Reducing Your Risk of Stroke

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What is a stroke?

- Ischemic
  - 85%
  - Loss of blood flow to tissue
  - Embolism-a clot travels from heart or blood vessel up to the brain
  - Thrombosis-clot forms locally
- Hemorrhagic
  - Bleeding into the brain
  - 15%

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Symptoms

- Any sudden changes can be a stroke
- Speech, sensation, vision, weakness, unsteadiness, headaches, confusion
- What to do if stroke suspected?
  - Call 911
  - Can intervene as long as 24 hrs after onset, including waking up with symptoms
  - Many advanced technologies continue to evolve

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Stroke Statistics

- 140,000 deaths per year
- 600,000 new strokes per year
- $34 Billion per year in cost
- Major source of diability

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Genetics

- Complex but probably contributes to 50% of risk
- Clotting disorders

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Hypertension

- 30% of Americans
- Often untreated and unknown
- Increases risk of heart disease and stroke
- Usually no symptoms
- 140/90, high
- 120/80, normal

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Smoking

- Causes 1/3 of cardiovascular deaths
- Raises triglycerides
- Lowers good cholesterol
- Increases plaque build up in vessels
- Lung disease can strain the heart

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Diabetes

- Elevated blood sugar
- Damages blood vessels
- Secondary effects on organs like heart, brain, kidneys

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Inactivity

- There is no magic amount.
- Move! Do something to get motivated.
- Increases risk of weight gain, high blood pressure, diabetes, depression

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Age

- Stroke can occur at any age
- Older age is risk factor for stroke
- Harder to recover from stroke with aging

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High Cholesterol

- Chronic effects on blood vessels
- Still feeling that lower is better
- Treatment with diet
- Medications may be indicated before stroke or after

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Others

- Trauma to blood vessels with stretch or just random tear in the wall (dissection)

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What can be done if stroke occurs?

- Acute blood thinners
  - Tissue plasminogen activator (tPA)
- Pull that clot out
  - Catheters
- Open that narrow carotid artery
  - Surgery or stenting
- Fix those heart abnormalities
  - Amazing techniques that Dr. Iyengar will discuss

Stroke: Straight from the heart

Srinivas Iyengar, MD
Director, Structural Heart
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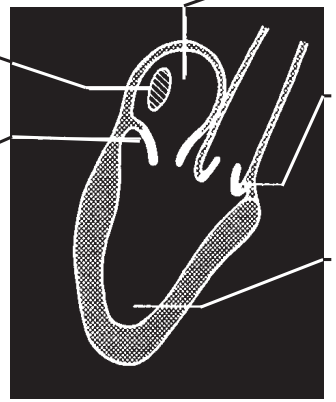
What causes stroke?

- Emboli from valves/LV
- Vascular (i.e., carotid/aortic)
- Bleeding
- AF (mainly LAA)
- Cryptogenic (i.e,. PFO)
- HTN

Sources of Cardiogenic Emboli



Paradoxical Emboli
- Patent foramen ovale
- Atrial septal defect

Mitral Valve
- Infective endocarditis
- Non-bacterial endocarditis
- Myxomatous valvulopathy
- Prosthetic valves
- Vegetations due to prothrombotic states

Left Atrium
- Atrial fibrillation
- Myxoma
- Atrial septal aneurysm

Aortic Valve
- Calcific stenosis
- Infective endocarditis
- Prosthetic valve

Left Ventricle
- Ischemic dyskinesis
- Cardiomyopathy
- Thrombi due to prothrombotic states

Lowell Satler MD, CRT 2010

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Atrial Fibrillation

- Irregular heart rhythm
- Basically, the top part of the heart (“atria”) don’t communicate electrically with the bottom (“ventricles”)
- Results in symptoms of SOB, light-headedness, and palpitations

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Causes

- High blood pressure.
- Heart attacks.
- CAD
- Abnormal heart valves.
- Heart defects you're born with (congenital)
- An overactive thyroid gland or other metabolic imbalance.
- Exposure to caffeine, tobacco or alcohol

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Diagnosis

- ECG is mandatory
- Not every “irregular heart rhythm” is AF!
- PVCs, APCs, skipped beats can all mimic feelings of AF
- AF does not have to be chronic, it can be short-lasting or come/go (i.e., PAF)

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Treatment

- Medications to control HR (i.e., beta-blockers, Ca-channel blockers) are first line
- Anti-arrhythmic medications can be used to control rhythm
- Cardioversion (either electrically or chemically) can be utilized for symptomatic AF
- Ablation (surgically or percutaneously) can also be utilized

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But what else does AF cause?

