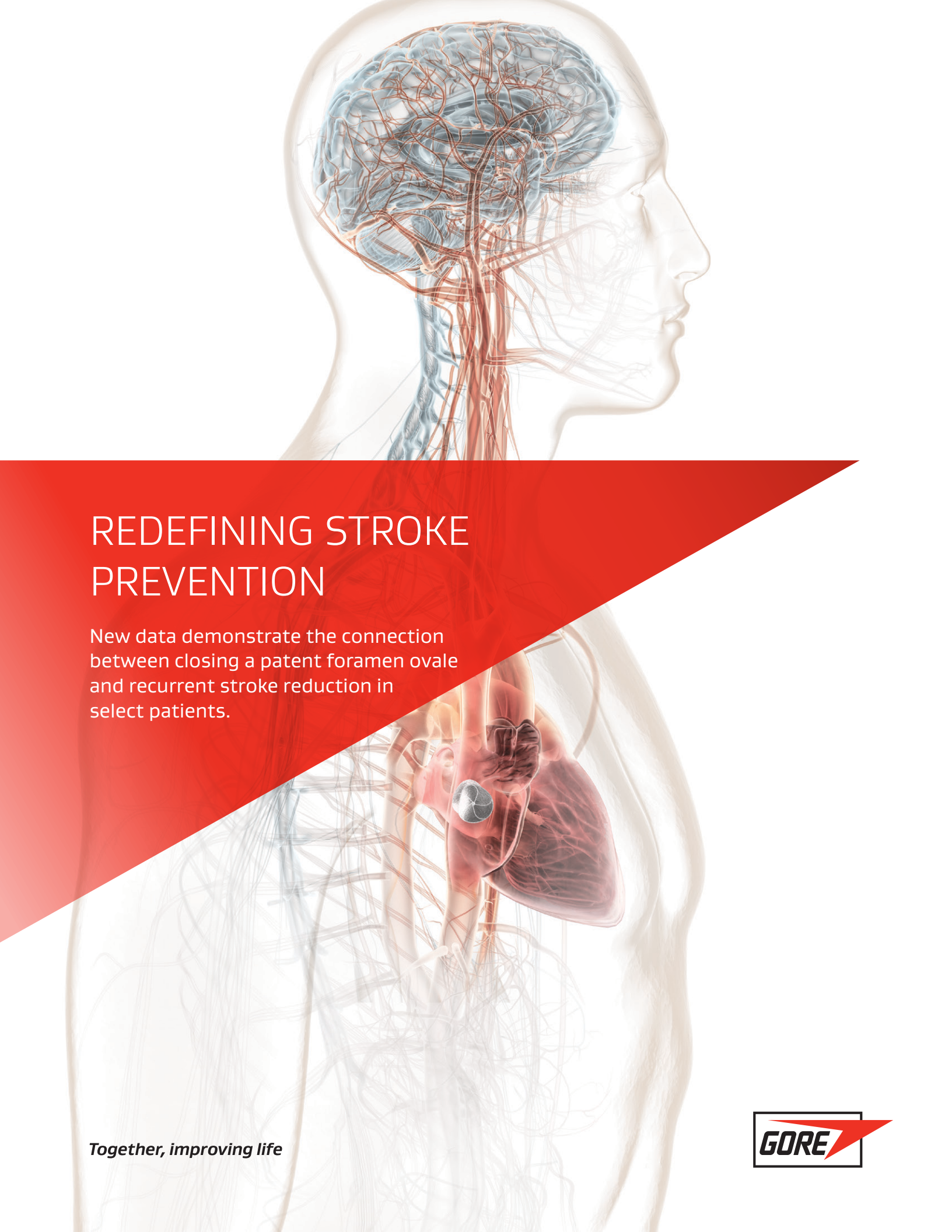


REDEFINING STROKE PREVENTION

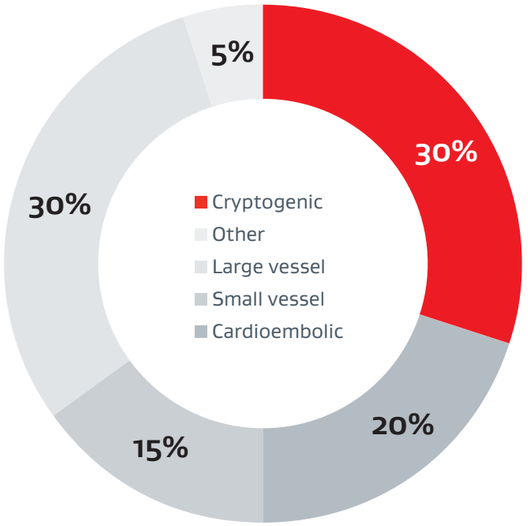
New data demonstrate the connection between closing a patent foramen ovale and recurrent stroke reduction in select patients.

