

REDEFINING STROKE PREVENTION

New data demonstrate the connection between closing a patent foramen ovale (PFO) and recurrent stroke reduction in select patients.

Together, improving life



Agenda

1. Prevalence of cryptogenic stroke and PFO
2. PFO closure efficacy data
3. PFO closure safety data
4. PFO closure patient selection
5. The procedure
6. Post-procedure care
7. PFO closure health economics
8. 2020 American Academy of Neurology Practice Advisory: PFO and secondary stroke prevention

The impact of stroke and recurrent events

- **Fifth leading cause of death** and the leading preventable cause of long-term severe disability.⁸
- Within the first 30 days, **one in eight strokes is fatal** and one in four strokes is fatal within the first year.⁹
- Stroke results in a persistent risk for **hospital readmission**.
 - Approximately 23% of all strokes are recurrent events.²
 - Approximately 21% of stroke patients are readmitted within 30 days.¹⁰
- Second cause of disability and costs the U.S. **\$34 billion** annually, including the cost of health care services, medications and lost productivity.¹¹
- 2020 estimated mean **lifetime cost*** of ischemic stroke for a single patient = **\$152,507**.¹²

* According to AHA, the mean lifetime cost of ischemic stroke in a single patient in 2014 was approximately \$140,048 in the United States. Cumulative rate of inflation from 2014 to 2020 is .65%. Estimated mean lifetime cost in 2020 = \$152,507.

Incidence of stroke and potential PFO connection

~795,000

People in the U.S. have a stroke annually.²

Of those 795,000 strokes,

87%

of those strokes are ischemic.³

Of the 87% of ischemic strokes,

~1/3

are cryptogenic.⁴

Of patients that have
cryptogenic strokes,

40–50%

have a PFO.⁵

Of patients with a PFO and prior
cryptogenic ischemic stroke,

20.4%

are at risk for recurrent stroke.⁶

Finally,

if there are no identifiable causes for a
stroke, then it could be due to the PFO.

Speakers

Both based in Richmond Virginia and work with Virginia Cardiology Specialists



- **James Garnett MD, FACC**
 - Structural and Interventional Cardiologist
 - UVA: Residency Internal Medicine
 - Wake Forest Baptist: Fellowships
 - General Cardiology and Interventional Cardiology



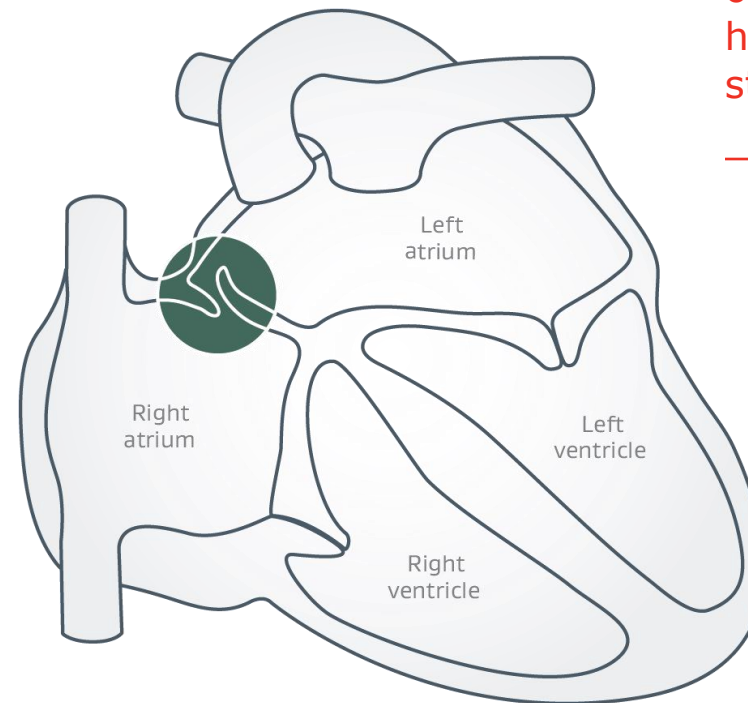
- **Matthew Chung MD**
 - Structural and Interventional Cardiologist
 - Duke: Residency Internal Medicine
 - Washington University in St Louis: Fellowships
 - General Cardiology and Interventional Cardiology
 - Duke: Fellowship in Structural Heart
 - Finalist 2016 Northwestern Cardiovascular Young Investigators Forum
 - Wash U 2018 Sobel Award for excellence in Cardiovascular Research

Cryptogenic stroke: The connection to patent foramen ovale

The American Heart Association states that the following conditions (but not limited to) should be considered if standard post-stroke workup has not determined probable causation for the cryptogenic stroke:¹

- Occult paroxysmal atrial fibrillation
- **PFO**
- Inherited thrombophilia
- Aortic arch atheroma

A PFO may permit emboli to travel from the right to the left atrium, possibly leading to a stroke.

