STROKE FROM THE HEART

"Decision making in patients with Patent Foramen Ovale" - Individualizing Care

MingMing Ning, M.D., MMSc.

Director, Cardio-Neurology
Department of Neurology, Massachusetts General Hospital
Associate Professor, Harvard Medical School
mmning@mgh.Harvard.edu

32th Annual Ischemic and Hemorrhagic Update:
Current Practices and Future Directions May 12, 2025

Patient: PFO and Pregnancy (1999)

- 25 year old woman **3 weeks post-partum**, traveling to see family – came directly from Logan Airport **after trans-atlantic flight**
- PE and found to have a PFO, **protein S deficiency** and **May-Thurner Syndrome** resulting in massive left leg DVT
- Large cerebellar stroke resulted in herniation

"PFO is not associated with increased risk of subsequent stroke…"
-- Practice Parameter: Recurrent stroke with PFO and atrial septal aneurysm: Report of the Quality Standards Subcommittee of the American Academy of Neurology. April, 2004.1042-1050

MingMing Ning
MD, MMSc

We have come a long way…

MGH Cardio-Neurology Clinic Experience

- 28 years (1990-2018) – evaluated **8134 stroke patients with cardiac abnormalities**
- PFO closure: n= 1342 (16%); Peri-procedure AE <1%; Post-closure stroke recurrence: <0.45% per year
- > 96.7% freedom from recurrent ischemic stroke at 5 yr followup, 91.5% at 10yr followup

Martin, Palacios et al. Circulation 2002; Kiernan, Palacios et al. Stroke 2009; Inglessis, Elmariah, Palacios et al. JACC 2013

PFO – First described in 1877 in a young woman with stroke. "Back door to the brain." PFO allows persistent direct communication between right and left atria, bypassing the lung's filtration, enabling peripheral clots to go to the brain. One-way valve. Highly dynamic 3-dimensional structure.

Associated with nearly **40% of all cryptogenic strokes (>150,000 strokes per year)**.

Major Challenges: High baseline prevalence of PFO in general population: 20-25% in all normal adults; only found out AFTER a stroke

Long-Term Experience and Outcomes With Transcatheter Closure of Patent Foramen Ovale

Ignacio Inglessis, MD,* Sammy Elmariah, MD, MPH,* Pablo A. Rengifo-Moreno, MD,* Ronan Margey, MD,* Caitlin O'Callaghan, NP,* Ignacio Cruz-Gonzalez, MD, PHD,*† Suzanne Baron, MD,* Praveen Mehrotra, MD,* Timothy C. Tan, MD, PHD,* Judy Hung, MD,* Zareh N. Demirjian, MD,‡ Ferdinando S. Buonanno, MD,§ MingMing Ning, MD,§ Scott B. Silverman, MD,§ Roberto J. Cubeddu, MD,*‖ Eugene Pomerantsev, MD, PHD,* Robert M. Schainfeld, DO,* G. William Dec, JR, MD,* Igor F. Palacios, MD*



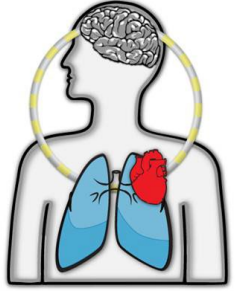


Percutaneous Transcatheter Closure of Patent Foramen Ovale in Patients With Paradoxical Embolism

Francisco Martín, MD; Pedro L. Sánchez, MD; Elizabeth Doherty, MD; Pedro J. Colon-Hernandez, MD; Gabriel Delgado, MD; Ignacio Inglessis, MD; Nandita Scott, MD; Judy Hung, MD; Mary Etta E. King, MD; Ferdinando Buonanno, MD; Zareh Demirjian, MD; Michael de Moor, MD; Igor F. Palacios, MD

Hagen et al. 1984; Lechat et al. 1988; Webster et al. 1988; Sacco et al. 1989; Adams et al. 1993; Petty et al. 1999; Meissner et al. 1999; Handke et al. 2007; Homma et al. 2002; Lamy et al. 2002; Overell et al. 2000; Mas et al. 2001. Messe et al 2004, Kizer et al. 2005; Hara et al. 2005; Wu et al 2007. Furlan, Reissman, Massaro et al 2012; Carroll, Saver, Thaler et al 2013.

MingMing Ning
MD, MMSc



"Stroke from the Heart…"

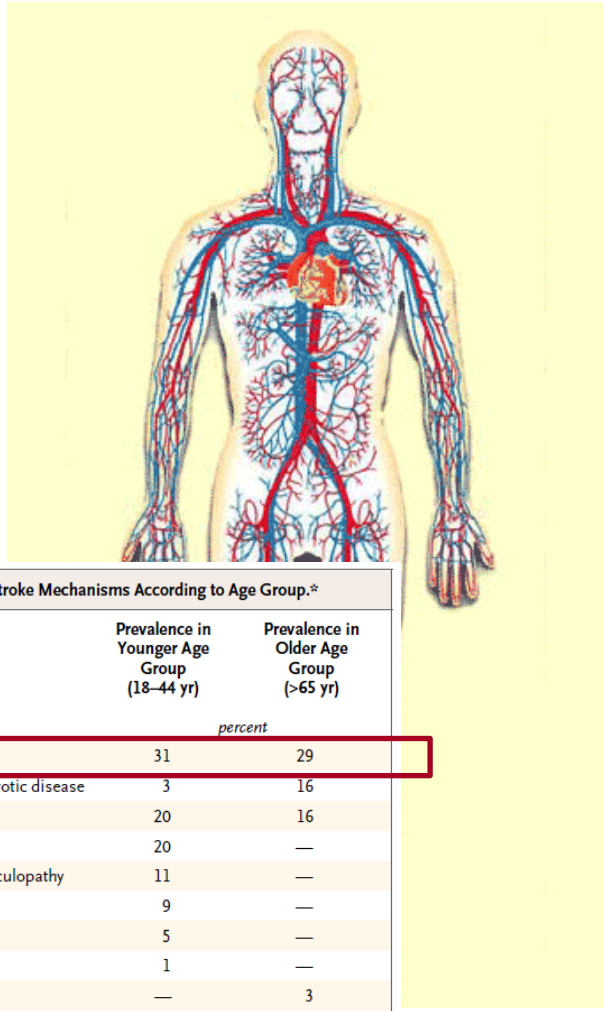


Table 2. Prevalence of Stroke Mechanisms According to Age Group.*

Stroke Mechanism	Prevalence in Younger Age Group (18–44 yr)	Prevalence in Older Age Group (>65 yr)
	percent	
Cardiac embolism	31	29
Large-vessel atherosclerotic disease	3	16
Small-vessel disease	20	16
Hematologic disease	20	—
Nonatherosclerotic vasculopathy	11	—
Illicit-drug use	9	—
Oral-contraceptive use	5	—
Migraine	1	—
Other	—	3
Unknown	—	36

Approximately 3-15% of ischemic strokes come from the large vessels of the head and neck (carotid artery and intracranial vessels).

15-30% come from the heart (emboli from cardiac arrhythmia -Afib etc)

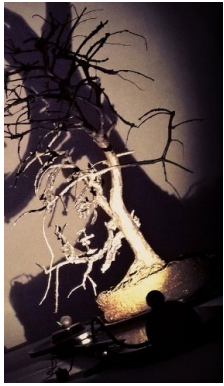
Additional 15-20% come from clots from the venous circulation IF there is a cardiac structural abnormality (PFO) allowing them to travel to the brain.

In all, up to **50%** of ischemic strokes may involve the heart.

Ning, Gonzalez. NEJM 2013 Oct 31;369(18):1736-48

MingMing Ning
MD, MMSc

Controversies in PFO Decision Making



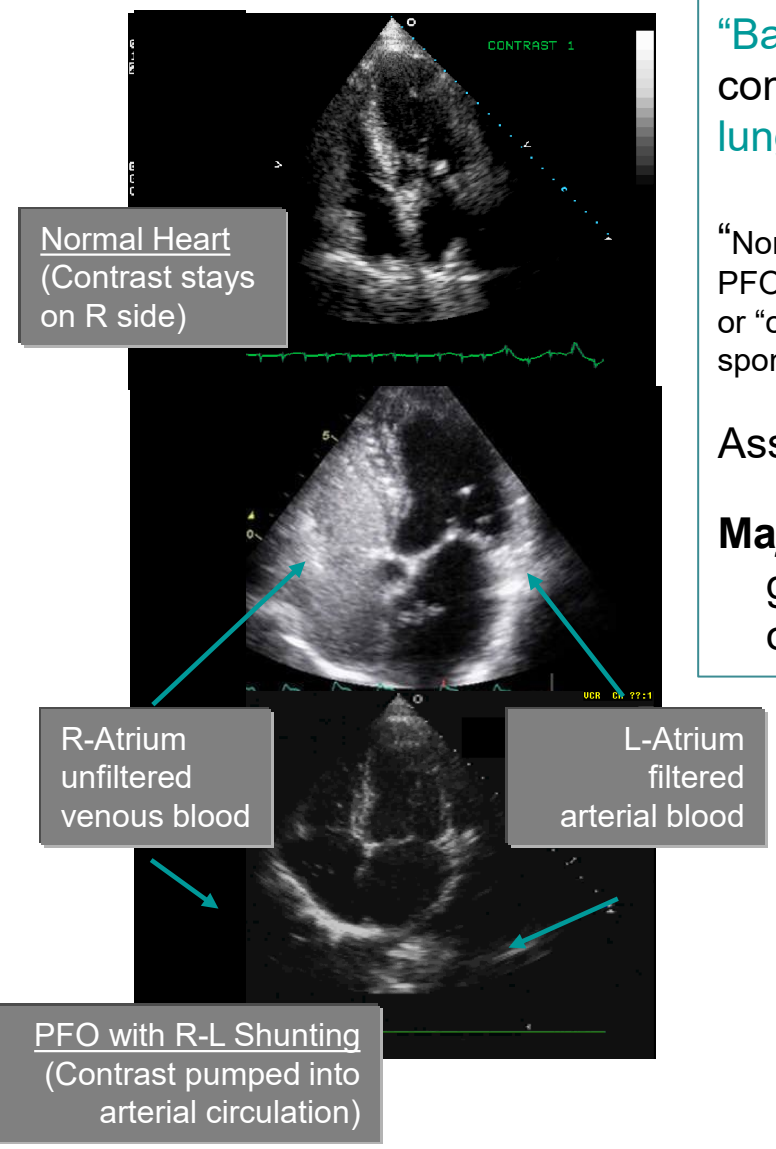
- *Q 1. "PFO is so common in healthy people (25%), it CAN'T cause strokes…"*
- *"Risk of PFO stroke is low - only 1%" …*
  "If they have other vascular risk factors, then PFO isn't why they had a stroke…"
- *-- **Risk prediction***