Together, improving life

GORE

CRYPTOGENIC STROKE: A common problem without consistently transparent causes

How many ischemic strokes are cryptogenic?



~1/3
of ischemic strokes are cryptogenic[1]

~200K
cryptogenic strokes occur annually in the U.S.[1]

~4.5M
cryptogenic strokes occur annually worldwide[1,2]

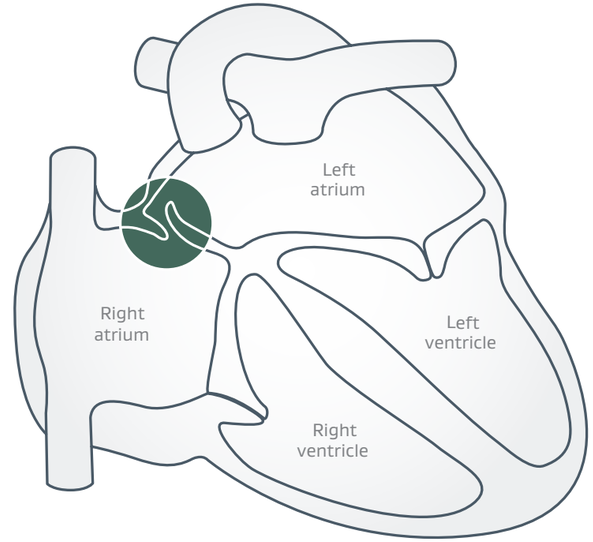
CRYPTOGENIC STROKE: The connection to patent foramen ovale (PFO)

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

40–50%
of patients who have had a cryptogenic stroke have a PFO[3]

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



Gore REDUCE Clinical Study

Prospective, randomized, multicenter, multinational, open label trial

664
PATIENTS ENROLLED
Cryptogenic stroke and PFO*/Ages 18-59

441
CLOSURE GROUP
GORE® Device† plus antiplatelet therapy

223
MEDICAL THERAPY GROUP
Antiplatelet therapy

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 ≥ 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

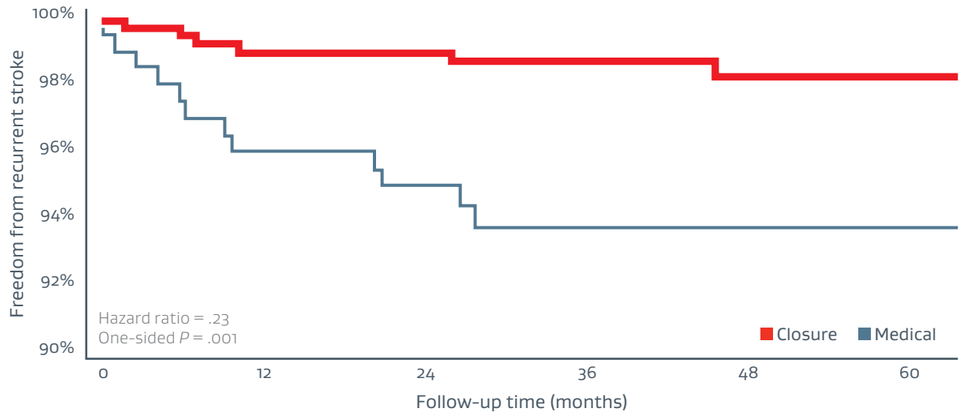
Image confirmation

- 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]

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%

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

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

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 serious device or procedure-related SAEs.[†,4]

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

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[§]
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% 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 algorithm may help identify patients most likely to benefit from PFO closure

STEP 1: Tissue diagnosis

Stroke-like symptoms in patients¶

Is the MRI positive for acute ischemic stroke?

- YES → **Acute ischemic stroke**
  Are there signs of advanced atherosclerosis on FLAIR Imaging?
  Note: Isolated acute infarcts without chronic associated ischemia are potentially from emboli.
  - NO → **STEP 2**: Vessel imaging
  - YES → Medical management
- NO → Medical management

STEP 2: Vessel imaging

Vessel imaging (CTA, MRA, carotid ultrasound)

Is there large vessel atherosclerosis?

- YES → Treat as appropriate
- NO → **Is there other vessel disease?**
  Dissection, RCVS, Moyamoya, Vasculitis, Microangiopathic disease
  - YES → Treat as appropriate
  - NO → **STEP 3**: Emboli workup

STEP 3: Emboli workup

Is there any major medical disease in the patient predisposing them to thrombosis?