- Stroke!!
- The left atrial appendage (LAA) which is in the left atrium can collect blood which forms clots that can break free in patients with AF.
- That's why we place patients with AF who have elevated risks for stroke on blood thinners.

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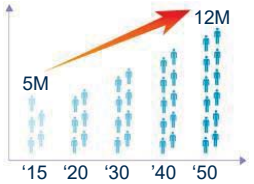
Blood Thinners

- Work very well as long as compliance is maintained and no side effects seen
- Warfarin- cheap but compliance with diet/testing an issue as well maintaining adequate levels
- NOACs- Costly, lack readily available reversal agents
- All the above can exacerbate bleeding

AF is a Growing Problem Associated with Greater Morbidity and Mortality

WATCHMAN™ LEFT ATRIAL APPENDAGE CLOSURE DEVICE

AF = most common cardiac arrhythmia, and growing



~5 M
people with AF in U.S., expected to more than double by 2050[1]

AF increases risk of stroke

5x
greater risk of stroke with AF[2]

- Higher stroke risk for older patients and those with prior stroke or TIA
- 15-20% of all strokes are AF-related
- AF results in greater disability compared to non-AF-related stroke

SH-432401-AC DEC2016

1. Go AS. et al, Heart Disease and Stroke Statistics—2013 Update: A Report From the American Heart Association. Circulation. 2013; 127: e6-e245.
2. Holmes DR, *Seminars in Neurology* 2010;30:528–536.
Wolf PA et al. Duration of Atrial Fibrillation and the Imminence of Stroke: The Framingham Study. Stroke 1983; 14:664-667

AF-related strokes are debilitating

WATCHMAN™ LEFT ATRIAL APPENDAGE CLOSURE DEVICE

Stroke

#1 cause of **adult disability** worldwide[1]

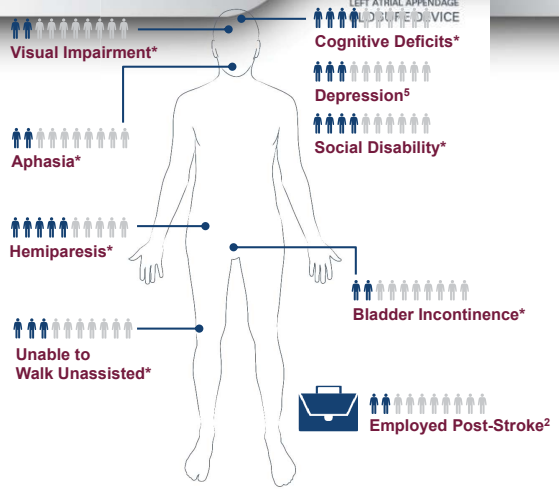
AF-related Stroke

1.5X higher **disability**[3**]

2X higher **mortality**[3**]

70% result in **death or permanent disability**[6]

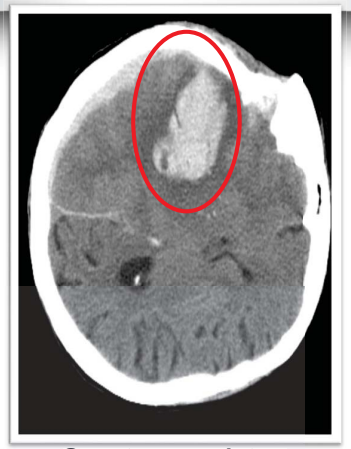
*at 6 months post-stroke[4]
**compared with stroke patients without AF



