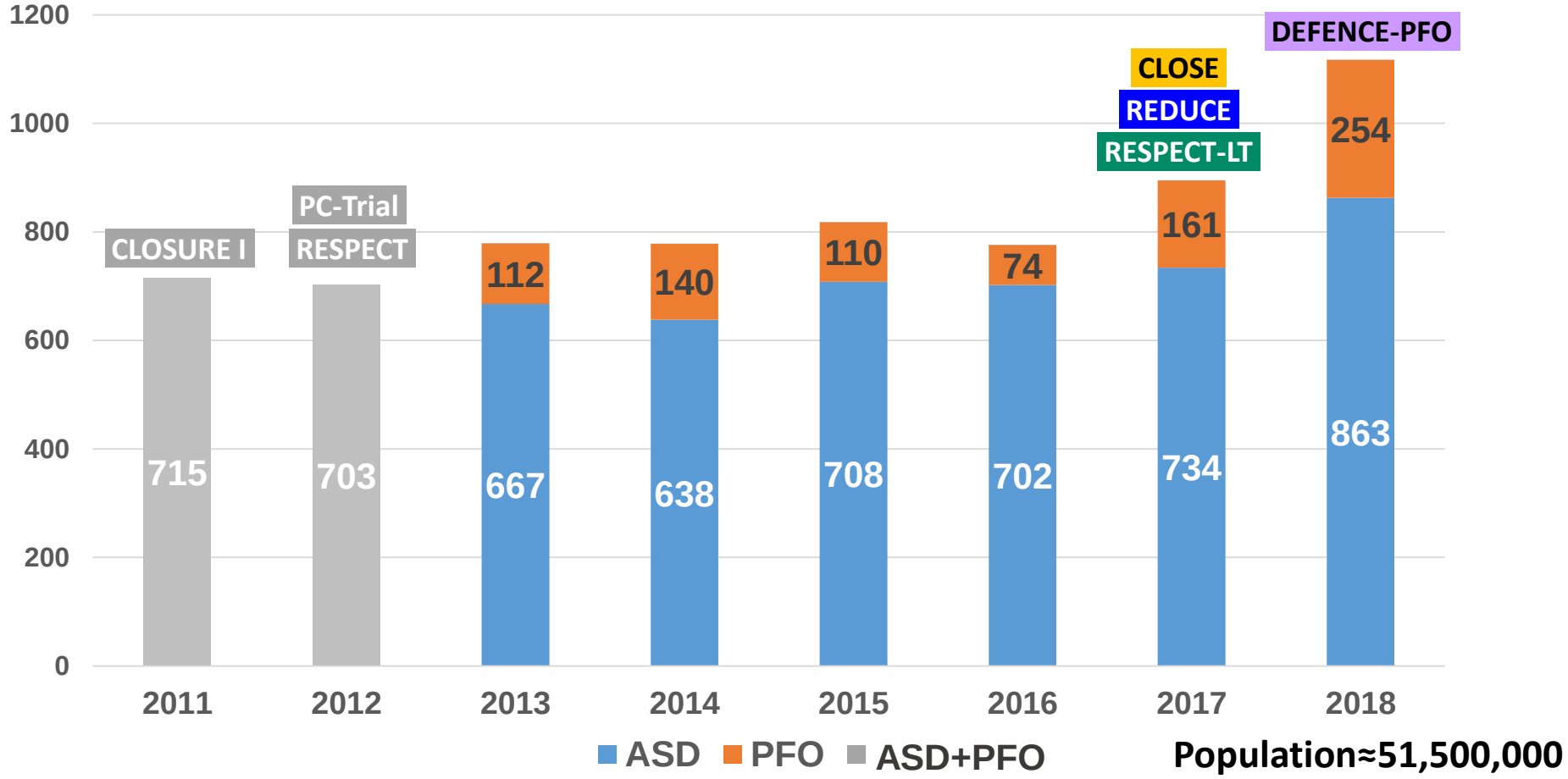
: 1200~2250 in Korean patient aged 20~60yrs



If PFO in CS 50% & PFO in control 20%
→ 37.5% of PFO are pathogenic

Alsheikh-Ali AA et al. Stroke 2009;40:2349-2355.
Thaler DE. Cardiac Intervention Today 2014:MARCH/APRIL

Annual Changes in Numbers of ASD/PFO Closure in Korea



cf) **IPOS registry (Italy, 2007/12~2008/11, 1yr) – 1035 PFO closures/50 centers (population≈60,000,000)**

Caputi L et al. Perspectives in Medicine 2012;1:236

Are we optimally treating our patient?