- *Q 2. "Risk of PFO is the same throughout life" "PFO is an outpatient issue only…" "PFO only allows clots to go through"*
- *Q 3. "All young stroke patients with PFO should have PFO closure…"*
- *Q 4. "He is 63 years old, he cannot have a PFO related stroke…"*
- *Q 5. "Checking hypercoagulable state in PFO stroke patients is expensive and does not change management…"*
- ***-- Risk factors***

- *Q 6. "Once they have PFO closure, they are safe and no need to see anymore…"*
- ***-- Prevention***

MingMing Ning
MD, MMSc

The PFO Paradox

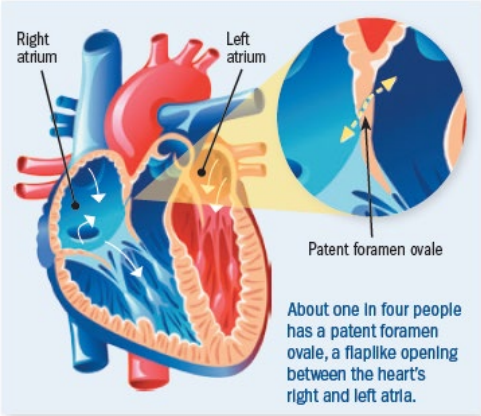


First described in 1877 in a young woman with stroke. "Back door to the brain." PFO allows persistent direct communication between right and left atria, bypassing the lung's filtration, enabling peripheral clots to go to the brain.

"Normal variant" → Fetus doesn't breathe (oxygenated blood via placenta through PFO) → In utero, ~3% circulation goes to lungs, rest goes through this "trap door" or "one-way valve" (the PFO) and bypasses lungs. At birth PFO typically closes spontaneously; Remains patent in ~ 20-25% adults

Associated with nearly 40% of all cryptogenic strokes.

Major Challenges: High baseline prevalence of PFO in general population: 20-25% in all normal adults; only found out AFTER a stroke

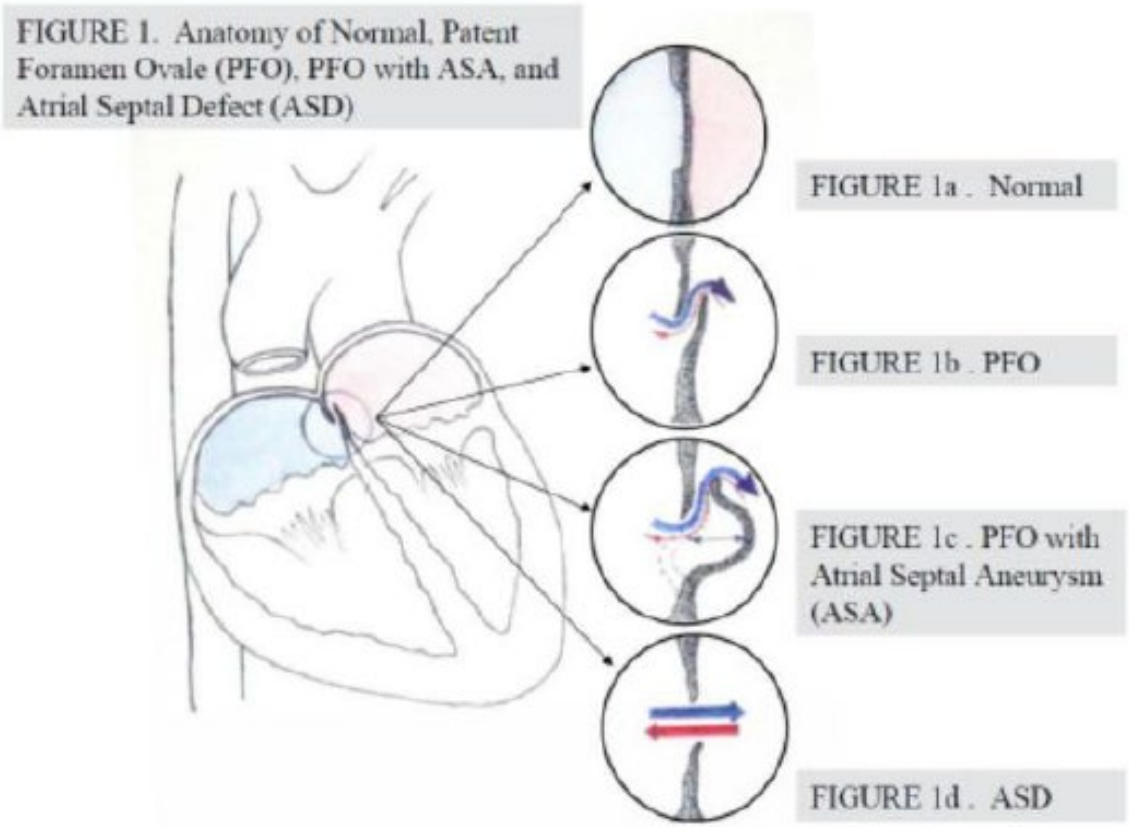


TTE- Courtesy Dr Judy Hung

Julie Corliss, Harvard Heart Letter.
Vol 31. Number 1. Sept 2020

MGH 1811
MingMing Ning
MD, MMSc

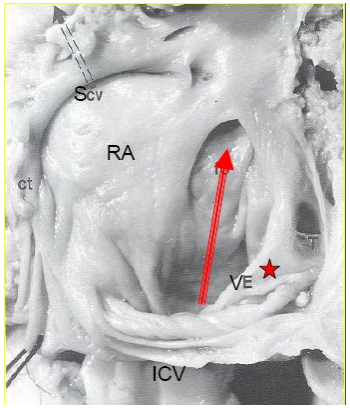
PFO as a “back door to the brain”



Ning et al Pharm Therap 2013

PFO as a One way valve
with unidirectional right- to -left shunting (Not a “hole”)

PFO Shunting enhances venous/arterial mixing



Courtesy of Dr Zoltan Turi

PFO – Congenital condition – in 20-25% adults
ASD – atrial septal defect – bidirectional shunting

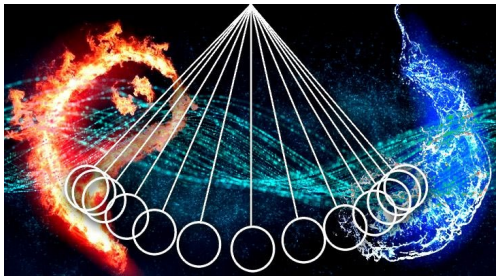
MGH 1811
MingMing Ning
MD, MMSc

"To Close or Not Close" The Pendulum Swings

"PFO cannot cause stroke because it happens in a quarter of the world's population"

"PFO should never be closed"

"PFO closure should be offered to all young stroke patients… with the absence of vascular risk factors such as HTN, diabetes or hyperlipidemia"



CLOSURE I (2012)
PC (2013)

RESPECT (2013 and 2017)
REDUCE (2017)
CLOSE (2017)

Regarding transcatheter device closure of a PFO, available data do not support a benefit to reduce the risk of recurrent stroke (Class III; LOE A).

Kernan WN, et al. 2014 AHA and ASA guidelines (affirmed by the American Academy of Neurology). *Stroke* , 45: 2160–2236

AAN 2014

- **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) (C).**

Steven R. Messé, MD; Gary S. Gronseth, MD; David M. Kent, MD, MSc; Jorge R. Kizer, MD, MSc; Shunichi Homma, MD; Lee Rosterman, DO; John D. Carroll, MD; Koto Ishida, MD; Navdeep Sangha, MD; Scott E. Kasner, MD, MSCE. Practice advisory update: Patent foramen ovale and secondary stroke prevention. Report of the Guideline Subcommittee of the American Academy of Neurology. *Neurology* 2020;94(20):876-885.
This practice advisory was endorsed by the Society for Cardiovascular Angiography and Interventions, the American Heart Association/American Stroke Association, and the European Academy of Neurology.

AAN 2020

MGH 1811
MingMing Ning
MD, MMSc

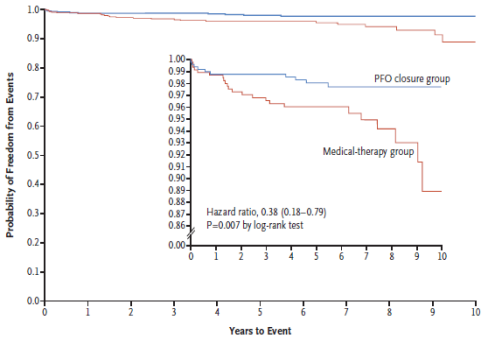
Landmark Trials (2017)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke

Jeffrey L. Saver, M.D., John D. Carroll, M.D., David E. Thaler, M.D., Ph.D., Richard W. Smalling, M.D., Ph.D., Lee A. MacDonald, M.D., David S. Marks, M.D., and David L. Tirschwell, M.D., for the RESPECT Investigators*

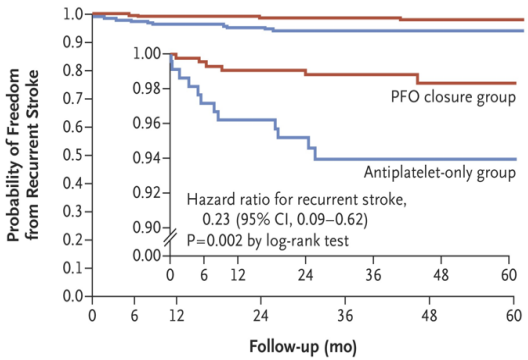


N=980
RESPECT
St Jude/Abbott

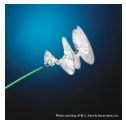
ORIGINAL ARTICLE

Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

Lars Søndergaard, M.D., Scott E. Kasner, M.D., John F. Rhodes, M.D., Grethe Andersen, M.D., D.M.Sc., Helle K. Iversen, M.D., D.M.Sc., Jens E. Nielsen-Kudsk, M.D., D.M.Sc., Magnus Settergren, M.D., Ph.D., Christina Sjöstrand, M.D., Ph.D., Risto O. Roine, M.D., David Hildick-Smith, M.D., J. David Spence, M.D., and Lars Thomassen, M.D., for the Gore REDUCE Clinical Study Investigators*