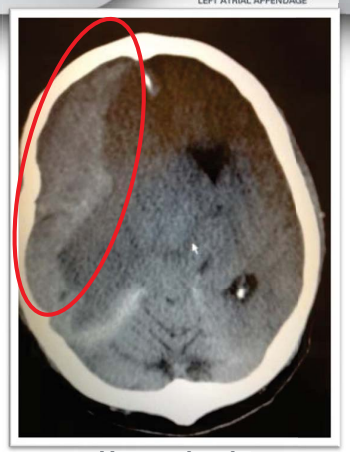
SH-432401-AC DEC2016

[1]Chee and Tan. *Med J Malaysia* 69.3 (2014): 119-23. [2]Sreedharan et al. *Journ of the neurological sciences* 332.1 (2013): 97-101. [3]Lamassa et al. *Stroke* 32.2 (2001): 392-398.[4]Kelly-Hayes et al. *Journ of Stroke and Cerebrovascular Diseases* 12.3 (2003): 119-126. [5]Loo and Gan. *International Journ of Stroke* 7.2 (2012): 165-167. [6]Holmes DR, *Seminars in Neurology* 2010;30:528–536.

Anticoagulant Therapy Carries Risk of Intracerebral Hemorrhage or Death



Spontaneous intra-parenchymal bleed



Hemorrhagic transformation

Validated Scoring Systems to Assess Stroke Risks

CHA_2DS_2VASc Score (Stroke Risk)[3]

	Condition	Points
C	Congestive heart failure	1
H	Hypertension (SBP>160)	1
A_2	Age ≥ 75 years	2
D	Diabetes mellitus	1
S_2	Prior stroke, TIA or thromboembolism	2
V	Vascular disease (PAD, MI)	1
A	Age 65-74 years	1
Sc	Sex category (Female)	1
	TOTAL POINTS	

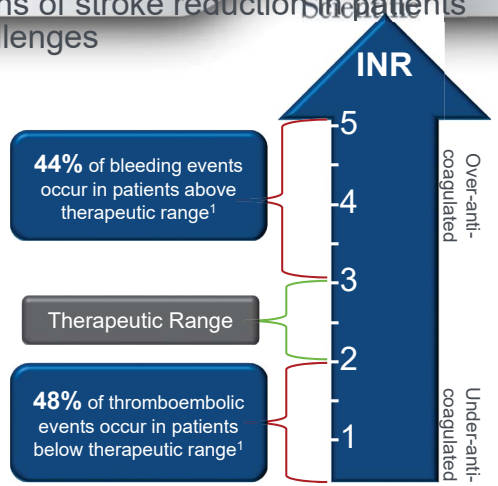
Score	Yearly Stroke Risk (%)		
	No Warfarin	With Aspirin[2]	With Warfarin[2]
0	0	0	0
1	1.3	1.0	0.5
2	2.2	1.8	0.8
3	3.2	2.6	1.1
4	4.0	3.2	1.4
5	6.7	5.4	2.3
6	9.8	7.8	3.4

3. *Chest.* 2010 Feb;137(2):263-72.

Stroke Treatment Option: Warfarin

Warfarin is an effective means of stroke reduction in patients with AF but can present challenges

- Many patients spend a significant amount of time outside of the therapeutic range.
- Warfarin tops the list for emergency hospitalizations for adverse drug events in older Americans[2]



1 Oake N, et al. *Can Med Assoc J.* 2007:176(11);1589−1594
2 Budnitz, MD, MPH. et al. *Annals of Internal Medicine.* 2007:147(11); 229

Challenge: Adherence and Major bleed rates with Novel Oral Anticoagulants (NOACs)

Treatment	Study Drug Discontinuation Rate	Major Bleeding (rate/year)
Rivaroxaban[1]	24%	3.6%
Apixaban[2]	25%	2.1%
Dabigatran[3] (150 mg)	21%	3.3%
Edoxaban[4] (60 mg / 30 mg)	33 % / 34%	2.8% / 1.6%
Warfarin[1-4]	17 – 28%	3.1 – 3.6%

For those that remain adherent, there is an annual compounding bleeding risk

1Connolly, S. NEJM 2009; 361:1139-1151 – 2 yrs follow-up (Corrected) 2Patel, M. NEJM 2011; 365:883-891 – 1.9 yrs follow-up, ITT 3Granger, C NEJM 2011; 365:981-992 – 1.8 yrs follow-up; 4Giugliano, R. NEJM 2013; 369(22): 2093-2104 – 2.8 yrs follow-up.