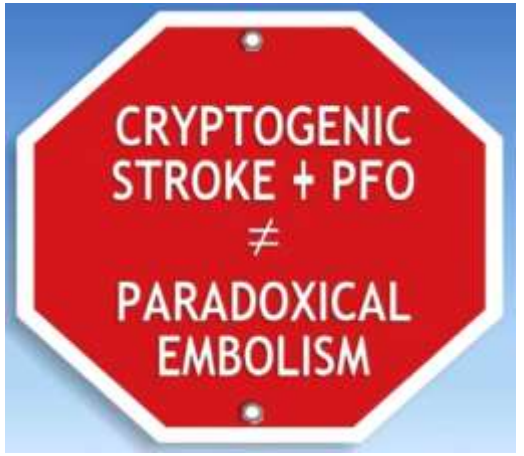
Still, many of us have skeptical concerns about therapeutic benefits of PFO closure

Major issue

How to stratify the risks &

How to select the patients

→ What is a high risk PFO?



High-risk PFOs

Risk of PFO
- the probability that the stroke was related to the PFO (attributable)
- the risk of stroke recurrence

Higher risk with

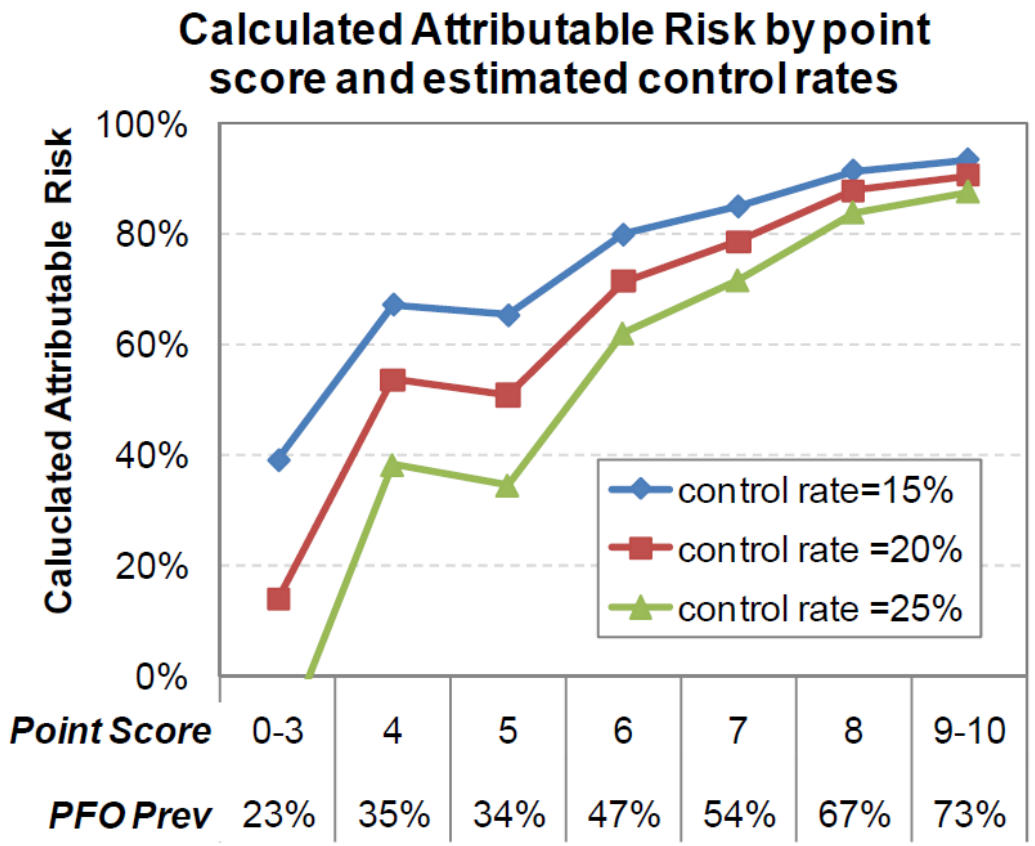
- Younger age
- Imaging topology: superficial/cortical
- No other vascular risk factor
  - DM
  - Hypertension
  - Hyperlipidemia
  - Smoking