E.g., Cancer, DVT / PE history, autoimmune disease or first degree relative with DVT / PE

- YES → Complete both the hematology and shunt workup
  - **Hematologist evaluation**
    Hematology workup including venous Doppler for DVT and CT of chest for PE
    → **Is there DVT or PE present?**
    - YES → Medical management; anticoagulant**
    - NO → No anticoagulant required

    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.
  - **Shunt evaluation**
    Evaluate for paradoxical embolism PFO testing: TCD, TTE or TEE bubble study
    → **Is a PFO present?**
    - YES → Refer for PFO closure plus medical management††
    - NO → Medical management; consider repeat testing over time if symptoms reoccur
- NO → **Cardiac evaluation**
  Evaluate for cardiac abnormalities. Is there any cardiac disease including valves, cardiomyopathy, atrial disease or is there occult atrial fibrillation?
  - NO → Conduct prolonged cardiac rhythm monitoring → **Is AFIB detected?**
    - NO → **STEP 3**: Emboli workup
    - YES → Medical management
  - YES → Medical management

AFIB, Atrial fibrillation; CT, Computed tomography; CTA, Computed tomography angiography; DVT, Deep vein thrombosis; FLAIR, Fluid-attenuated inversion recovery; MRA, Magnetic resonance angiography; MRI, Magnetic resonance imaging; PE, Pulmonary embolism; RCVS, Reversible cerebral vasoconstriction syndrome; TCD, Transcranial doppler; TEE, Transesophageal echocardiography; TTE, Transthoracic echocardiogram.

Used with permission from John J. Volpi, M.D., BA Neurology Houston, Texas. This algorithm represents John J. Volpi, M.D.'s general clinical practice.

All content about medical diagnosis and treatment is for general information purposes only. This information is not intended or implied to be a substitute for professional medical diagnosis, treatment or care. Every medical situation is unique to the patient and requires appropriate clinical judgment from a qualified physician.

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

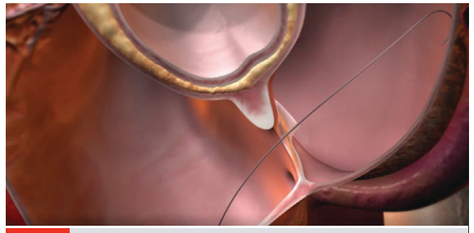
Permanent implant for PFO closure

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

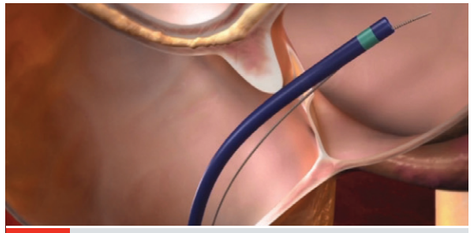
FDA approved, the implant conforms to the anatomy of the heart and creates a framework on which the patient's own tissue will eventually grow over and through, thus closing the PFO.

98%
Effective closure rate
At twelve months[‡‡,4]

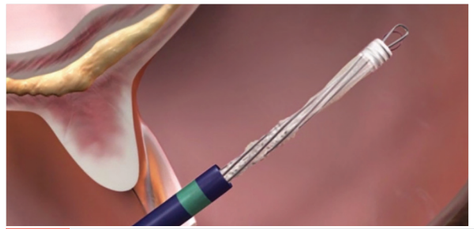
The procedure, step by step[††]

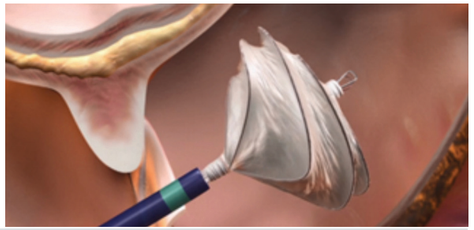


1 A small incision is made in the right groin. A catheter is threaded via guidewire through the vein and up to the heart. The guidewire is threaded through the PFO from the right to left atrium.



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

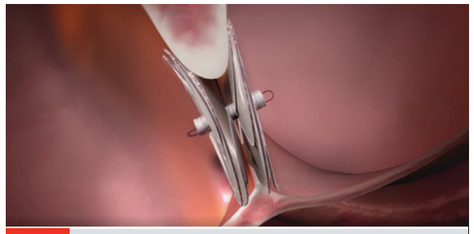




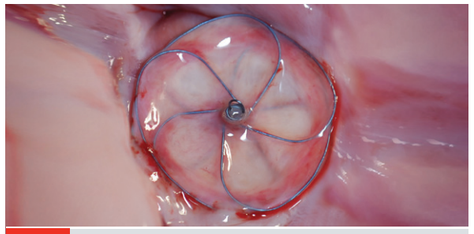
3 The physician opens the first disc of the PFO closure device inside the left atrium.