Results from different clinical investigations are not directly comparable.
Information provided for educational purposes only

Non-Valvular Atrial Fibrillation (NVAF), Stroke, and Current Treatment Options

- AF is a Growing Problem Associated with Greater Morbidity and Mortality
  - 5x increased risk of stroke
  - 90% of clots formed in LA come from LAA
- Current treatments with warfarin or NOACS are effective, but many patients stop taking the medications
  - ~1 in 4 patients discontinue blood thinners after 2 years
- Anti-coagulation bleeding risk compounds over time; may not be viable as a long-term solution for some patients

WATCHMAN LAAC Device Overview

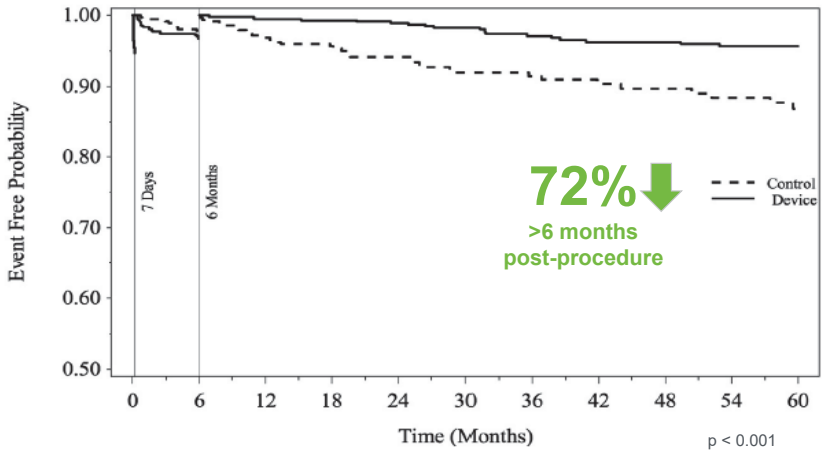
Boston Scientific

Designed specifically for the left atrial appendage

- Nitinol frame radially expands to maintain position in LAA
- 10 fixation anchors engage LAA tissue for stability and retention
- Polyethylene terephthalate (PET) membrane designed to block emboli from exiting the LAA

WATCHMAN Major Bleeding Reduction Superior to Warfarin 6-months Post Procedure

Freedom of Major Bleeding Over 3 Adjunctive Pharmacotherapy Intervals



Price, M. J., V. Y. Reddy, et al. JACC: CV Interv 2015; 8(15): 1925-1932

PROTECT AF:
WATCHMAN Disabling Stroke Reduction Superior to Warfarin

WATCHMAN™

Significant Reduction in Disabling Strokes

PROTECT AF	Event Rate (per 100 pt-yrs) WATCHMAN N=463	Warfarin N=244	Rate Ratio (95% CrI)	Posterior Probabilities, % Non-Inferiority	Superiority
Stroke (all)	**1.5**	**2.2**	**0.68** (0.42, 1.37)	**>99**	**83**
Disabling	**0.5**	**1.2**	**0.37** (0.15, 1.00)	**>99**	**98**
Non-disabling	**1.0**	**1.0**	**1.05** (0.54, 2.80)	**89**	**34**

Disabling stroke defined as Modified Rankin Score 3-6

Bayesian – Posterior prob for NI must be ≥97.5%; Posterior Prob for Superiority must be >95%
Reddy, et al. JAMA. 2014

Patient Populations

Non-Valvular A-Fib Population

High Risk for Stroke (CHA_2DS_2-VASC ≥ 2)

Tolerant to OAC

Balance stroke risk reduction benefit vs. bleeding risk

Patients w/ appropriate rationale to seek a non-pharmacologic alternative to warfarin

- History of bleeding
- Fall risks / previous trauma
- Non-compliant / Labile INR's
- Lifestyle

Contraindicated

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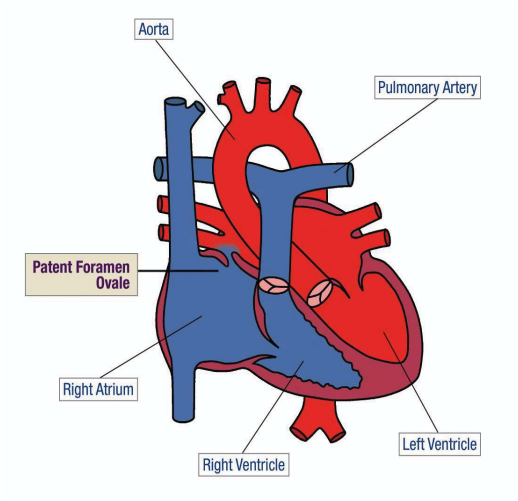
Patent Foramen Ovale (PFO)