- Anatomic features of PFO
  - Larger PFO size
  - Large amount of R-L shunt (microbubbles)
  - Atrial septal aneurysm
  - hypermobile septum
  - Eustachian valve or Chiari network
  - Long-tunnel PFO
  - Low angle PFO
- Clinical features
  - History of DVT or PE
  - Presence of endocardial pacing lead
  - Consistent features of embolic infarct
  - Valsalva maneuver at onset
  - Waking-up at onset
  - recent prolonged travel

Am J Med 2000;109:456–62, J Am Soc Echocardiogr 2004;17:231–3, J Am Coll Cardiol 1995;26:203–10, J Am Soc Echocardiogr 2019;32:811-6, Neurology 2013;81:619–25, Circulation 1998;97:1946–51, Circulation 2013;128:1433–41, J Neurol Sci 2008;275:121-7

An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke

Kent DM et al. Neurology 2013;81:619–625



✓ ***RoPE score - stratify patients with CS + PFO***

1. ***PFO attributable fraction (probability of PFO is pathogenic)***
2. ***Risk of stroke recurrence***

TABLE 1. RoPE SCORE CALCULATOR

Characteristic	Points	Score
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 (y)		
18–29	5	
30–39	4	
40–49	3	
50–59	2	
60–69	1	
≥ 70	0	

RoPE : Risk of Paradoxical Embolism

Identification of High-Risk Patent Foramen Ovale Associated With Cryptogenic Stroke: Development of a Scoring System

Rie Nakayama, MD, Yoichi Takaya, MD, Teiji Akagi, MD, Nobuhisa Watanabe, RDCS, Madoka Ikeda, RDCS, Koji Nakagawa, MD, Norihisa Toh, MD, and Hiroshi Ito, MD, *Okayama, Japan*

J Am Soc Echocardiogr 2019;32:811-6

Table 2 Echocardiographic PFO characteristics

Variables	Patients with CS (n = 57)	Patients without CS (n = 50)	P value
Height of PFO, mm	2.4 ± 1.6	1.6 ± 0.9	.002
Large-size PFO, ≥2 mm	11 (19)	3 (6)	.042
Length of PFO, mm	9.1 ± 4.3	8.3 ± 4.2	.319
Long-tunnel PFO, ≥10 mm	29 (51)	14 (28)	.016
ASA	23 (40)	6 (12)	.001
Hypermobile interatrial septum	40 (70)	8 (16)	<.001
Prominent Eustachian valve or Chiari's network	24 (42)	7 (14)	.001
Large RL shunt at rest	11 (19)	1 (2)	.004
Large RL shunt during Valsalva maneuver	38 (67)	19 (38)	.001
Angle between IVC and PFO, degrees	29 ± 16	37 ± 14	.007
Low-angle PFO (≤10°)	14 (25)	4 (8)	.022

Data are presented as mean ± SD or n (%) of patients.