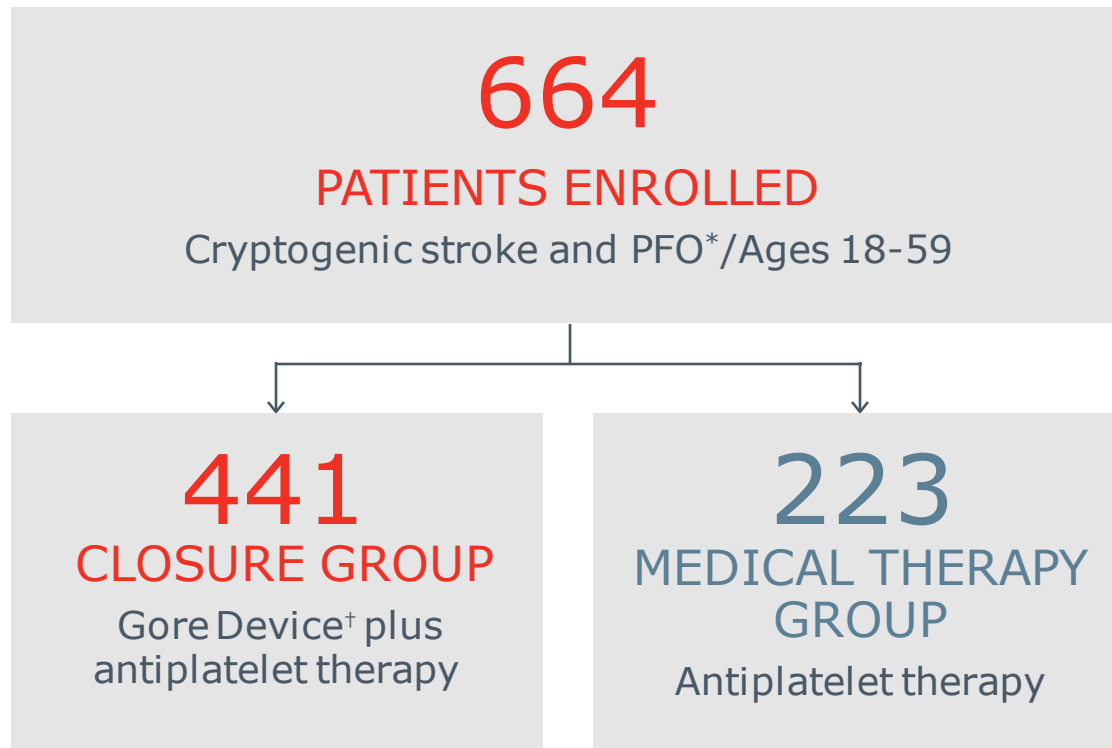


40–50%

of patients who have had a cryptogenic stroke have a PFO³

Gore REDUCE Clinical Study

Prospective, randomized, multicenter, multinational, controlled, open-label trial



Endpoints

- Freedom from recurrent clinical ischemic stroke through at least 24 months
- Incidence of new brain infarct (defined as clinical ischemic stroke or silent brain infarct) through 24 months

Patient selection

- Cryptogenic ischemic stroke within 180 days
 - Ischemic stroke = clinical symptoms \geq 24 hours or with MRI evidence of infarction
 - Cryptogenic
 - No stenosis > 50 percent or ulcerated plaque in relevant intra- or extra-cranial vessels
 - No atrial fibrillation or high risk source of cardioembolism
 - Non-lacunar (based on syndrome and/or size)
 - No evidence of hypercoagulable disorder
 - No other known cause of stroke
- PFO*
- No indication for anticoagulation
- No uncontrolled diabetes mellitus, hypertension, autoimmune disease, alcohol or drug abuse