- A patent foramen ovale (PFO) is a persistent, usually flap-like opening between the atrial septum primum and secundum at the location of the fossa ovalis
- In utero, the foramen ovale serves as a physiologic conduit for right-to-left shunting
- After birth, with the establishment of pulmonary circulation, the increased left atrial blood flow and pressure results in functional closure of the foramen ovale
- This functional closure is subsequently followed by anatomical closure of the septum primum and septum secundum

Patent Foramen Ovale (PFO)

- Persistent flap-like opening: atrial septum primum and secundum
- In utero, physiologic right-to-left shunting
- After birth, increased left atrial blood flow and pressure closes flap
- Anatomical closure follows



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Patent Foramen Ovale (PFO)

- The association between PFO and cryptogenic stroke has been identified increasingly over the last twenty years
- Prevalence of PFO in the general population ranges from 15% to 25%
- In patients with cryptogenic stroke prevalence of PFO is 40% to 60%
- Evidence is mounting to seek a better alternative than just prescribing anti-platelet medications (i.e., ASA, Plavix)

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Cryptogenic stroke

- Defined as cerebral ischemia of obscure or unknown origin
- The cause of CS remains undetermined because the event is transitory or reversible, investigations did not look for all possible causes, or because some causes truly remain unknown
- One third of the ischemic strokes is cryptogenic

Finsterer J, Acta Neurol Belg. 2010 Jun;110(2):135-47.

Cryptogenic Stroke

- 700,000 strokes/yr in US
- 80-85% ischemic
- 30-40% of strokes remain defined as cryptogenic

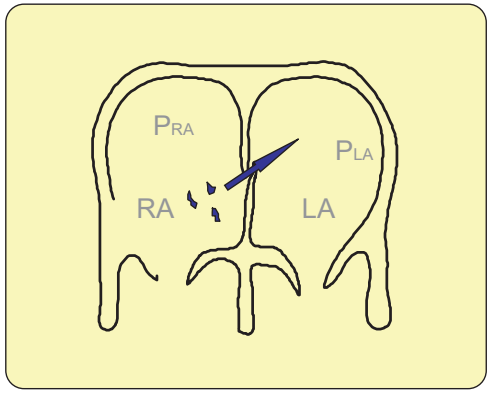
- 40-60% frequency of PFO among cryptogenic strokes
- ~100,000 strokes/yr with PFO as only identified potential etiology

Kim D, Saver JL. Reviews in Neurological Diseases 2005;2(1):1-7

Presumed Mechanism of Stroke with PFO

Pressure in RA > Pressure in LA:

- Early systole
- Valsalva
- Coughing
- Pulmonary hypertension
- COPD
- Pregnancy
- Asthmatics
- Wind instruments
- Decompression sickness (diving)
- High altitude flying
- Obstructive sleep patterns



Lowell Satler MD CRT 2010

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PFO closure studies

- Historically, a number of trials had not shown a major benefit from PFO closure for stroke reduction compared to medical therapy.
- However, a number of these studies had “signals” of a positive benefit with device utilization.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 21, 2013 VOL. 368 NO. 12

Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism

Bernhard Meier, M.D., Bindu Kalesan, Ph.D., Heinrich P. Mattle, M.D., Ahmed A. Khattab, M.D., David Hildick-Smith, M.D., Dariusz Dudek, M.D., Grethe Andersen, M.D., Reda Ibrahim, M.D., Gerhard Schuler, M.D., Antony S. Walton, M.D., Andreas Wahl, M.D., Stephan Windecker, M.D., and Peter Jüni, M.D., for the PC Trial Investigators*

PC Trial: Percutaneous Closure of Patent Foramen Ovale (PFO) in Cryptogenic Embolism

414 patients with PFO and prior ischemic stroke, TIA, or peripheral thrombotic event.