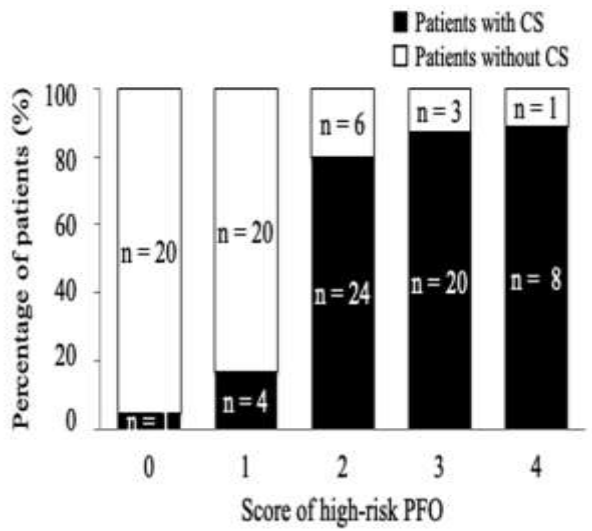
Table 3 Factors related to CS

Variable	Univariate analysis		Multivariate analysis 1		Multivariate analysis 2	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Large-size PFO, ≥2 mm	2.54 (1.16-5.59)	.02	0.83 (0.24-2.62)	.754	1.16 (0.33-3.94)	.815
Long-tunnel PFO, ≥10 mm	2.66 (1.19-5.97)	.017	3.27 (1.11-10.6)	.032	3.16 (1.04-10.5)	.042
ASA	4.96 (1.82-13.5)	.002	3.33 (0.94-13.0)	.064	2.51 (0.68-10.3)	.171
Hypermobile interatrial septum	11.4 (4.43-29.1)	<.001	9.09 (2.84-33.5)	<.001	7.26 (2.19-27.5)	.001
Eustachian valve or Chiari's network	4.47 (1.72-11.6)	.002	4.71 (1.45-17.2)	.009	4.58 (1.41-16.9)	.011
Large RL shunt during Valsalva maneuver	5.86 (2.51-13.7)	<.001	3.63 (1.23-11.3)	.020	3.87 (1.27-12.6)	.018
Low-angle PFO, ≤10°	3.74 (1.14-12.3)	.029	5.80 (1.38-29.7)	.016	5.12 (1.10-30.3)	.037
Age	4.34 (1.80-10.5)	.001			2.99 (0.77-12.3)	.112
Hypertension	2.84 (1.12-7.20)	.023			1.64 (0.43-6.77)	.473

Variables for multivariate analysis 1 included large PFO, long-tunnel PFO, the presence of ASA, the presence of hypermobile interatrial septum, the presence of prominent Eustachian valve or Chiari's network, the large RL shunt during Valsalva maneuver, and low-angle PFO. Variables for multivariate analysis 2 added age and the prevalence of hypertension.

Table 4 Large-size high-risk PFO score calculator

Variables	Point
Long-tunnel PFO ≥10 mm	1
Hypermobile interatrial septum	1
Eustachian valve or Chiari's network	1
Large RL shunt during Valsalva maneuver	1
Low-angle PFO ≤10°	1



Recurrent stroke predictors differ in medically treated patients with pathogenic vs other PFOs

Thaler DE et al. Neurology 2014;83:221–226

→ **Tried to combine the RoPE score with other (echo/clinical) features to predict recurrent stroke risk**