Image confirmation

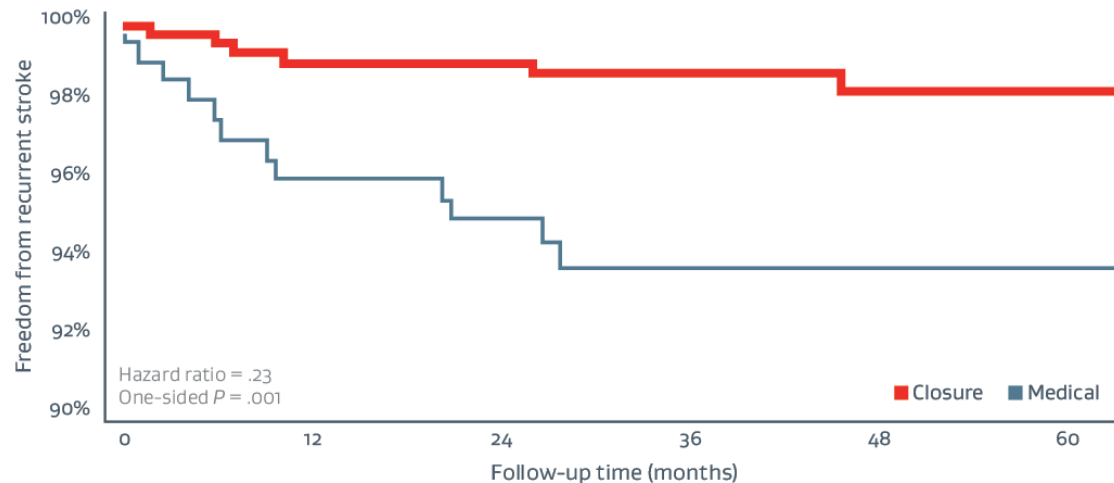
- MRI at baseline and at two years or at time of event

PFO closure: Proven to reduce recurrent stroke risk

REDUCE Study: As published in *New England Journal of Medicine*⁴

REDUCE Study sub-analysis

- As effective for patients 18–45 as patients 46–59 years^{†,4}
- All PFO shunt sizes and anatomies benefited from PFO closure^{†,4}



77% RELATIVE STROKE REDUCTION
with PFO CLOSURE + medical therapy
versus medical therapy alone.^{†,4}

4X THE PROTECTION against recurrent stroke than
medical therapy alone^{†,4}

Stroke risk reduction^{†,4}

| Closure group | Medical therapy group | Absolute stroke reduction [†] |
|---------------|-----------------------|--|
| 1.4% (6/441) | 5.4% (12/223) | 4% |

Safety profile

PFO closure plus medical therapy: Proven to be as safe as medical management alone^{†,4}

There was no significant difference in the overall serious adverse event (SAE) rate between the PFO closure and medical management group in the REDUCE Study.^{†,4}

REDUCE Study: any SAE

| Closure (N = 441) | Medical (N = 223) | P value [§] |
|-------------------|-------------------|----------------------|
| 102 (23.1%) | 62 (27.8%) | .22 |

REDUCE Study: SAEs related to the procedure or device^{||}

Low device/procedure SAE rates^{†,4}

6 (1.4%)

device-related

11 (2.5%)

procedure-related

No statistical difference in risk of serious atrial fibrillation, bleeding, deep vein thrombosis or pulmonary embolism with PFO closure.^{†,4}

REDUCE Study: SAEs of interest

| | Closure (N = 441) | Medical (N = 223) | P value [§] |
|---------------------------|-------------------|-------------------|----------------------|
| Any serious adverse event | 102 (23.1%) | 62 (27.8%) | .22 |
| Atrial fibrillation | 10 (2.3%) | 1 (0.4%) | .11 |
| Bleeding | 8 (1.6%) | 6 (2.7%) | .57 |
| Deep vein thrombosis | 0 | 2 (0.9%) | .11 |
| Pulmonary embolism | 2 (0.5%) | 1 (0.4%) | 1.00 |
| Migraine | 2 (0.5%) | 1 (0.4%) | 1.00 |

Low risk of device or procedure-related SAEs.^{†,4}

Safety profile

Understanding the risk of atrial fibrillation following PFO closure.