4-Year Follow-up	Closure (n = 214)	Medical Therapy (n = 210)	*P* Value
Primary Composite[a]	3.4%	5.2%	0.34
Nonfatal Stroke	0.5%	2.4%	0.14
TIA	2.5%	3.3%	0.56

[a] Death, nonfatal stroke, TIA, or peripheral embolism.

Conclusion: Percutaneous PFO closure does not reduce the risk of subsequent events in patients with cryptogenic thromboembolism.

Meier B, et al. *N Engl J Med.* 2013;368:1083-1091.

tctmd The Source for Interventional Cardiovascular News and Education

CARDIOVASCULAR RESEARCH FOUNDATION

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

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

N Engl J Med 2013;368:1092-100.
DOI: 10.1056/NEJMoa1301440

CONCLUSIONS

In the primary intention-to-treat analysis, there was no significant benefit associated with closure of a patent foramen ovale in adults who had had a cryptogenic ischemic stroke. However, closure was superior to medical therapy alone in the prespecified per-protocol and as-treated analyses, with a low rate of associated risks. (Funded by St. Jude Medical; RESPECT ClinicalTrials.gov number, NCT00465270.)

RESPECT: Closure of Patent Foramen Ovale (PFO) vs. Medical Therapy After Cryptogenic Stroke

980 pts randomized to medical therapy (warfarin or ≥1 antiplatelet) or closure using the Amplatzer PFO Occluder.

Recurrent Strokes per 100-Pt Yrs	Closure	Medical Therapy	*P* Value
Intention to Treat[a]	0.66	1.38	0.08
Per Protocol	0.46	1.30	0.03
As Treated	0.39	1.45	0.007

[a] Primary analysis.

Conclusion: In patients with cryptogenic stroke, percutaneous PFO closure does not appear to prevent recurrent stroke, although secondary analyses suggest possible efficacy.

Carroll JD, et al. *N Engl J Med.* 2013;368:1092-1100.

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CARDIOVASCULAR RESEARCH FOUNDATION

ORIGINAL ARTICLE

Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

Jean-Louis Mas, M.D., Geneviève Derumeaux, M.D., Benoît Guillon, M.D., Evelyne Massardier, M.D., Hassan Hosseini, M.D., Ph.D., Laura Mechtouff, M.D., Caroline Arquizan, M.D., Yannick Béjot, M.D., Ph.D., Fabrice Vuillier, M.D., Olivier Detante, M.D., Ph.D., Céline Guidoux, M.D., Sandrine Canaple, M.D., et al., for the CLOSE Investigators*

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

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CLOSE trial

- Randomized 663 patients with cryptogenic stroke to PFO closure, antiplatelet therapy alone, or oral anticoagulation
- PFO closure (plus long-term antiplatelet therapy) bested the antiplatelet therapy group
- No strokes occurred over a mean of 5.3 years among those randomized to PFO, whereas 14 strokes occurred in the antiplatelet-only group (HR 0.03; 95% CI 0-0.12).
- Three strokes occurred in the anticoagulation group, but there was inadequate statistical power to compare these outcomes with the other two groups.
- Conclusion: Among patients 16 to 60 years of age who had had a recent cryptogenic stroke attributed to PFO with an associated atrial septal aneurysm or large interatrial shunt, the rate of stroke was lower with PFO closure plus long-term antiplatelet therapy than with antiplatelet therapy alone