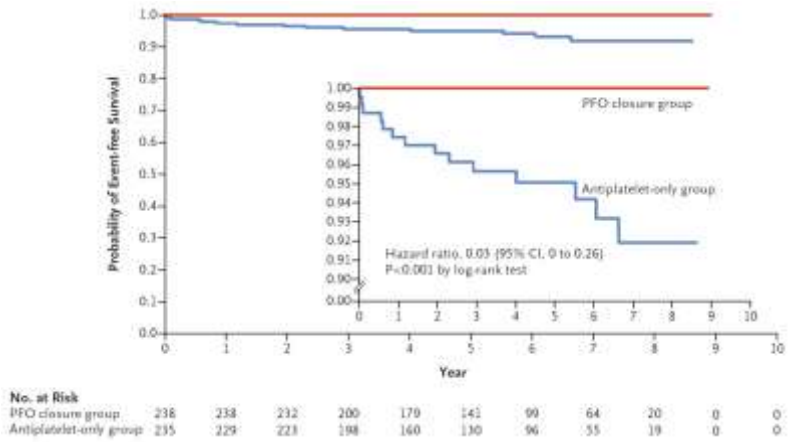
Predictors of stroke recurrence

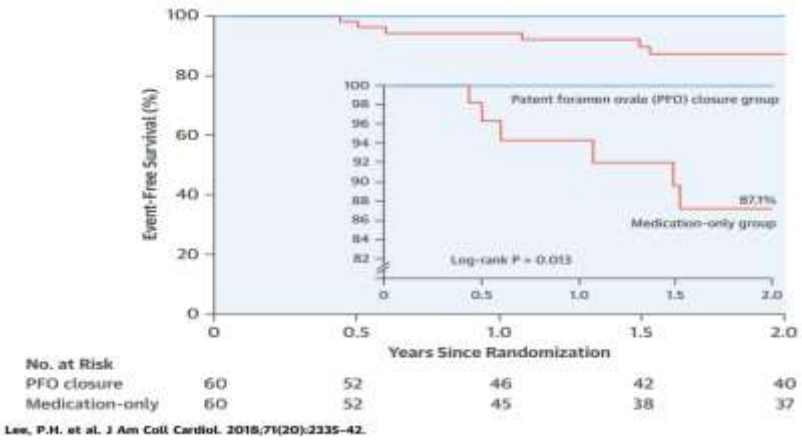
✓ **Low RoPE score (≤6) group (estimated PFO attributable fraction 40%)**
- older age
- antiplatelet (vs warfarin) treatment
- PFO characteristics (shunt size, hypermobile septum) - less influential

✓ **High RoPE score (>6) group (estimated PFO attributable fraction 80%)**
- echocardiographic features (septal hypermobility and a small shunt)
- prior (clinical) stroke/TIA

Any clues from recent RCTs which showed powerful Tx effect?

	CLOSE		DEFENCE-PFO	
Age (yrs)	PFO closure	42.9±10.1	PFO Closure	49± 15
	APLT	43.8±10.5	Medication	54±12
	ACGL	43.8±9.5		
High risk PFO/screened	NA		38.9%	
High risk PFO feature	Large shunt alone 60-70%		PFO size	3.2±1.5 / 3.2±1.1
	Large shunt + ASA 24-32%		ASA	8.3% / 13.3%
	ASA (mild-mod shunt) 5-9%		Hypermobility	46.7% / 45.0%
RoPE Score	7.4±1.3 / 7.2±1.3 / 7.3±1.2		NA	





At present, no single variable allows a quantitative prediction of recurrences. Also the risk cannot be quantitatively scored, and should be based on interdisciplinary qualitative clinical evaluation.

Eurointervention 2019;14:1350

- ✓ **Observations hard to explain with current knowledge**
  - **Frequent CS in elderly patients with PFO and ASA**

    Echocardiography 2004 Aug;21(6):517-22. Clin Neurol Neurosurg. 2008;110:779-83.
  - **Increased recurrent stroke in small shunts more than large shunts**

    Mas JL et al. N Engl J Med 2001;345:1740

- ✓ **There may be more PFO-related stroke mechanism and unrecognized (or underscored) combined risk factors than we know**

  ex) Paradoxical embolism vs. Thrombus in situ

  Cardiac Intervention Today 2014:March/April

What are we missing?

- undetected patients at risk -

Secular Trends in Ischemic Stroke Characteristics in a Rapidly Developed Country

Results From the Korean Stroke Registry Study (Secular Trends in Korean Stroke)

Keun-Hwa Jung, MD, PhD; Seung-Hoon Lee, MD, PhD; Beom Joon Kim, MD; Kyung-Ho Yu, MD, PhD; Keun-Sik Hong, MD, PhD; Byung-Chul Lee, MD, PhD; Jae-Kyu Roh, MD, PhD; Korean Stroke Registry Study Group

Circ Cardiovasc Qual Outcomes 2012;5:327-34

Performance of diagnostic work-ups of ischemic stroke in Korea (2010):

CT - 52%, MRI - 90.1%, MRA - 65.6%

TFCA - 8.6%

TTE - 54.4%, TEE - 8.1%

Holter - 17.2%

AHA/ASA Guideline

2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Stroke 2018;49:e46–e99

4. Routine use of echocardiography in all patients with AIS to plan subsequent secondary preventive treatment is not cost-effective and is not recommended.	III: No Benefit	B-NR
5. In selected patients with AIS, echocardiography to provide additional information to plan subsequent secondary preventive treatment may be reasonable.	IIb	B-R

Current evidence on cost-effectiveness is insufficient to justify routine use of echocardiography in stroke patients. Those patients with known or newly discovered atrial fibrillation by ECG will benefit from oral anticoagulation regardless of echocardiographic findings. The risk of recurrent stroke associated with most echocardiographic lesions and the efficacy of treatment in reducing that risk are unclear. The estimated yield and accuracy of echocardiography in detecting intracardiac thrombus indicate that for unselected patients, transthoracic echocardiography and transesophageal echocardiography will produce at least as many false-positive as true-positive diagnoses. Intracardiac thrombus occurs almost exclusively in patients with clinical