REDUCE Study: atrial fibrillation or flutter events^{†,4}

| | Closure (N = 441) | Medical (N = 223) | P value ⁵ |
|--|-------------------|-------------------|----------------------|
| Any atrial fibrillation or flutter | 29 (6.6%) | 1 (0.4%) | < .001 |
| Serious atrial fibrillation or flutter | 10 (2.3%) | 1 (0.4%) | .11 |
| Serious device-related atrial fibrillation or flutter | 2 (0.5%) | - | - |
| Serious procedure-related atrial fibrillation or flutter | 0 | - | - |

The REDUCE Study found post-implant atrial fibrillation generally does not result in long-term arrhythmia complications or require lifetime use of anticoagulation.^{†,4,5}

- The majority of atrial fibrillation and flutter events were non-serious.⁴
- Most of the atrial fibrillation and flutter events were resolved in two weeks.⁴

REDUCE Study: atrial fibrillation and flutter post-implant^{†,4}

| Non-serious events | Cases that resolved within 2 weeks of onset | Subject with atrial fibrillation that had a recurrent stroke |
|--------------------|---|--|
| 19/29 (66%) | 17/29 (59%) | 1 |

1.4 percent of all closure subjects in the REDUCE Study had ongoing non-serious atrial fibrillation or atrial flutter at the time of data analysis^{†,4}

Patient selection algorithm

The following three-step algorithm can help identify patients most likely to benefit from PFO closure.