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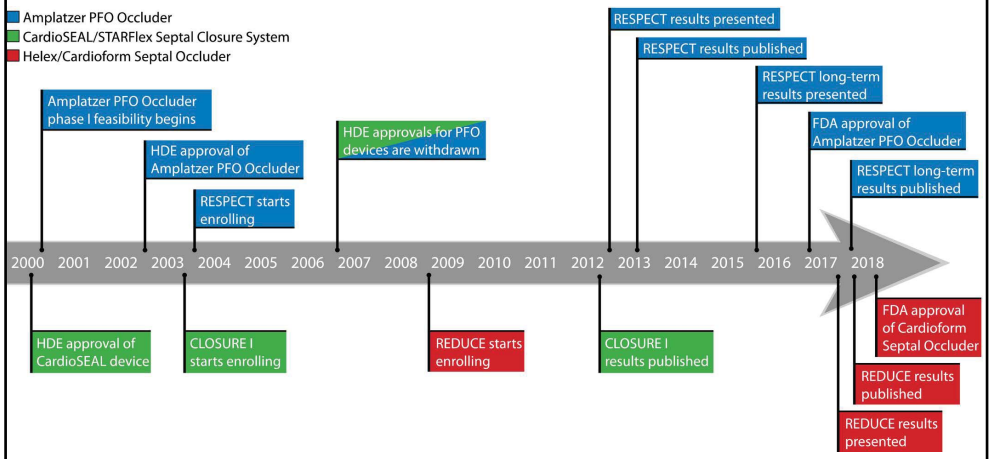
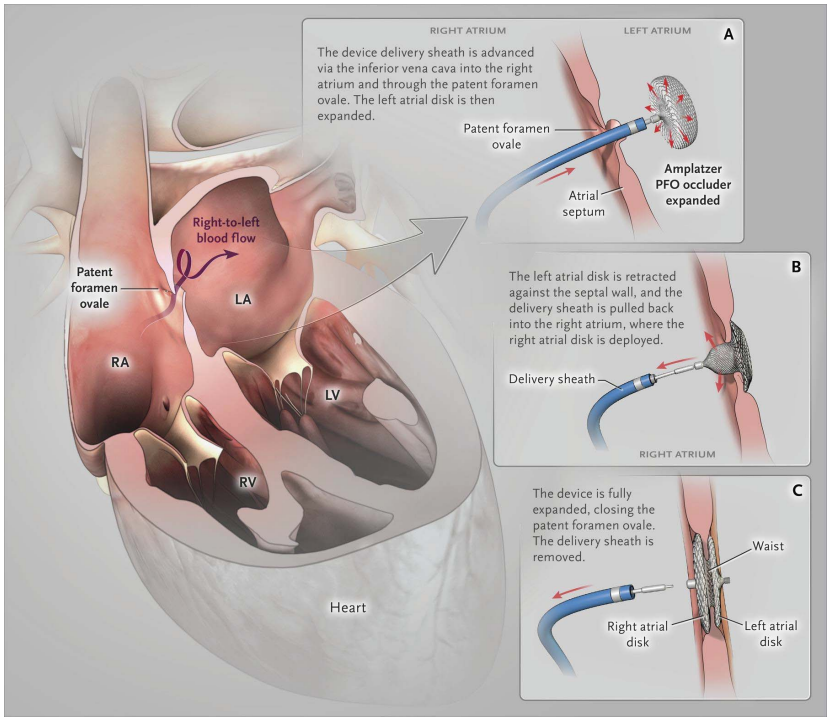
REDUCE trial

- Gore Helex Septal Occluder or the Gore Cardioform Septal Occluder (both WL Gore & Associates) against medical therapy alone, 2:1, in 664 patients
- Medical therapy consisted of aspirin alone, aspirin plus dipyridamole, or clopidogrel, with use of other antiplatelet agents or anticoagulants prohibited
- PFO closure was associated with significantly lower incidence of clinical ischemic stroke at 1.4% versus 5.4% (HR 0.23; 95% CI 0.09-0.62)
- Incidence of new brain infarctions was also significantly lower in the PFO closure group, although silent brain infarctions were no different



Patent Foramen Ovale Closure for Stroke Prevention and Other Disorders, Volume: 7, Issue: 12, DOI: (10.1161/JAHA.117.007146)



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Where to do we go now?

- Every patient who has a history of TIA/CVA needs a professional neurologic evaluation.
- If a PFO is found, alternate reasons for CVA need to be evaluated first (i.e., AF, carotid).
- If a patient indeed has a documented neurologic event and has no other viable explanation other than a PFO, then closure can be considered.

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Future directions

- But what about anti-coagulation therapy (i.e., Coumadin, NOACs) when compared to closure?
- Trials are ongoing
- If a patient has an alternate reason to be on AC tx (i.e., mechanical valves, hypercoagulable state) than would not push to close.

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Conclusions

- Stroke can occur from a number of different avenues
- Therapies to reduce stroke burden are essential to reduce morbidity/mortality associated with this condition
- Exciting to see future technologies develop

Thank You!

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