N=664
REDUCE
Gore

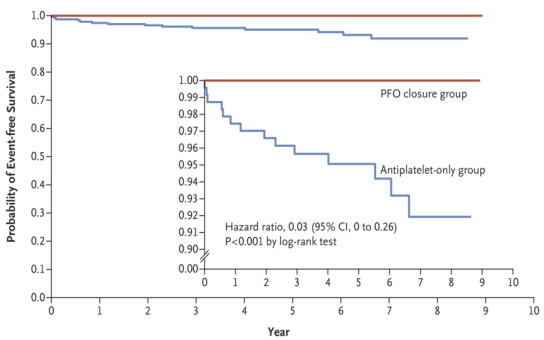


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 14, 2017 VOL. 377 NO. 11

Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

J.-L. Mas, G. Derumeaux, B. Guillon, E. Massardier, H. Hosseini, L. Mechtouff, C. Arquizan, Y. Béjot, F. Vuillier, O. Detante, C. Guidoux, S. Canaple, C. Vaduva, N. Dequatre-Ponchelle, I. Sibon, P. Garnier, A. Ferrier, S. Timsit, E. Robinet-Borgomano, D. Sablot, J.-C. Lacour, M. Zuber, P. Favrole, J.-F. Pinel, M. Apoil, P. Reiner, C. Lefebvre, P. Guérin, C. Piot, R. Rossi, J.-L. Dubois-Randé, J.-C. Eicher, N. Meneveau, J.-R. Lusson, B. Bertrand, J.-M. Schleich, F. Godart, J.-B. Thambo, L. Leborgne, P. Michel, L. Pierard, G. Turc, M. Barthelet, A. Charles-Nelson, C. Weimar, T. Moulin, J.-M. Juliard, and G. Chatellier, for the CLOSE Investigators*



N=663
French Ministry
Of Health

Multiple devices -
>50% amplatzer

MingMing Ning
MD, MMSc

Summary Data from Large Randomized PFO trials

Trials	CLOSURE (2012)		RESPECT Final (2017)		REDUCE (2017)		CLOSE (2017)	
	PFO closure	Medical therapy	PFO closure	Medical therapy	PFO closure	Medical therapy	PFO closure	Medical therapy
Patient in each group	N=447	N=462	N=499	N=481	N=441	N=223	N=238	N=235
Randomization ratio	1:1		1:1		2:1		1:1	
Recruiting period	2003 ~ 2008		2003 ~ 2011		2008 ~ 2015		2007 ~ 2016	
Sites and countries	87 sites in US and Canada		69 sites in the US and Canada		63 sites in Canada, Denmark, Finland, Norway, Sweden, UK, US		32 sites in France and 2 sites in Germany	
Duration (yr)	2		5.9 (Median)		3.2 (Median)		5.4 (Mean)	5.2 (Mean)
Age (Mean)	46.3±9.6	45.7±9.1	45.7±9.7	46.2±10.0	45.4±9.3	44.8±9.6	42.9±10.1	43.8±10.5
Age (Range)	18-60		18-60		18-59		16-60	
Gender (Male)	233 (52.1)	238 (51.5)	268 (53.7)	268 (55.7)	261 (59.2)	138 (61.9)	137 (57.6)	142 (60.4)
Atrial septal aneurysm	168 (37.6)	165 (35.7)	180 (36.1)	170 (35.3)	86 (20.4)	NA	81 (34.0)	74 (31.5)
			Shunting					
Trace	(44.1)	(50)	108 (21.6)	114 (23.7)	77 (18.1)	43 (19.9)		
Moderate	250 (55.9)	231 (50.0)	138 (27.7)	121 (25.2)	166 (39.1)	94 (43.5)		
Substantial			247 (49.5)	231 (48.0)	182 (42.8)	79 (36.6)	216 (90.8)	223 (94.9)
Effective closure rate	86.10%		96.1%		75.6% (grade 0)		93.00%	
Risk Reduction Number needed to treat			RR 2.3% in 5.9 yrs NNT42		RR 4.0% in 3.2 yrs NNT 25		RR 6.0 in 5.3yrs NNT 17	
Atrial Fibrillation post-procedure (%)			3.0% NS	1.5% NS	6.6%	0.4%	4.6%	0.9%

RESPECT the largest with longest follow-up, highest effective closure rate;
REDUCE achieved primary endpoint in ITT (NNT 28);
CLOSE enrollment large shunting only, smallest NNT.
All trials only enrolled age <=60, no venous hypercoagulability

MingMing Ning
MD, MMSc

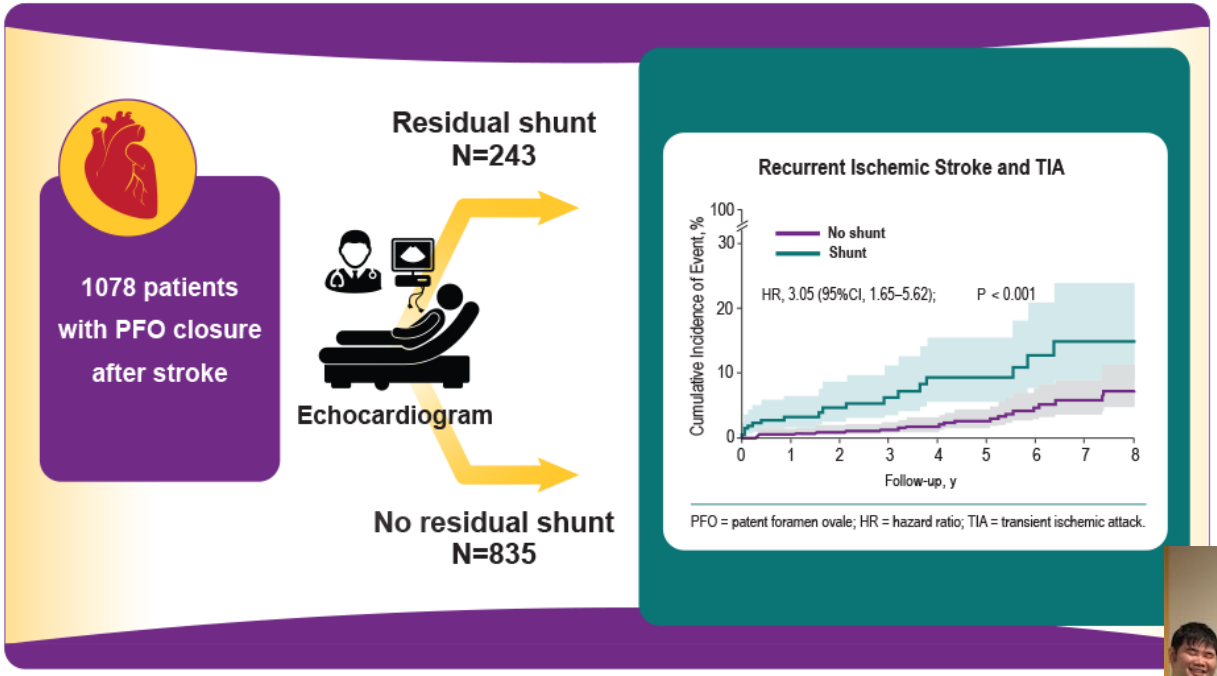
Degree of PFO residual shunting is associated with stroke recurrence

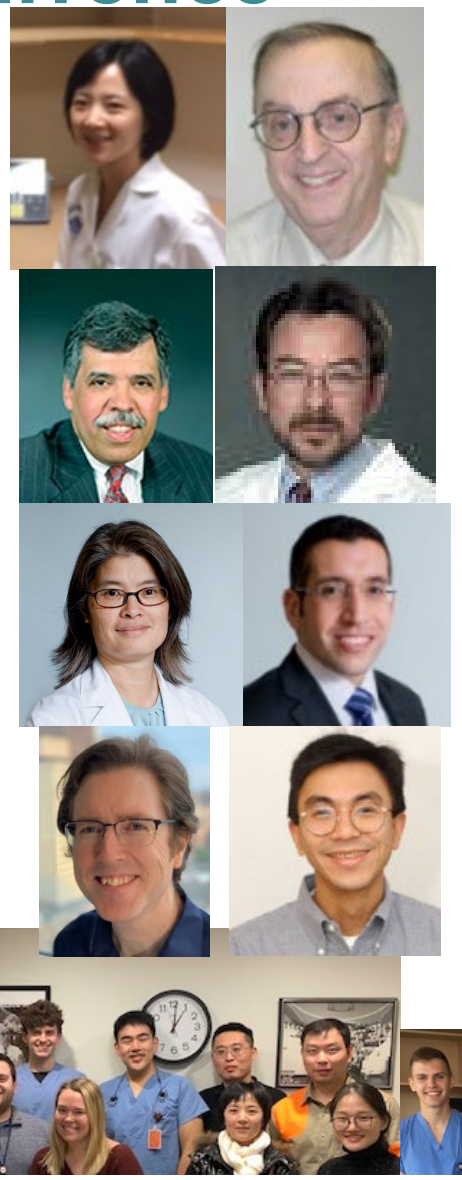
Annals of Internal Medicine ORIGINAL RESEARCH

Residual Shunt After Patent Foramen Ovale Closure and Long-Term Stroke Recurrence

A Prospective Cohort Study

Wenjun Deng, PhD; Shanye Yin, PhD; David McMullin, PhD; Ignacio Inglessis-Azuaje, MD; Sammy Elmariah, MD, MPH; Judy Hung, MD; Eng H. Lo, PhD; Igor F. Palacios, MD*; Ferdinando S. Buonanno, MD*; and MingMing Ning, MD, MMSc*