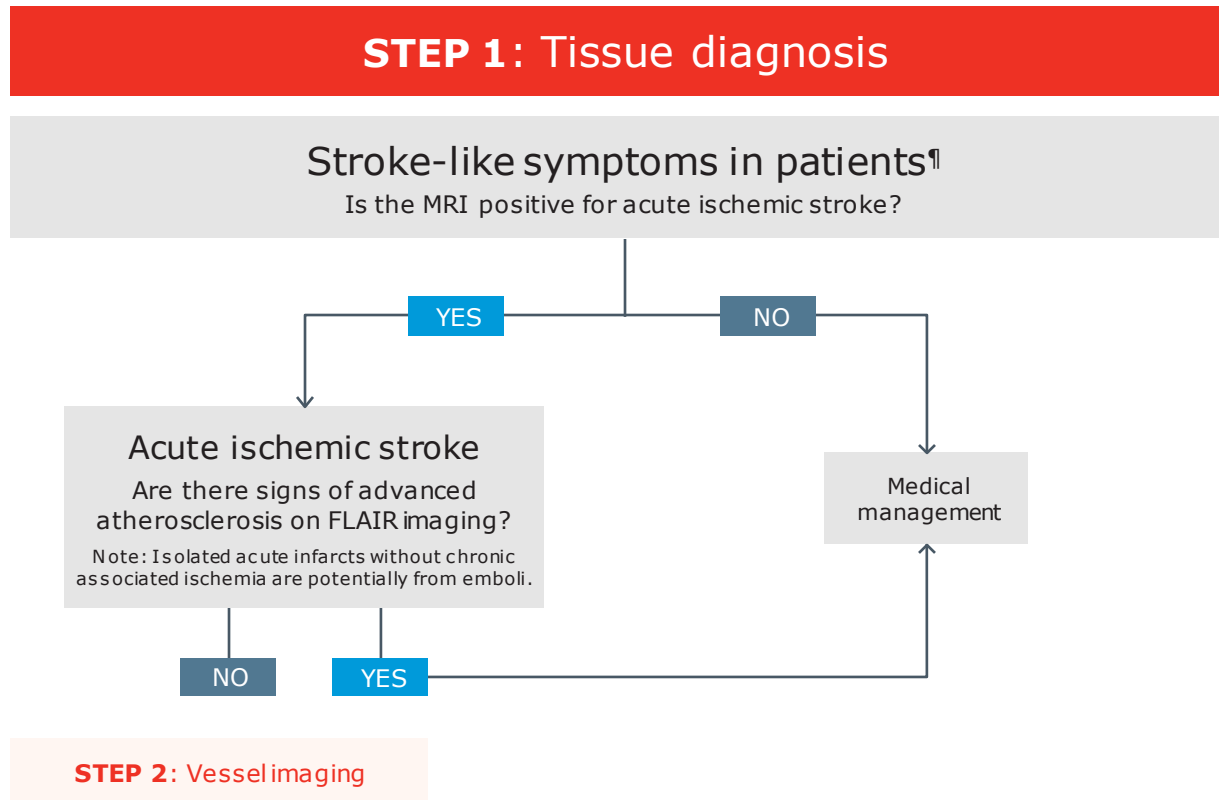


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Patient selection algorithm

Step 1



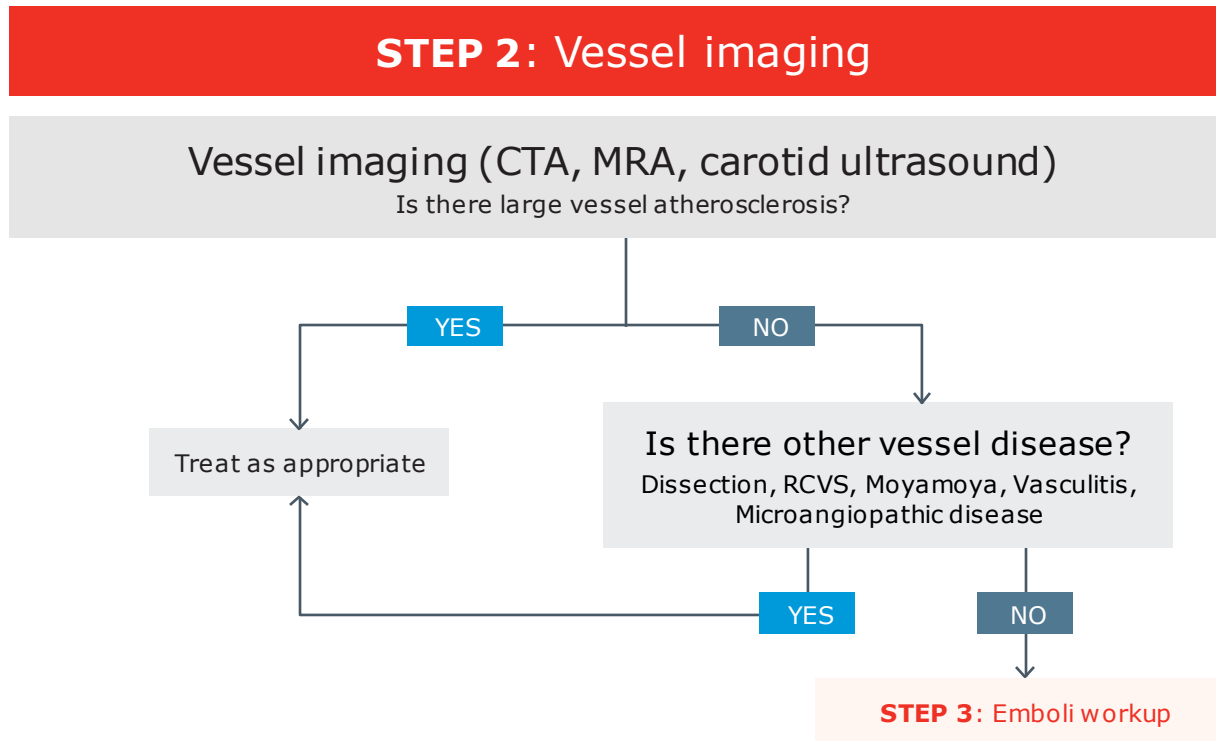
FLAIR, Fluid-attenuated inversion recovery.