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.

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[‖ ‖]

See ***Instructions for Use*** for complete information on patient care.

Post-procedural 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)
  - Clopidogrel (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]

Access additional PFO therapy resources provided by Gore at

PFOEDUCATION.COM

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]	2020 AAN Practice Advisory:[9]
▪ Clinicians should not routinely offer PFO closure outside of a research setting due to insufficient evidence to ascertain the effectiveness of PFO closure	▪ 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
▪ Clinicians may offer patients with no indication for anticoagulation, antiplatelet medications	▪ In patients who opt to receive medical therapy alone without PFO closure, clinicians may recommend an antiplatelet medication such as aspirin or anticoagulation

Access additional PFO guideline information provided by Gore at

PFOGUIDELINES.COM

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 IFU or presence of atrial 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.

II 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 echo core lab.

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

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

1. Cryptogenic Stroke Initiative. American Heart Association / American Stroke Association, Inc. website. Accessed July 10, 2020. https://www.stroke.org/en/professionals/stroke-resource-library/post-stroke-care/cryptogenic-stroke-initiative#:~:text=Potential%20Causes&text=Patent%20Foramen%20Ovale%20(PFO)%20%E2%80%93,in%20and%20on%20artery%20walls.
2. World Health Organization. The World Health Report 2002 – reducing risks, promoting healthy life. http://www.who.int/whr/2002/en/. Published 2002. Accessed October 5, 2018.
3. Caswell J. Holes in the heart. Stroke Connection 2011:16-17. https://scmag-digi.stroke.org/strokeconnection/january_february_2011?article_id=961624&pg=NaN#pgNaN.
4. Søndergaard L, Kasner SE, Rhodes JF, *et al*; Gore REDUCE Study Investigators. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *New England Journal of Medicine*. 2017;377(11):1033-1042.
5. Volpi JJ, Ridge JR, Nakum M, Rhodes JF, Sondergaard L, Kasner SE. Cost-effectiveness of percutaneous closure of a patent foramen oval compared with medical management in patients with a cryptogenic stroke: from the US payer perspective. *Journal of Medical Economics*. 2019;22(9):883-890.
6. Mirzada N, Ladenvall P, Hansson PO, Eriksson P, Taft C, Dellborg M. Quality of life after percutaneous closure of patent foramen ovale in patients after cryptogenic stroke compared to a normative sample. *International Journal of Cardiology*. 2018;257:46-49.
7. https://www.aan.com/PressRoom/Home/PressRelease/3790.
8. Messé SR, Gronseth G, Kent DM, et al. Practice advisory: recurrent stroke with patent foramen ovale (update of practice parameter): Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2016;87(8):815-821. https://neurology.org/content/87/8/815.full.
9. Messé SR, Gronseth GS, Kent DM, et al. Practice advisory update summary: patent foramen ovale and secondary stroke prevention: Report of the Guideline Subcommittee of the American Academy of Neurology. *Neurology*. In press. https://www.aan.com/Guidelines/Home/GuidelineDetail/991.

Consult Instructions for Use
eifu.goremedical.com

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. ℞ Only

INDICATIONS FOR USE IN THE U.S.: The GORE® CARDIOFORM Septal Occluder is a permanently implanted device indicated for the percutaneous, transcatheter closure of the following defects of the atrial septum: Ostium secundum atrial septal defects (ASDs); patent foramen ovale (PFO) 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. CONTRAINDICATIONS: The GORE® CARDIOFORM Septal Occluder is contraindicated for use in patients: Unable to take antiplatelet 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. ℞ Only

This information is intended for education and awareness only. Patients should consult their physician for information on the risks associated with the devices and surgical procedures discussed in this document. All surgical procedures carry potential health risks. Not all patients will be candidates for treatment with these devices, and individual outcomes may vary.

Products listed may not be available in all markets.

In some jurisdictions, ASPIRIN is a trademark of Bayer Intellectual Property GmbH or its affiliated companies.

W. L. Gore & Associates, Inc.
goremedical.com

Asia Pacific +65 6733 2882 **Australia/New Zealand** 1800 680 424 **Europe** 00800 6334 4673
United States Flagstaff, AZ 86003 800 437 8181 928 779 2771