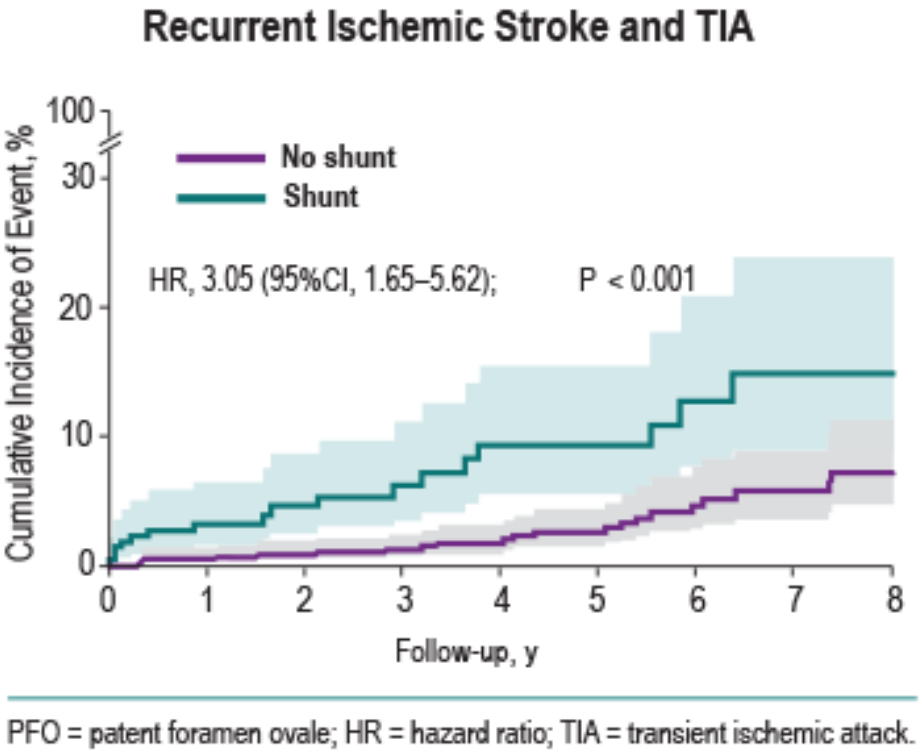




Deng et al. Ann Intern Med. 2020 Jun 2;172(11):717-725.

Degree of PFO residual shunting is associated with stroke recurrence

- N=1078 PFO closure pts
- **Residual shunt** after PFO closure was associated with **increased incidence of recurrent stroke or TIA**
  2.32 vs 0.75 events per 100 patient-years
  (**HR 3.05** [95% CI 1.65 - 5.62]; *P* < 0.001)
- **Moderate or large residual shunts** were associated with a **higher risk for stroke or TIA recurrence**
  (**HR 4.50** [95% CI 2.20 - 9.20]; P < 0.001)
- Effect of small residual shunts was indeterminate
  (HR 2.02 [95% CI 0.87 - 4.69]; P = 0.102).

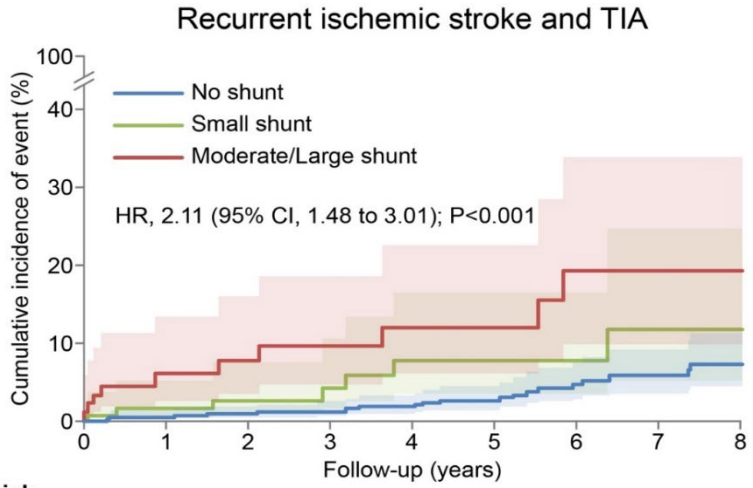


PFO = patent foramen ovale; HR = hazard ratio; TIA = transient ischemic attack.

Deng et al. *Ann Intern Med*, 2020;172:717-725
doi.org/10.7326/M19-3583

MingMing Ning
MD, MMSc

Management of Residual Shunt



Number at risk									
No shunt	835	694	562	468	383	287	200	146	96
Small shunt	150	109	82	64	49	32	26	20	16
Moderate/large shunt	93	62	54	42	34	28	22	17	10

Shunt size	24 hr	1 m	6 m	1 yr	2 yr	3 yr	4 yr	5 yr
No shunt	53.5%	64.0%	70.5%	80.2%	83.0%	86.4%	88.5%	88.9%
Small shunt	31.4%	24.8%	21.2%	12.6%	11.7%	8.4%	6.3%	6.3%
Moderate/large shunt	15.0%	11.1%	8.3%	7.2%	5.4%	5.2%	5.2%	4.8%

Appendix Table 4. Residual shunt rate over time.

Follow the patient!

Deng et al. Ann Intern Med. 2020 Jun 2;172(11):717-725.

Practical Recommendations

First, we recommend long-term clinical follow-up (at least 5 years) with a multidisciplinary team involving primary care physicians to ensure adherence. To gauge shunt size, TTE with bubbles should be performed every 3 to 6 months during the first year and every 6 to 12 months thereafter.

Second, because residual shunt diminishes over time as a closure device becomes further epithelialized (Supplement Table 9, available at Annals.org), stepping up medical treatment, such as anticoagulant or dual-antiplatelet therapy, for the first year is reasonable until the shunt stabilizes.

Third, we suggest maximizing the management of PFO-specific risk factors, such as hypercoagulable states; deep venous thrombosis prevention; and, as patients age, treatment of traditional stroke risk factors and acquired hypercoagulability (such as age-appropriate cancer screening and management of hyperhomocysteinemia).

Finally, for high-risk patients with a persistent moderate or large shunt, we recommend multidisciplinary assessment by neurologists, cardiologists, hematologists, vascular specialists, and primary care clinicians to determine the optimal management plan, whether with second device closure or lifelong anticoagulant therapy.

MGH 1811
MingMing Ning
MD, MMSc

Exclusion Criteria of Various PFO RCTs

- **Any hypercoagulable disorder requiring anticoagulation**
- **Venous hyper-coagulability**
- Uncontrolled diabetes mellitus or hypertension
- Intracardiac thrombus or tumor
- Acute or recent (within 6 months) myocardial infarction or unstable angina
- Left ventricular aneurysm or akinesis
- Mitral valve stenosis or severe mitral regurgitation irrespective of etiology
- Aortic valve stenosis (gradient >40 mmHg) or severe aortic valve regurgitation
- Mitral or aortic valve vegetation or prosthesis
- **Pregnant or desire to become pregnant within the next year**
- **Age <18 years and age >60 years**
- Organ failure (kidney, liver or lung)
- **Long Term AC requirement**
- **Stroke with mRS>3**
- Aortic arch plaques protruding >4mm into the lumen
- Left ventricular dilated cardiomyopathy with LVEF <35%
- Subjects with other source of right to left shunts identified at baseline, including an atrial septal defect and/or fenestrated septum
- Small PFO Shunt
- Etc, etc etc
- **NOT EXCLUDED**: HTN, DM, Hyperlipidemic

What to do if your patient is not a GOOD trial patient (>70% clinic patients)?

MingMing Ning
MD, MMSc

From Mechanism to Clinical Trial
➔ Individualization

Emerging inherited and acquired risk factors associated with PFO-related stroke.

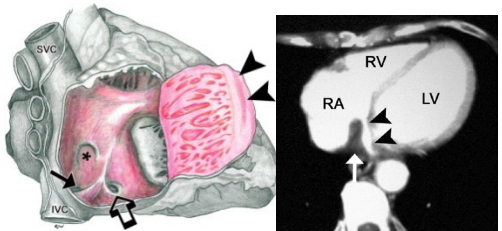
Organ involved	Inherited	Acquired
Cardiac	Atrial septal aneurysm Chiari's network Eustachian valve	
		Valsalva maneuver (weight lifting, position change etc.)
Circulatory	Hypercoagulable state	Hypercoagulable state
Pulmonary/upper airway		Provoked exercise desaturation Obstructive sleep apnea
Peripheral vascular	May–Thumer's syndrome	DVT, pelvic clots, and venous catheter related Air/long-distance travel Scuba diving
Neurologic	Migraine with aura	Migraine with aura

Mechanism of PARADOXIAL EMBOLISM

1. **Shunting as conduit of clot (Clinical trial and Cohort study) – "Back door to the brain"**
2. **WHERE DID THE CLOT COME FROM? HOW DID THEY FORM?**

Ning, Lo Buonanno et al. Pharmacol Ther. 2013 Aug;139(2):111-23
Ning, Gonzales. NEJM. 2013 Oct 31;369(18):1736-48

Sacco et al. 1989; Hagen et al. 1984; Lechat et al. 1988; Webster et al. 1988; Adams et al. 1993; Petty et al. 1999; Meissner et al. 1999; Handke et al. 2007; Homma et al. 2002; Lamy et al. 2002; Overell et al. 2000; Mas et al. 2001. Messe et al 2004, Kizer et al. 2005; Hara et al. 2005; Wu et al 2007; Furlan et al 2012, Messe SR et al 2004. Florez JC et al. 2003. Cramer SC et al 2004.Greer DM, Buonanno FS. 2001. Ning et al. Stroke 2008. Kiernan TJ et al. Stroke 2009. Kent , Thaler et al . Neurology 2013. Saver et al 2013



Where do clots come from?