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Patient selection algorithm

Step 2



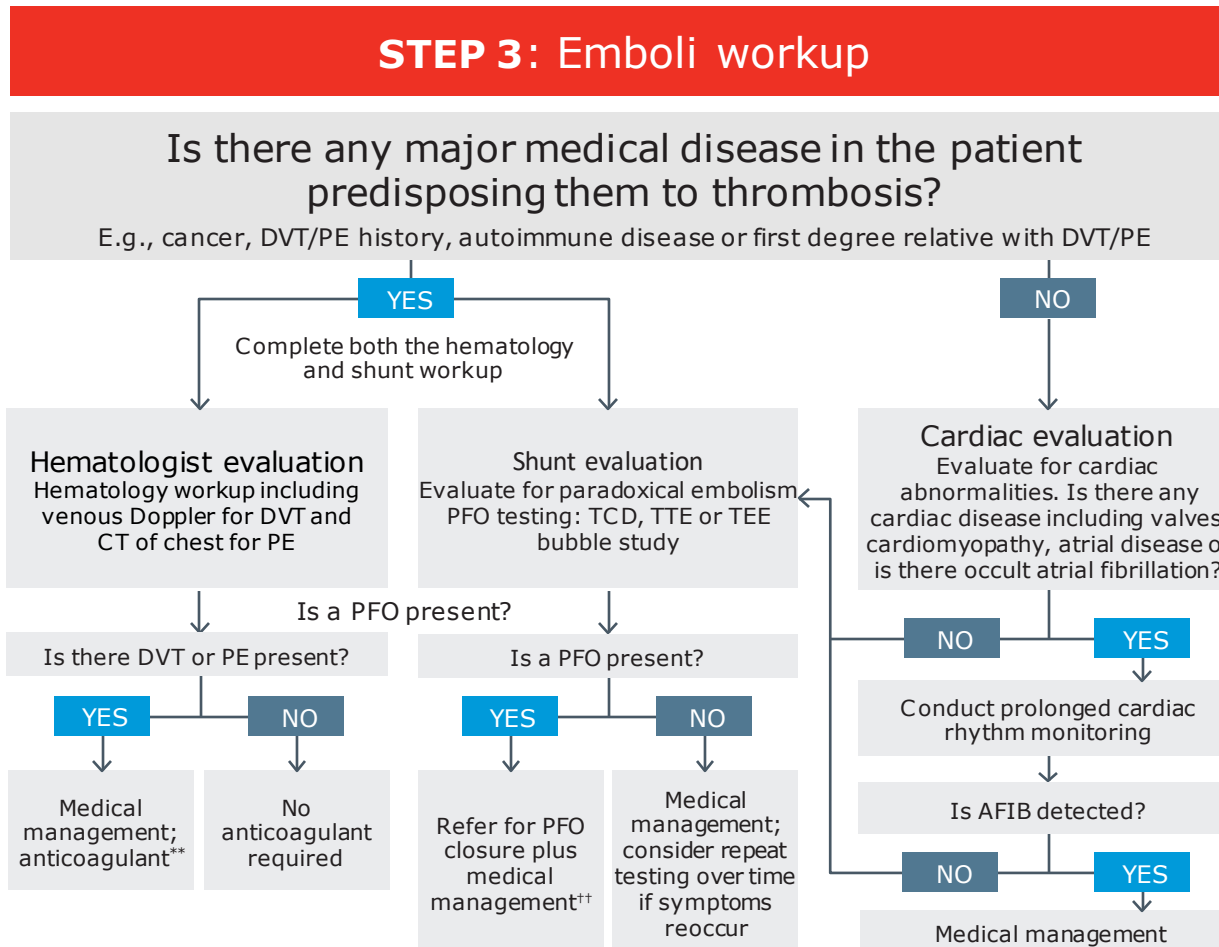
CTA, Computed tomography angiography; MRA, Magnetic resonance angiography; RCVS, Reversible cerebral vasoconstriction syndrome.

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Patient selection algorithm

Step 3



Duration of anticoagulant use varies by case, and the decision to maintain its use in conjunction with PFO closure should be at the physician's discretion.

A FIB, Atrial fibrillation; CT, Computed tomography; DVT, Deep vein thrombosis; MRI, Magnetic resonance imaging; PE, Pulmonary embolism; TCD, Transcranial doppler; TEE, Transesophageal echocardiography; TTE, Transthoracic echocardiogram.

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PFO closure procedure

Procedure basics

PFO closure is a minimally invasive transcatheter procedure, usually performed under general anesthesia or conscious sedation in a catheterization laboratory.

Average procedural timeframes

1-2 hours

Total length of procedure

1 day

Time from admit to discharge

Permanent implant for PFO closure

The GORE® CARDIOFORM Septal Occluder is a permanent implant that prevents emboli from traveling from the right to the left atrium.

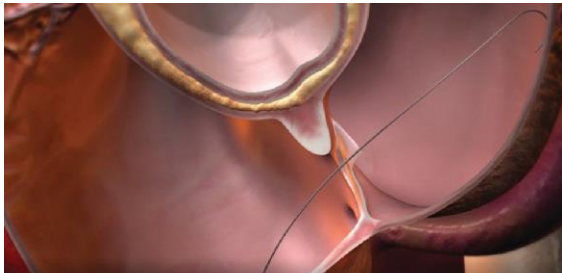


FDA approved, the implant conforms to the anatomy of the heart and creates a framework on which the patient's own tissue will eventually grow over and through, thus closing the PFO.