AHA/ASA Guideline

2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Stroke 2018;49:e46–e99

6.3. Cardiac Evaluation	COR	LOE
2. The clinical benefit of prolonged cardiac monitoring to detect atrial fibrillation after AIS is uncertain.	IIb	B-R
3. In some patients with AIS, prolonged cardiac monitoring to provide additional information to plan subsequent secondary preventive treatment may be reasonable, although the effect on outcomes is uncertain.	IIb	C-EO

In patients with TIA or ischemic stroke and atrial fibrillation detected by ECG at the time or within the preceding 24 months, oral anticoagulation begun within 3 months is superior to aspirin for the prevention of vascular death, stroke, MI, and systemic embolism (HR, 0.60; 95% CI, 0.41–0.87).[287] With prolonged cardiac monitoring by a variety of techniques, atrial fibrillation is newly detected in nearly a quarter of patients with stroke or TIA.[288] However, in the few RCTs of prolonged cardiac monitoring after stroke with clinical end points, no significant benefit of oral anticoagulation for stroke prevention in such patients has been demonstrated.[289–294] In CRYSTAL AF (Study of Continuous Cardiac Monitoring to Assess Atrial Fibrillation After Cryptogenic Stroke), at 36 months, atrial fibrillation was detected in 30% of 221 patients with implantable cardiac monitors and in 3% of 220 control subjects (P<0.001), but the occurrence of TIA or ischemic stroke was 9% in the implantable cardiac monitor group and 11% in the control group (P=0.64).[291,292] In Find-AF$_{RANDOMISED}$ (Finding Atrial Fibrillation in Stroke–Evaluation of Enhanced and Prolonged Holter Monitoring), atrial fibrillation was detected in 14% of 200 patients with 10-day Holter monitoring at baseline, 3 months, and 6 months versus 5% of 198 patients in the standard care group who had at least 24 hours of rhythm monitoring (P=0.002). There was no significant difference in recurrent stroke at 12 months (3.7% versus 5.4%; P=0.46).[294] Other smaller studies have also failed to show a difference in outcomes.[290,293,295] All of these studies were underpowered for the secondary clinical end points. Thus, the appropriate patient selection criteria for prolonged cardiac monitoring and the clinical benefits of doing so remain uncertain at this time. Further randomized trials are planned or ongoing and are needed to clarify best practice.

4. Routine use of echocardiography in all patients with AIS to plan subsequent secondary preventive treatment is not cost-effective and is not recommended.	III: No Benefit	B-NR
5. In selected patients with AIS, echocardiography to provide additional information to plan subsequent secondary preventive treatment may be reasonable.	IIb	B-R

Current evidence on cost-effectiveness is insufficient to justify routine use of echocardiography in stroke patients. Those patients with known or newly discovered atrial fibrillation by ECG will benefit from oral anticoagulation regardless of echocardiographic findings. The risk of recurrent stroke associated with most echocardiographic lesions and the efficacy of treatment in reducing that risk are unclear. The estimated yield and accuracy of echocardiography in detecting intracardiac thrombus indicate that for unselected patients, transthoracic echocardiography and transesophageal echocardiography will produce at least as many false-positive as true-positive diagnoses. Intracardiac thrombus occurs almost exclusively in patients with clinical evidence of heart disease but is rare even in them.[296] Additional research on how to identify patients likely to harbor intracardiac thrombus, on recurrent stroke risk in patients with intracardiac thrombus, and on the efficacy of oral anticoagulation in reducing that risk is needed.[296–298] Five RCTs have evaluated mechanical closure of echocardiographically detected patent foramen ovale to prevent recurrent stroke in patients without obvious cause for their index stroke.[299–304] All 5 suffered from potential bias resulting from unblinded investigators determining which events should be referred for blinded end-point adjudication. Three had many more patients lost to follow-up than stroke end points, making their results unreliable.[299,301–303] Of 2 RCTs with 1% lost to follow-up, 1 showed no benefit of closure over antithrombotic therapy alone over a 2-year period of 12 strokes (2.9%) versus 13 strokes (3.1%; P=0.79),[304] and the other showed a reduction in all stroke versus antiplatelet therapy alone over a mean of 5.3 years of 0 versus 14 (P< 0.001) with rates at 5 years of 0% and 5%. There was, however, no change in disabling stroke, 0 versus 1 (P=0.63), over the duration of the trial.[300] These 2 trials had different highly restrictive eligibility criteria, used different closure devices, and had different guidelines for antithrombotic therapy.