May-Thurner Syndrome in Patients With Cryptogenic Stroke and Patent Foramen Ovale

An Important Clinical Association

Thomas J. Kiernan, MD; Bryan P. Yan, MD; Roberto J. Cubeddu, MD; Pablo Rengifo-Moreno, MD; Vishal Gupta, MD; Ignacio Inglessis, MD; MingMing Ning, MD; Zareh N. Demirjian, MD; Michael R. Jaff, DO; Ferdinando S. Buonanno, MD; Robert M. Schainfeld, DO; Igor F. Palacios, MD

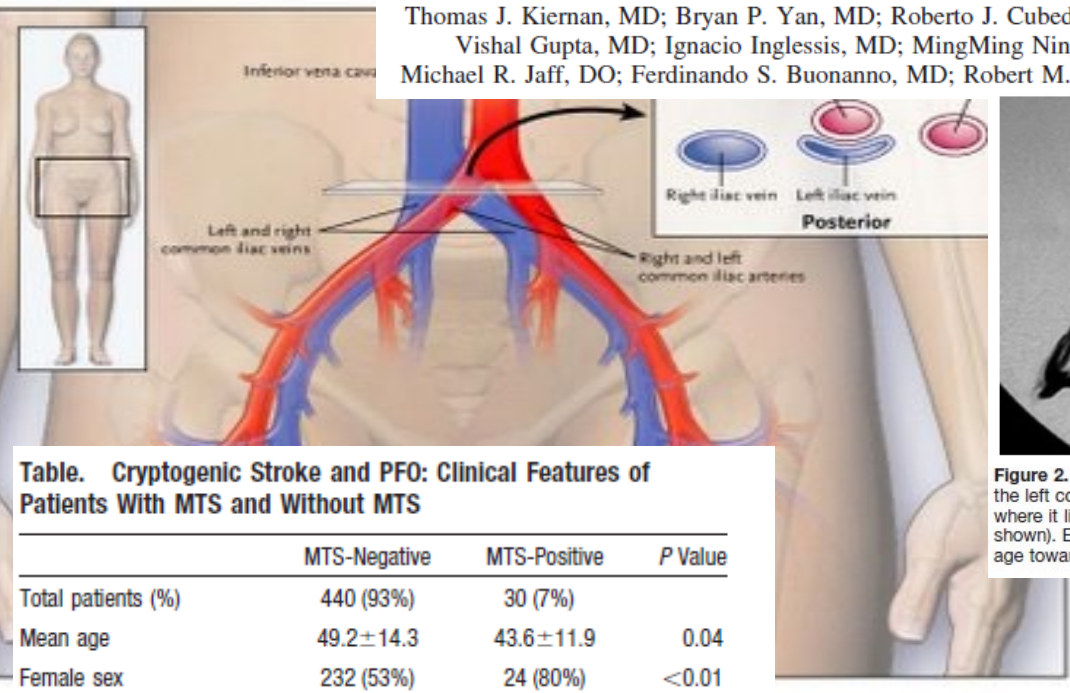


Table. Cryptogenic Stroke and PFO: Clinical Features of Patients With MTS and Without MTS

	MTS-Negative	MTS-Positive	*P* Value
Total patients (%)	440 (93%)	30 (7%)	
Mean age	49.2±14.3	43.6±11.9	0.04
Female sex	232 (53%)	24 (80%)	<0.01
Hypertension	136 (31%)	4 (14%)	0.06
Hypercholesterolemia	165 (38%)	4 (14%)	0.04
Current smoker	33 (8%)	8 (27%)	<0.01
Family history of coronary artery disease	64 (15%)	4 (14%)	1.0
Diabetes	22 (5%)	5 (2%)	0.02
Hypercoagulable condition	103 (24%)	12 (40%)	0.04
Atrial septal aneurysm/ hypermobile atrial septa	301 (68%)	21 (70%)	0.07
Device size	21.25±7.12	21.25+/- 7.10	1.0

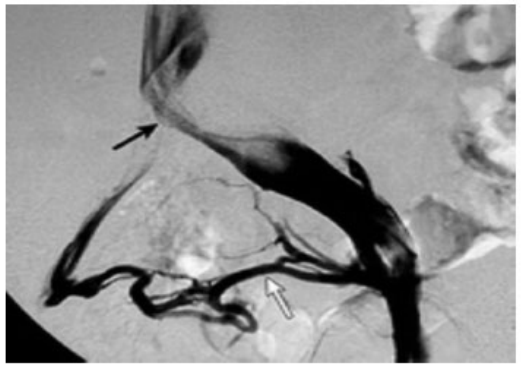
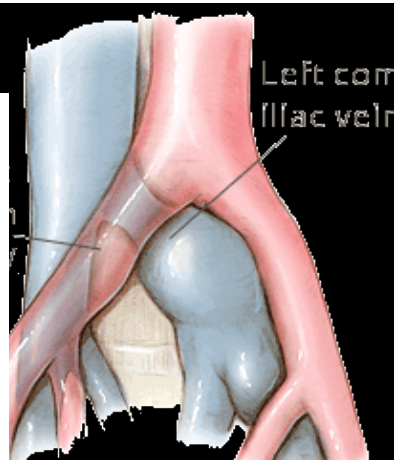


Figure 2. Venographic study demonstrating severe stenosis of the left common iliac vein (black arrow) at the precise location where it lies beneath the right common iliac artery (artery not shown). Extensive pelvic collaterals (white arrow) provide drainage toward the unaffected right iliac venous system.



Congenital Anatomical Variant - Pelvic Venous Abnormality
May-Thurner Syndrome
(MTS) as a risk factor for PFO related stroke
6.3% of PFO stroke pts have MTS on pelvic MRV

- More in women, smokers, diabetics…
- Importance of additional risk factors

Greer, Buonanno 2002, Cramer et al 2004;
Kiernan, Palacios et al. Stroke. 2009

MingMing Ning
MD, MMSc

Where do clots come from?

"**Economy class syndrome**" or "**Traveler's Stroke**" has been associated with long-distance flights (>6h/5000km), where prolonged immobility increases the chance of thrombosis in lower extremities resulting in pulmonary embolism.

Back-of-envelope math for stroke related to travel:

Baseline incidence of severe Pulmonary Embolism approx 0.01 cases per million passengers for <5,000 km traveled; increases 150-fold in >5,000 km or >6 hours in flight.

10% of healthy air travelers develop asymptomatic deep vein thrombosis (DVT) after prolonged flights.

High prevalence → >25% PFO in the normal population

Long distance travel increased risk of PFO-related stroke. **Additional risk factors** such as concurrent **hypercoagulable state, May-Thurners Anatomy, and migraine with aura heightened risk of "economy class stroke."**

Cruickshank et al. Lancet 1988; Lapostelle et all. NEJM. 2001; Perez-Rodriguez E et al. Arch Intern Med 2003; Scurr et al. Lancet. 2001; Isayev Y et al. Neurology 2002; Foerch C et al. Neurology. 2002;Ayo-Martín et al. Cerebrovasc Dis 2008. Ning et al. Neurology 2012.

MGH 1811
MingMing Ning
MD, MMSc

How did the CLOT FORM?

- *What is the FULL thrombophilia (hypercoagulable) panel?*

- **Venous** > Arterial:
  → Protein C/S, Factor V Leiden
  → Prothrombin Gene Mutation, ATIII

- **Arterial = Venous**
  → Antiphospholipid Antibodies (IgG, IgM, Lupus Anticoagulant (LA), anti-beta2glycoprotein…)

- **Arterial** > Venous
  → Homocysteine

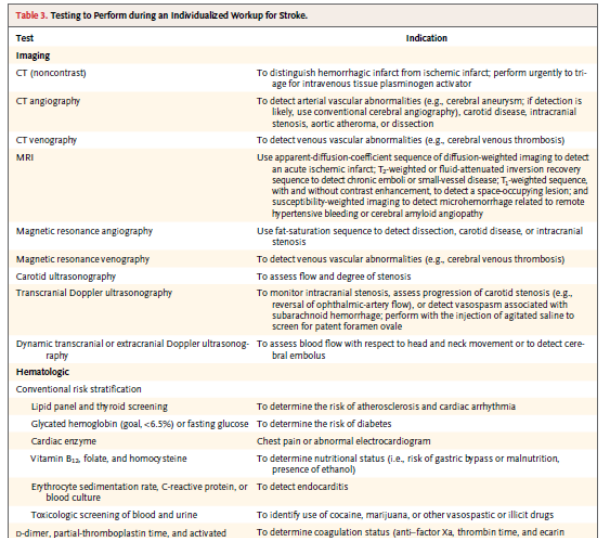


Table 3. Testing to Perform during an Individualized Workup for Stroke.

Test	Indication
Imaging	
CT (noncontrast)	To distinguish hemorrhagic infarct from ischemic infarct; perform urgently to triage for intravenous tissue plasminogen activator
CT angiography	To detect arterial vascular abnormalities (e.g., cerebral aneurysm; if detection is likely, use conventional cerebral angiography), carotid disease, intracranial stenosis, aortic atheroma, or dissection
CT venography	To detect venous vascular abnormalities (e.g., cerebral venous thrombosis)
MRI	Use apparent-diffusion-coefficient sequence of diffusion-weighted imaging to detect an acute ischemic infarct; T_2-weighted or fluid-attenuated inversion recovery sequence to detect chronic emboli or small-vessel disease; T_1-weighted sequence, with and without contrast enhancement, to detect a space-occupying lesion; and susceptibility-weighted imaging to detect microhemorrhage related to remote hypertensive bleeding or cerebral amyloid angiopathy
Magnetic resonance angiography	Use fat-saturation sequence to detect dissection, carotid disease, or intracranial stenosis
Magnetic resonance venography	To detect venous vascular abnormalities (e.g., cerebral venous thrombosis)
Carotid ultrasonography	To assess flow and degree of stenosis
Transcranial Doppler ultrasonography	To monitor intracranial stenosis, assess progression of carotid stenosis (e.g., reversal of ophthalmic-artery flow), or detect vasospasm associated with subarachnoid hemorrhage; perform with the injection of agitated saline to screen for patent foramen ovale
Dynamic transcranial or extracranial Doppler ultrasonography	To assess blood flow with respect to head and neck movement or to detect cerebral embolus
Hematologic	
Conventional risk stratification	
Lipid panel and thyroid screening	To determine the risk of atherosclerosis and cardiac arrhythmia
Glycated hemoglobin (goal, <6.5%) or fasting glucose	To determine the risk of diabetes
Cardiac enzyme	Chest pain or abnormal electrocardiogram
Vitamin B_{12}, folate, and homocysteine	To determine nutritional status (i.e., risk of gastric bypass or malnutrition, presence of ethanol)
Erythrocyte sedimentation rate, C-reactive protein, or blood culture	To detect endocarditis
Toxicologic screening of blood and urine	To identify use of cocaine, marijuana, or other vasospastic or illicit drugs
D-dimer, partial-thromboplastin time, and activated	To determine coagulation status (anti–factor Xa, thrombin time, and ecarin

Table 3. (Continued.)