98%

Effective closure rate
at twelve months^{††,4}

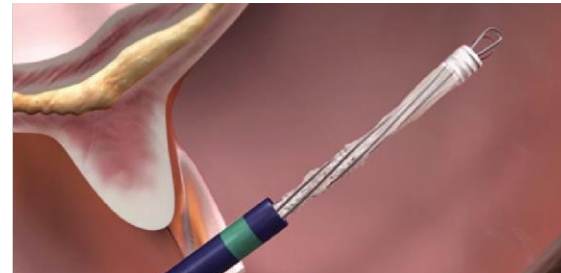
The procedure, step by step^{††}



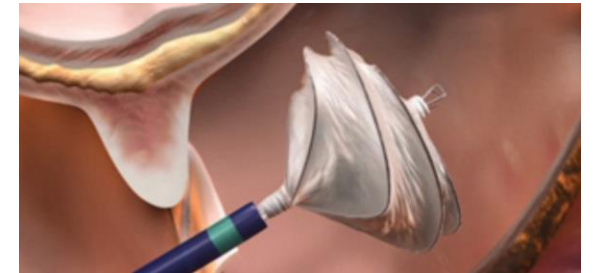
1 A small incision is made in the right groin. A catheter is threaded via guidewire through the vein and up to the heart. The guidewire is threaded through the PFO from the right to left atrium.



2 The device is navigated over the guidewire via the catheter and through the PFO.



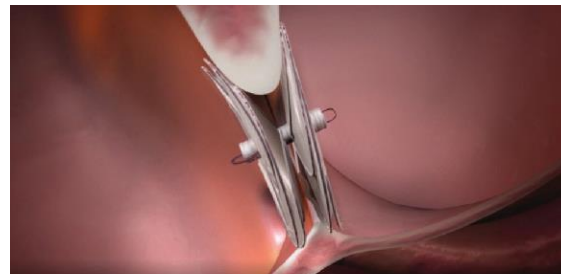
3 The physician opens the first disc of the PFO closure device inside the left atrium.



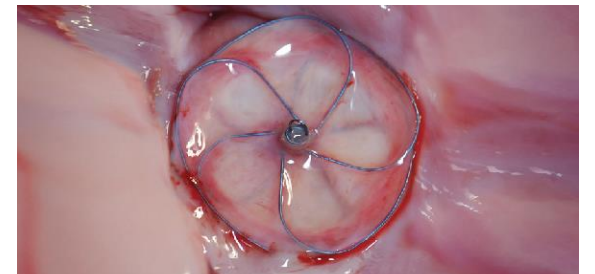
4 The first disc is positioned to appose the left side of the septum.



5 The device's second disc is opened and positioned to appose the right side of the septum, closing the PFO.



6 The two discs are locked together in their final position, and the device is released from the catheter.



7 The device serves as a scaffold onto which the patient's own cells grow into new tissue.

Conforms with the natural anatomy of the heart

Long-term results continue to demonstrate a legacy of patient safety.^{19,20}

- Soft, conformable device.
- Creates framework for patient's own tissue to eventually grow over and through, thus closing the PFO.
- Designed to minimize wall injury, allowing tissue ingrowth for short- and long-term performance.
- No reported erosions at original follow-up or during extended follow-up.^{19,20}

* Effective closure defined as freedom from large shunt > 25 bubbles as detected by transthoracic echocardiography adjudicated by Echo Core Lab.



99%

Effective closure rate
at 24 months^{*,21}

Post-procedure therapy and care§§

Post-procedural follow-up visit protocol

DISCHARGE

Physical exam, TTE

1 MONTH

Physical exam, TTE

6 MONTHS

Physical exam, TTE

12 MONTHS

Physical exam, TTE^{II}

Post-procedure care medical therapy protocol

Day 1+

- One of the following antiplatelet options:
 - ASPIRIN Acetylsalicylic Acid (81-325 mg daily)
 - Combination: ASPIRIN Acetylsalicylic Acid (50-100 mg daily)/dipyridamole (225-400 mg daily)
 - PLAVIX® Clopidogrel Bisulfate (alone) (75 mg daily)
- Antiplatelet therapy should be used indefinitely

Physicians should evaluate patient need for antibiotic therapy following device implantation.

Following implant, most patients can return to their prior lifestyle after two weeks.