6.6-3. The usefulness of screening for thrombophilic states is unknown.

→ however, Tx recommendations are different for non-cardioembolic vs. cardioembolic IS.

- ✓ **Cardioembolic stroke is increasing in recent stroke statistics**

  → ***possibly reflect a tendency to escape from potentially misleading guidelines***

TOAST Classification

TABLE 1. TOAST Classification of Subtypes of Acute Ischemic Stroke

Large-artery atherosclerosis (embolus/thrombosis)*
Cardioembolism (high-risk/medium-risk)*
Small-vessel occlusion (lacune)*
Stroke of other determined etiology*
Stroke of undetermined etiology
a. Two or more causes identified
b. Negative evaluation
c. Incomplete evaluation

TOAST, Trial of Org 10172 in Acute Stroke Treatment.
*Possible or probable depending on results of ancillary studies.

Stroke 1993;24:35

a level of suspicion lower than probable cause **may lead to "under-diagnosis" of the disease, which in turn result in "under-utilization" of a reasonable and attractive treatment option**

Missing Windows

Patients with PFO &

- **Obstructive sleep apnea induced desaturation (R-L shunt)**
- **Sleep apnea**
- **Decompression sickness**
- **High-altitude pulmonary edema**
- **Economy class stroke syndrome**
- **Pacemaker & internal cardioverter-defibrillator carriers**
- **Migraine**
- **Platypnea–orthodeoxia / exercise desaturation**
- **High-risk activities**
  - *Weight lifters, brass musicians, glass blowers, tile setters (frequent Valsalva maneuvres)*
  - *Frequent flyers, pilots (high-risk for deep venous thrombosis)*
  - *Deep sea divers, military pilots, astronauts, etc.*
- **Brain abscess**
- **Venous thromboembolism/thrombophilia *(role of anticoagulation vs. PFO closure)***

→ would potentially benefit most from PFO closure

Johansson MC et al. Eur Respir J 2007;29:149, Kujime S et al. Intern Med. 2012;51(14):1851-5, Torti SR et al. Eur Heart J. 2004 Dec;25(23):2173-4, Allemann Y et al. JAMA. 2006;296:2954-2958, Heckmann J G et al. Heart. 2006 Sep;92(9):1265-8, DeSimone CV et al. Circulation 2013;128:1433

Wrap up

1. **Percutaneous closure of PFO in CS : treatment is safe & effective – *RCTs***
2. **We have more "optimal" candidates who may benefit from percutaneous closure of PFO *- rough estimation from previous epidemiologic studies and current stroke statistics***
3. **This entity is drawing more attention with improved recognition than before, with resultant better detection rate of the patients at risk**

I would prefer…

not a more *restrictive*, but a rather *specified and optimized* utilization of PFO closure to take the precious opportunity to save more patients with CS and PFO from the recurrence of life-threatening disaster

The future..

Table 2 Some of the questions about PFO closure that remain to be answered.

Which patients (aged < 60 years) with PFO-associated ischaemic stroke benefit a lot, just a little or not at all from PFO closure?
Do patients who were excluded from RCTs, particularly those aged > over 60 years or with a competitive cause of stroke, benefit from PFO closure?
Could oral anticoagulants be an alternative to PFO closure?
What is the long-term clinical relevance of AF induced by PFO closure?
Will new PFO closure devices improve closure rates and decrease closure complications?
What is the optimal duration of antiplatelet therapy following PFO closure?
What are the mechanisms of PFO- and ASA-associated strokes?
What is the role of PFO closure in the primary prevention of stroke?

Hopefully, ongoing efforts to answer the remained questions with better knowledge on risk profiles and stratification would lead to optimal patient selection and improvement of patient outcome