Test	Indication
Homocysteine and lipoprotein(a)	Ischemic stroke; use to determine arterial hypercoagulability as risk factor for diffuse intracranial or extracranial stenosis
Fibrillin-1 (*FBN1*), collagen type I (*COL1A1*), collagen type II (*COL1A2*), and *GLA*	Ischemic stroke; use to detect spontaneous dissection with high suspicion for collagen vascular disease (i.e., Marfan's syndrome, osteogenesis imperfec Ehlers–Danlos syndrome) or Fabry's disease (deficiency in α-galactosidase
Partial-thromboplastin time, activated partial-thromboplastin time, and von Willebrand factor	General workup for hemorrhagic stroke; perform tests for other clotting factor abnormality is detected

Ning, Gonzalez. NEJM 2013 Oct 31;369(18):1736-48

MingMing Ning
MD, MMSc

PFO with hypercoagulable state has higher risk of stroke recurrence and responds to closure

Patent Foramen Ovale Attributable Cryptogenic Embolism With Thrombophilia Has Higher Risk for Recurrence and Responds to Closure

Kai Liu, MD, PhD,[a,b,*] Bo Song, MD, PhD,[a,b,*] Igor F. Palacios, MD,[a] Ignacio Inglessis-Azuaje, MD,[a] WenJun Deng, PhD,[a] David McMullin, PhD,[a] XiaoYing Wang, MD, PhD,[c] Eng H. Lo, PhD,[a,d] YuMing Xu, MD, PhD,[b] Ferdinando S. Buonanno, MD,[a] MingMing Ning, MD[a,d]

ABSTRACT

OBJECTIVES The aim of this study was to investigate the effect of management on the risk for patients with cryptogenic ischemic stroke or transient ischemic attack.

BACKGROUND The combination of patent foramen ovale (PFO) and hypercoagulability may g for paradoxical embolism. However, previous randomized controlled trials evaluating the efficac excluded these potential high-risk patients.

METHODS Patients diagnosed with PFO attributable cryptogenic embolism were prospectively, recruited from January 2005 to March 2018. The relationship between thrombophilia and recurre in overall patients. Multivariate Cox regression was conducted to assess the relative risk for recurr medical therapy groups.

RESULTS A total of 591 patients with cryptogenic embolism with PFO were identified. The media was 53 months, and thrombophilia significantly increased the risk for recurrent events (hazard r confidence interval [CI]: 1.09 to 3.16; p = 0.024). PFO closure was superior to medical therapy (HR: 0.16; 95% CI: 0.09 to 0.30; p < 0.001). Of the 134 patients (22.7%) with thrombophilia, th the risk for recurrence events between the PFO closure (6 of 89) and medical therapy (15 of 45 95% CI: 0.08 to 0.74; p = 0.012). There was no potential heterogeneity in the further subgrou

CONCLUSIONS Patients with cryptogenic stroke with PFO and hypercoagulable state had incr stroke or transient ischemic attack. PFO closure provided a lower risk for recurrent events compar alone. (J Am Coll Cardiol Intv 2020;13:2745-52) © 2020 Published by Elsevier on behalf of th Cardiology Foundation.

– PFO closure was superior to medical therapy in overall patients (HR: 0.16; 95% CI: 0.09 to 0.30; p < 0.001)

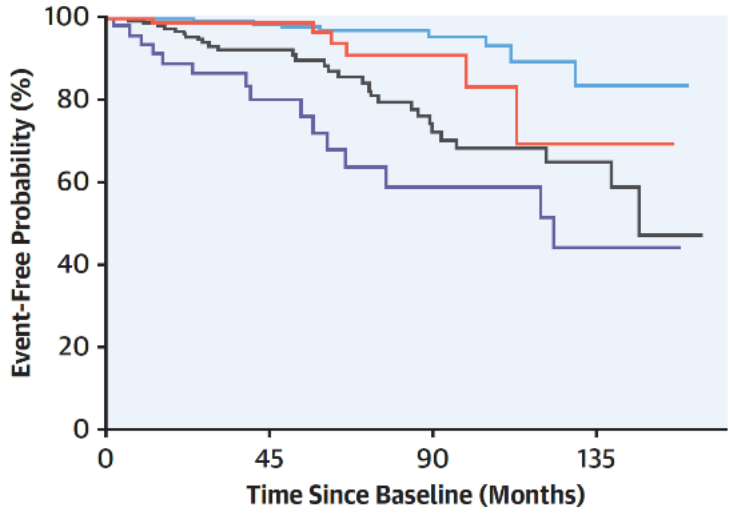
– ? Closure + Anticoagulation

Liu, Song, Palacios et al. JACC -Int. 2020 Dec 14;13(23):2745-2752

- **Pts with hypercoagulable state have highest risk of recurrence** (N=591; HR: 1.85; CI:1.09 to 3.16; p=0.024)
- (**4-15% per year stroke recurrence on med alone**)

- **In hypercoagulable pts, risk for recurrence was lower with PFO closure than medical therapy alone** (HR: 0.25; CI: 0.08 to 0.74; p = 0.012)

CENTRAL ILLUSTRATION Kaplan-Meier Cumulative Estimates of the Rate of the Primary Endpoint in Different Groups



No. at Risk:

Patent foramen ovale closure + without thrombophilia	282	151	63	6
Patent foramen ovale closure + with thrombophilia	89	51	19	2
Medical therapy + without thrombophilia	175	74	38	14
Medical therapy + with thrombophilia	45	23	10	4

Liu, K. et al. J Am Coll Cardiol Intv. 2020;13(23):2745-52.

PFO is a Multi-Organ System Disease with PFO-specific Risk Factors - OPPORTUNISTIC

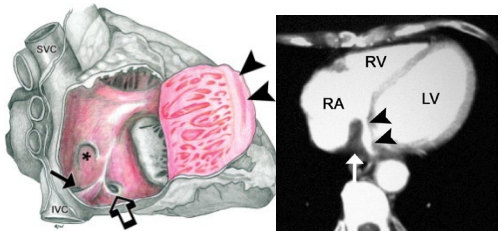
Emerging inherited and acquired risk factors associated with PFO-related stroke.

Organ involved	Inherited	Acquired
Cardiac	Atrial septal aneurysm Chiari's network Eustachian valve	
		Valsalva maneuver (weight lifting, position change etc.)
Circulatory	Hypercoagulable state	Hypercoagulable state
Pulmonary/upper airway		Provoked exercise desaturation Obstructive sleep apnea
Peripheral vascular	May–Thurner's syndrome	DVT, pelvic clots, and venous catheter related Air/long-distance travel Scuba diving
Neurologic	Migraine with aura	Migraine with aura

Ning, Lo Buonanno et al. Pharmacol Ther. 2013 Aug;139(2):111-23
Ning, Gonzales. NEJM. 2013 Oct 31;369(18):1736-48

MGH 1811
MingMing Ning MD, MMSc

Sacco et al. 1989; Hagen et al. 1984; Lechat et al. 1988; Webster et al. 1988; Adams et al. 1993; Petty et al. 1999; Meissner et al. 1999; Handke et al. 2007; Homma et al. 2002; Lamy et al. 2002; Overell et al. 2000; Mas et al. 2001. Messe et al 2004, Kizer et al. 2005; Hara et al. 2005; Wu et al 2007; Furlan et al 2012, Messe SR et al 2004. Florez JC et al. 2003. Cramer SC et al 2004.Greer DM, Buonanno FS. 2001. Ning et al. Stroke 2008. Kiernan TJ et al. Stroke 2009. Kent , Thaler et al . Neurology 2013. Saver et al 2013



Blood - COVID and CLOTTING

- Meta-analysis: 66 studies (n= 28,173) to estimate risk of VTE in COVID-19
- Overall VTE risk in hospitalized patients with COVID-19 is 14%, “despite rigorous thromboprophylaxis”
- ICU highest - 23% ; Non-ICU 8%; Risk of potentially life-threatening pulmonary embolism: 10 and 18%
- “patients who developed DVT/PE had significantly higher **D-dimer**… indicates an activated coagulation system. This finding might be used to help develop personalized, risk-stratified thromboprophylaxis strategies in the future”

“DVT was detected in almost half of the hospitalised COVID patients who had been systematically screened for thrombosis using ultrasound.”

Stroke and Thromboprophylaxis in the era of COVID-19

Alice Ma, MBBS • Carlos S. Kase, MD • Ashkan Shoamanesh, MD • Mohamad Abdalkader, MD • Aleksandra Pikula, MD • Anvitha Sathya • Luciana Catanese, MD • Alun T. Ellis, MBBCh,MSc • Thanh N. Nguyen, MD,FRCPc • Show less

Published: October 09, 2020 • DOI: https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105392

	Indication	LMWH, suggested doses CrCl <30 ml/min	Heparin CrCl <30ml/min
Standard Dose	No identifiable risk factors	Enoxaparin 40 mg qd	Heparin 5000 u bid
Consider high intensity dose	Weight >100 kg SIC>4 D Dimer >6x normal	Enoxparin 40 mg bid	No bolus and low ptt goal
Consider full anticoagulation	Confirmed DVT/PE Established indication for anticoagulation	1 mg/kg enoxaparin bid	Bolus and standard apt goal 55-90 seconds