Post-procedural patient activity level

Day 1

Hospital rest for up to one day

Day 14+

Strenuous physical routine

PFO closure health economics

PFO closure demonstrates economic and quality of life benefits

In select patients, PFO closure plus medical therapy reduces stroke burden costs and improves quality of life compared to medical management alone.^{5,6}

Cost-effective

After 2.3 years, closing a PFO is more cost-effective than medical management alone.⁵

Improves quality of life

Patients who underwent PFO closure reported significantly higher physical vitality, general health, mental health and social functioning than non-closure patients.⁶

American Academy of Neurology Practice Advisory Update: PFO and secondary stroke prevention

New guidance from the American Academy of Neurology (AAN) concludes that closure of a PFO may be recommended for some people who have had a stroke.

The 2020 practice advisory updates a 2016 advisory that concluded there was not enough evidence to support routine PFO closure to prevent a second stroke. Since then, new studies reported that for people with stroke due to a PFO, closure in addition to taking medication to prevent blood clots reduced the risk of future strokes better than medication alone.⁷

2016 versus 2020 AAN Practice Advisory

2016 AAN Practice Advisory:⁸

- Clinicians should not routinely offer PFO closure outside of a research setting due to insufficient evidence to ascertain the effectiveness of PFO closure
- Clinicians may offer patients with no indication for anticoagulation, antiplatelet medications

2020 AAN Practice Advisory:⁹

- In patients younger than 60 years with a PFO and embolic-appearing infarct and no other mechanism of stroke identified, clinicians may recommend closure following a discussion of potential benefits and risks
- In patients who opt to receive medical therapy alone without PFO closure, clinicians may recommend an antiplatelet medication such as ASPIRIN Acetylsalicylic Acid or anticoagulation

WL Gore Cardioform Indication

- Ostium secundum atrial septal defects
- Patent foramen ovale to reduce the risk of recurrent ischemic stroke in patients, predominantly between the
- ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as
- determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke

Footnotes and references

* PFO confirmed by transesophageal echocardiography (TEE) with bubble study demonstrating right-to-left shunt at rest or during Valsalva maneuver. Patients with PFO eligible regardless of shunt size within sizing parameters of the *Instructions for Use* or presence of a trial septal aneurysm.

† The REDUCE Study determined safety and efficacy of patent foramen ovale (PFO) closure with the GORE® CARDIOFORM Septal Occluder or GORE® HELEX® Septal Occluder plus antiplatelet medical management compared to antiplatelet medical management alone in patients with a PFO and history of cryptogenic stroke. All PFO anatomies were incorporated into this study within indicated sizing parameters of the *Instructions for Use*.

‡ The 4% represents the difference between 5.4% and 1.4% respectively.

§ P values were calculated with the use of Fisher's exact test.

|| Subjects may have experienced both device- and procedure-related SAEs.

¶ Treatment of 60-70 year olds is still under investigation.

** REDUCE Study did not include patients on anticoagulants.

†† Refer to *Instructions for Use*.

‡‡ GORE® CARDIOFORM Septal Occluder effective closure rate results in device group subjects who received a study device. Effective closure defined as freedom from large shunt > 25 bubbles as detected by transthoracic echocardiography adjudicated by echocore lab.

§§ Recovery and follow up based on REDUCE Study protocols.

||| In instances where device stability is in question, fluoroscopic examination without contrast is recommended.

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INDICATIONS FOR USE IN AUSTRALIA, CANADA AND EUROPE: The GORE® CARDIOFORM Septal Occluder is a permanently implanted device indicated for the percutaneous, transcatheter closure of atrial septal defects (ASDs), such as ostium secundum and patent foramen ovale. **CONTRAINDICATIONS:** The GORE® CARDIOFORM Septal Occluder is contraindicated for use in patients: Unable to take anti-platelet or anticoagulant medications such as aspirin, heparin or warfarin; with anatomy where the GORE® CARDIOFORM Septal Occluder size or position would interfere with other intracardiac or intravascular structures, such as cardiac valves or pulmonary veins; with active endocarditis, or other infections producing bacteremia, or patients with known sepsis within one month of planned implantation, or any other infection that cannot be treated successfully prior to device placement; with known intracardiac thrombi. Refer to *Instructions for Use* at eifu.goremedical.com for a complete description of all applicable indications, warnings, precautions and contraindications for the markets where this product is available. ^{Rx Only}

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