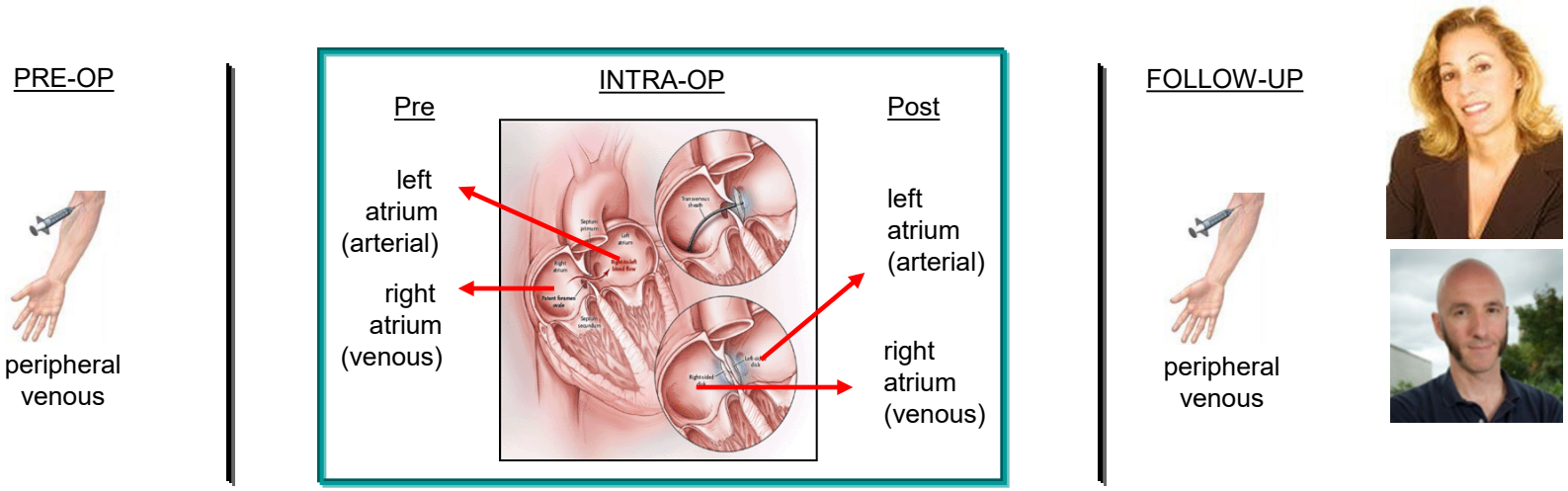
JSCVD in press Oct 2020

Courtesy of Dr Thanh Nguyen

Nopp, Moik, Ay et al.*Thrombosis and Haemostasis*, 2020
Ma, Kase, Nguyen et al. JSCVD. Oct 2020

MingMing Ning
MD, MMSc

Role of the Lung in PFO – Silent Hero



Neurovascular Mediators Decrease in Arterial Blood Post PFO Closure

- **Serotonin (5-HT)** decreased immediately post PFO closure.
- **Oxidized cholesterol** particles also decreased rapidly.
- This suggests that prior to closure, neurovascular mediators had been avoiding lung filtration via PFO.

AHA ISC Siekert Lecture 2011; Ning et al Stroke, 2011, Stroke 2015; Deng et al. Neurology, 2021

Proteomic signatures of serum albumin-bound proteins from stroke patients with and without endovascular closure of PFO are significantly different and suggest a novel mechanism for cholesterol efflux

Lopez *et al. Clinical Proteomics* 2015, **12**:2
http://www.clinicalproteomicsjournal.com/content/12/1/2

Mary F Lopez[1*], Bryan Krastins[1], David A Sarracino[1], Gregory Byram[1], Maryann S Vogelsang[1], Amol Prakash[1], Scott Peterman[1], Shadab Ahmad[1], Gouri Vadali[1], Wenjun Deng[2], Ignacio Inglessis[2], Tom Wickham[2], Kathleen Feeney[2], G William Dec[2], Igor Palacios[2], Ferdinando S Buonanno[2], Eng H Lo[2] and MingMing Ning[2]

Heart – Brain Signaling in PFO Related Stroke: Differential Plasma Proteomic Expression Patterns Revealed with a Two-Pass LC-MS/MS Discovery Workflow

J Investig Med. 2012 December ; 60(8): 1122–1130.

Mary F Lopez[1], David A Sarracino[1], Maryann Vogelsang[1], Jennifer N Sutton[1], Michael Athanas[1], Bryan Krastins[1], Alejandra Garces[1], Amol Prakash[1], Scott Peterman[1], Zareh Demirjian[2], Inglessis-Azuaje I Ignacio[2], Kathleen Feeney[2], Mikaela Elia[2], David McMullin[2], G William Dec[2], Igor Palacios[2], Eng H Lo[2], Ferdinand Buonanno[2], and MingMing Ning[2]

[1]ThermoFisher Scientific BRIMS, 790 Memorial Dr., Cambridge, MA 02139

[2]Clinical Proteomics Research Center and Cardio-Neurology Clinic, Dept of Massachusetts General Hospital, Harvard Medical School, Boston, MA

Risk of Clotting

Established

- **Venous** > Arterial:
  → Protein C/S, Factor V Leiden
  → Prothrombin Gene Mutation, ATIII

- **Arterial = Venous**
  → Antiphospholipid Antibodies (IgG, IgM), Lupus Anticoagulant (LA), anti-beta2glycoprotein

- **Arterial** > Venous
  → Homocysteine

Disorder	Incidence, %
Antiphospholipid antibody syndrome	28
Activated protein C resistance	25
Elevated coagulation factor VIII levels	25
Malignancy	15
Sticky platelet syndrome	14
Protein C deficiency	10
Protein S deficiency	10
Homocystinemia	10
Prothrombin G20210A	5-10
Plasminogen deficiency	2-3
Dysfibrinogenemia	1.5
Plasminogen activator inhibitor increase	1-3
Tissue plasminogen activator deficiency	1

Thomas, Arch Intern Med,

Emerging

- **COVID related**:
  → anti-phospholipid related hypecoagulability
  → complement pathways
  → endothelial activation of clotting

- **Age, Cancer, Pregnancy** etc

- **PFO physiology** enhancing clot formation
  → 5-HT, hcy, ox-chol

MGH 1811
MingMing Ning
MD, MMSc

- Mrs M just had her 3th child; her PFO was closed after her first child when she had a PFO related stroke 3 years ago

- In addition to PFO closure, hematology, high risk OB work with patient at pre-conception, during and post. D-dimer routinely checked and followed

- **Most risk during early trimester and within 6-8 weeks post partum (most hypercoagulable)** – LMWH each pregnancy and at least 2 months post partum

- PLAN AHEAD AND FOLLOW CLOSELY

Chen L, Deng W, Palacios I, Inglessis-Azuaje I, McMullin D, Zhou D, Lo EH, Buonanno F, Ning M. J Investig Med. 2016 Jun;64(5):992-1000.

Box 1 Recommendations for clinical treatment and workup for patent foramen ovale (PFO) stroke patients who wish to undergo pregnancy

1. Pre-conception counseling from a specialist multidisciplinary team with neurological, cardiac, hematological, and obstetric experts, along with the primary care physician.
2. Delivery planning should be a multidisciplinary effort (among, eg, the obstetrician, cardiologist, anesthesiologist, neurologist, hematologist, and patient) communicated well in advance of the due date.
3. Hypercoagulable panel blood testing to stratify clotting risk (eg, D-dimer, partial-thromboplastin time, activated partial-thromboplastin time, protein C, protein S, antiphospholipid antibodies, anti-β2glycoprotein, lupus anticoagulant, prothrombin gene mutation, antithrombin III, homocysteine, Factor V Leiden)
4. Pelvic magnetic resonance venography or CT venography to look for the May-Thurner Syndrome (MTS)—increased abdominal girth during pregnancy can worsen MTS due to compression of abdominal vasculature, increasing the risk of pelvic venous thrombosis
5. Cardiac workup including EKG to detect myocardial infarction and arrhythmia; Holter monitoring or extended cardiac monitoring to detect cardiac arrhythmia, especially atrial fibrillation; Transthoracic echocardiograph to assess PFO features, such as atrial septal aneurysm (ASA) and the degree of shunting during valsalva.
6. For patients with high-risk status such as hypercoagulation state, consider ASA+/−low molecular weight heparin during pregnancy.
7. PFO endovascular closure may be considered for secondary prevention of stroke in patients with PFO

MingMing Ning
MD, MMSc

PFO is an etiology for stroke in young and older adults

- PFO is an etiology for stroke in young and older adults (Handke 2007) - **Age range from 44-75**

After adjusting for age, plaque thickness, risk factors (CAD, HTN etc**), PFO was independently associated with cryptogenic stroke in both the younger group** (**odds ratio, 3.70**; 95% CI, 1.42 to 9.65; **P = 0.008**) and **the older group** (**odds ratio, 3.00**; 95% CI, 1.73 to 5.23; **P<0.001**).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Patent Foramen Ovale and Cryptogenic Stroke in Older Patients

Michael Handke, M.D., Andreas Harloff, M.D., Manfred Olschewski, M.Sc., Andreas Hetzel, M.D., and Annette Geibel, M.D.

ABSTRACT

BACKGROUND

Studies to date have shown an association between the presence of patent foramen ovale and cryptogenic stroke in patients younger than 55 years of age. This association has not been established in patients 55 years of age or older.

METHODS

We prospectively examined 503 consecutive patients who had had a stroke, and we compared the 227 patients with cryptogenic stroke and the 276 control patients with stroke of known cause. We examined the prevalences of patent foramen ovale and of patent foramen ovale with concomitant atria transesophageal echocardiography. We also patients (<55 years of age) and those for the 3

RESULTS

The prevalence of patent foramen ovale was with cryptogenic stroke than among those w younger patients (43.9% vs. 14.3%; odds ratio 1.89 to 11.68; P<0.001) and older patients (28.3 1.70 to 5.01; P<0.001). Even stronger was the

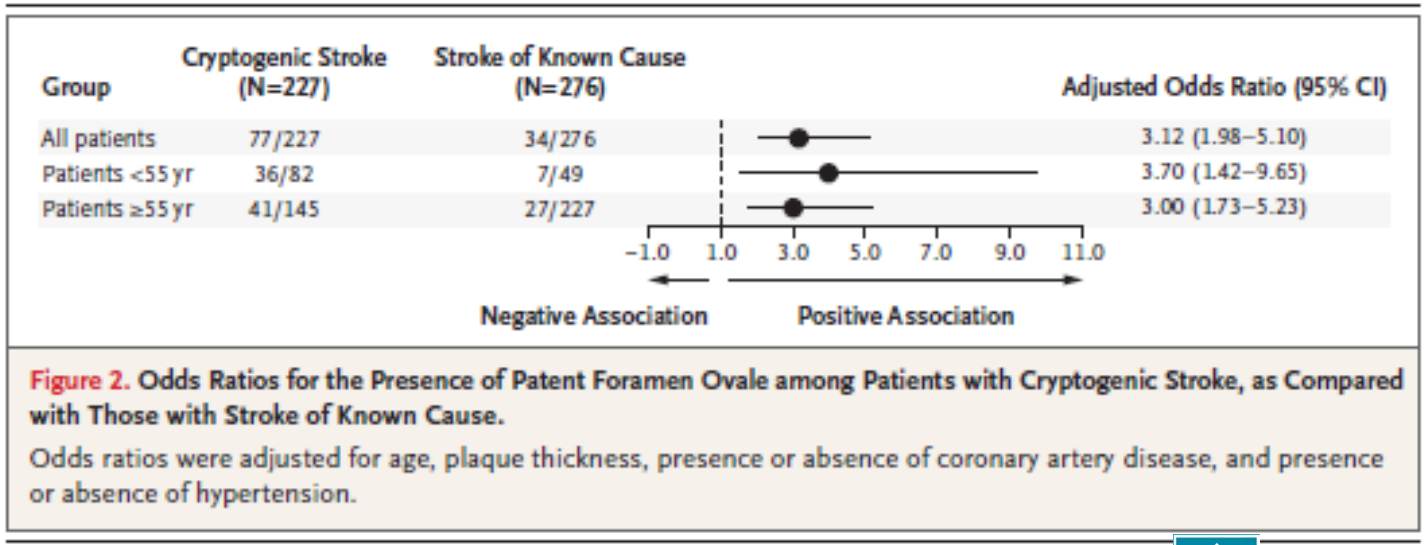
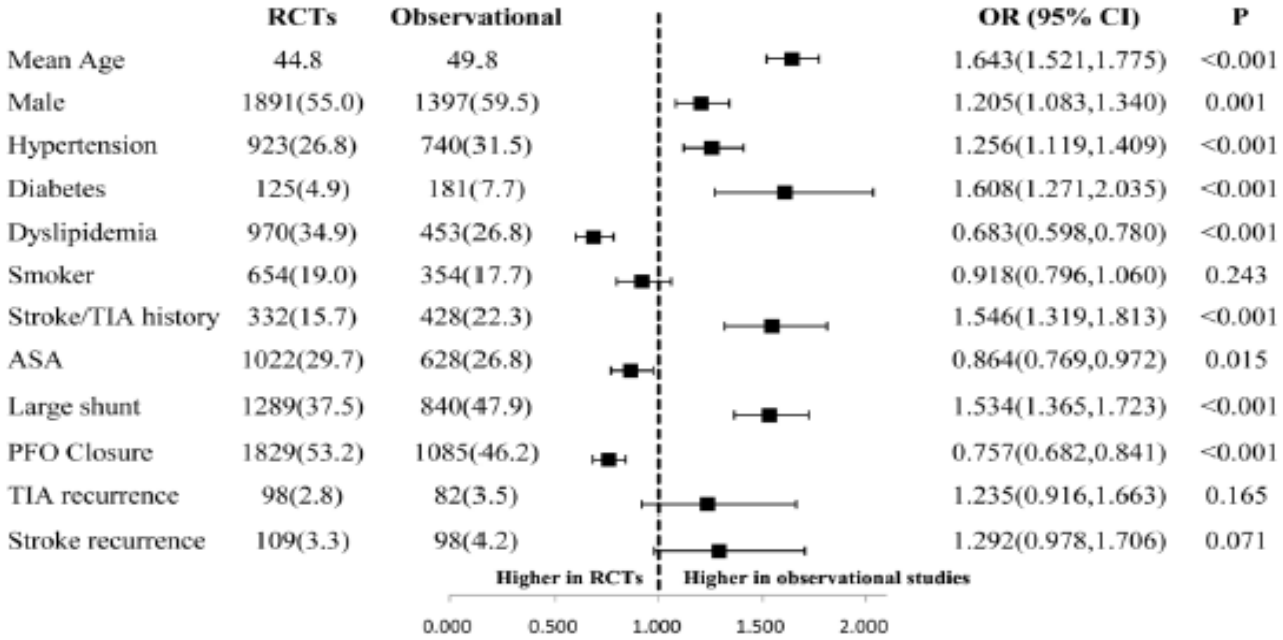


Figure 2. Odds Ratios for the Presence of Patent Foramen Ovale among Patients with Cryptogenic Stroke, as Compared with Those with Stroke of Known Cause.

Odds ratios were adjusted for age, plaque thickness, presence or absence of coronary artery disease, and presence or absence of hypertension.

MingMing Ning
MD, MMSc

Meta-analysis All Non-RCT Observational Studies Comparing PFO endovascular closure vs Medical Treatment



3456 cryptogenic stroke/TIA (N = 1514 closure vs N= 1942 medical therapy); F/U17.6～70.8 M

→ **Recurrent stroke and/or TIA significantly lower in closure** vs medical therapy (3.7% vs 10.4%; OR 0.35; CI - 0.26-0.48; *P*<0.00001) supporting RCT data.

→ **Benefit did not differ in age (<60yo vs >60yo)**

→ **Anti-coagulant** (VKA) therapy was associated with a lower rate of recurrent events vs anti-platelet therapy (8.4% versus 15.8%; OR 0.48, 95% CI 0.30 to 0.75; P=0.001), but increased the **risk of bleeding** (4.4% versus 0.37%; OR 8.67, 95% CI 2.76 to 27.19; P=0.0002).

Liu K, Song B, Deng WJ, Palacios I, Inglessis I, Wang X, Lo EH, Buonanno F, Ning MM et al. Stroke 2018

MGH 1811
MingMing Ning
MD, MMSc

Newer anticoagulant with even lower bleeding risk emerging…

ORIGINAL ARTICLE

Abelacimab for Prevention of Venous Thromboembolism

Peter Verhamme, M.D., B. Alexander Yi, M.D., Ph.D., Annelise Segers, M.D., Janeen Salter, B.S.N., Daniel Bloomfield, M.D., Harry R. Büller, M.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the ANT-005 TKA Investigators*

ABSTRACT

BACKGROUND
The role of factor XI in the pathogenesis of postoperative venous thromboembolism is uncertain. Abelacimab is a monoclonal antibody that binds to factor XI and locks it in the zymogen (inactive precursor) conformation.

METHODS
In this open-label, parallel-group trial, we randomly assigned 412 patients who were undergoing total knee arthroplasty to receive one of three regimens of abelacimab (30 mg, 75 mg, or 150 mg) administered postoperatively in a single intravenous dose or to receive 40 mg of enoxaparin administered subcutaneously once daily. The primary efficacy outcome was venous thromboembolism, detected by mandatory venography of the leg involved in the operation or objective confirmation of symptomatic events. The principal safety outcome was a composite of major or clinically relevant nonmajor bleeding up to 30 days after surgery.

RESULTS
Venous thromboembolism occurred in 13 of 102 patients (13%) in the 30-mg abelacimab group, 5 of 99 patients (5%) in the 75-mg abelacimab group, and 4 of 98 patients (4%) in the 150-mg abelacimab group, as compared with 22 of 101 patients (22%) in the enoxaparin group. The 30-mg abelacimab regimen was noninferior to enoxaparin, and the 75-mg and 150-mg abelacimab regimens were superior to enoxaparin ($P<0.001$). Bleeding occurred in 2%, 2%, and none of the patients in the 30-mg, 75-mg, and 150-mg abelacimab groups, respectively, and in none of the patients in the enoxaparin group.

CONCLUSIONS
This trial showed that factor XI is important for the development of postoperative venous thromboembolism. Factor XI inhibition with a single intravenous dose of abelacimab after total knee arthroplasty was effective for the prevention of venous thromboembolism and was associated with a low risk of bleeding. (Funded by Anthos Therapeutics; ANT-005 TKA EudraCT number, 2019-003756-37.)

"Atrial Fibrillation Study with Abelacimab Stopped Early by the Data Monitoring Committee Due to an Overwhelming Reduction in Bleeding as Compared to a DOAC (Direct Oral Anticoagulant)"

Published: Sep 18, 2023

"CAMBRIDGE, Mass.---- AZALEA-TIMI 71 Phase 2 study in 1,287 patients with atrial fibrillation at moderate-to-high risk of stroke, met its primary endpoint. The study has been **stopped early by the Data Monitoring Committee due to an overwhelming reduction in the composite of major and clinically relevant non-major bleeding** in patients taking abelacimab compared with patients taking rivaroxaban, a leading standard-of-care DOAC. In addition, abelacimab is the first and only Factor XI inhibitor to demonstrate an unprecedented reduction in major bleeding compared to a DOAC… Full results of AZALEA-TIMI 71 will be presented at an upcoming scientific congress."

•***Abelacimab - Dual-Acting Factor XI / XIa Inhibitor***

Question for the near future:

Can emerging ultra low bleed risk AC alter the risk and benefit profile for PFO treatment?

Summary…

- **Multi-disciplinary approach** and understanding **mechanisms of brain-heart signaling** are key to treatment of PFO related stroke**. Find the "provoking" risk factor in workup**

- **Remember the patients excluded from clinical trials: Hypercoagulable PFO patients are at the HIGHEST risk of recurrence.**
  Clotting status obtained from hypercoagulable panel is crucial to tailor therapy.
- Cost effective to curb disability of recurrent stroke

- **New opportunistic risk such as COVID increase injury** via clotting and systemic endothelial injury, highlighting the importance of pulmonary detoxification in PFO.

- **PFO right-to-left shunting is a novel hypercoaguable state –** enhance venous arterial mixing;
- bypassing lung's detoxification of hypercoagulable molecules from venous blood

MASSACHUSETTS GENERAL HOSPITAL

Cardio-Neurology Clinic

Phone: 617-724-4458
MassGeneral Hospital for Children

The Massachusetts General Hospital Cardio-Neurology Clinic provides comprehensive neurological evaluation and care for patients with cerebrovascular disorders related to the heart, including patent foramen ovale (PFO).

mmning@mgh.harvard.edu