Fetal heart development, patent foramen ovale and closure using the GORE® CARDIOFORM Septal Occluder

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The information provided is intended to be general guidance based on current medical practices in the field. The steps described here may not be complete, and are not intended to be a replacement for the *Instructions for Use* or the education, training and professional judgment of Healthcare Providers. Licensed Healthcare Providers remain responsible for making decisions about patient care and the use of medical technologies.

Topics

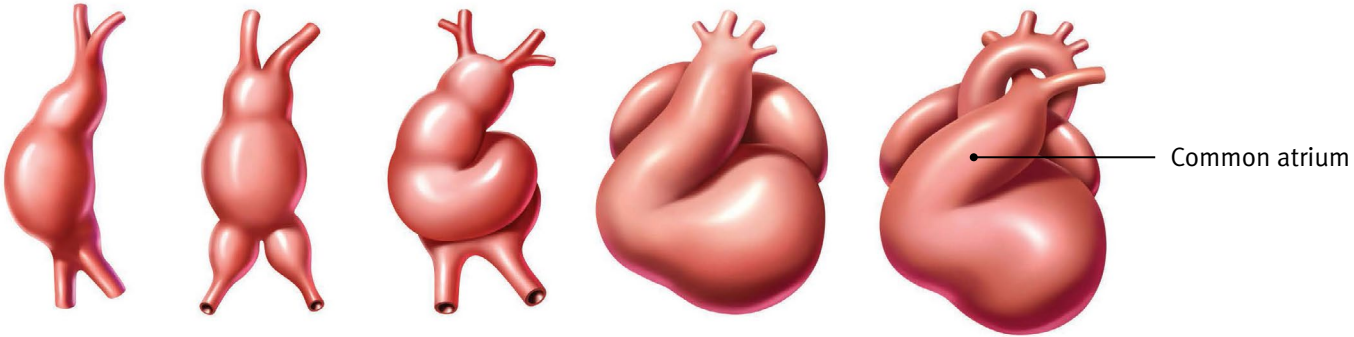
- Fetal heart development
- Patent foramen ovale (PFO)
- PFO and stroke
- PFO diagnosis
- PFO treatment options
- Gore REDUCE Clinical Study
- Imaging techniques for interventional treatment
- PFO closure with GORE® CARDIOFORM Septal Occluder
- Procedural equipment
- Follow-up and complications

Objectives

- Refresh on fetal heart anatomy and prevalence of PFO.
- Identify PFO anatomy variations that may be seen in practice to optimize future PFO closure procedures.
- Gain insight on the prevalence of cryptogenic stroke and understand the correlation between PFO and stroke.
- Learn techniques to diagnose a PFO in patients.
- Know the facts about the options available for patients who have been diagnosed with a presumed paradoxical embolism.
- Have a deep understanding of the Gore REDUCE Clinical Study and its impact on PFO closure therapy.
- Learn about utilizing GORE® CARDIOFORM Septal Occluder for PFO closure.

Fetal heart development

Embryonic development of the heart



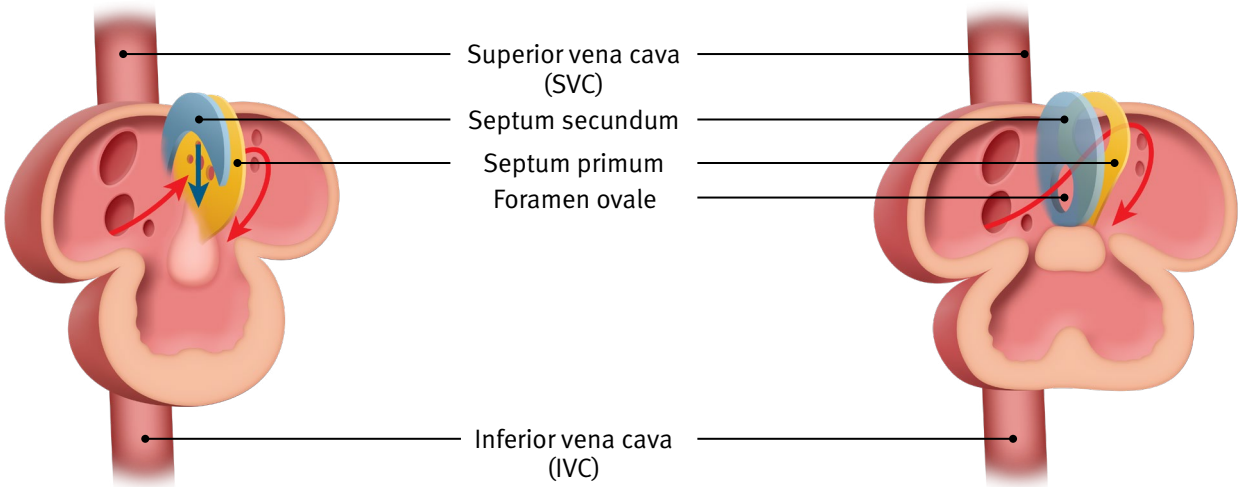
Day 28

- Starts as a simple tube
- Twists to final configuration
- One common atrium at day 28

Fetal development of the atrial septum

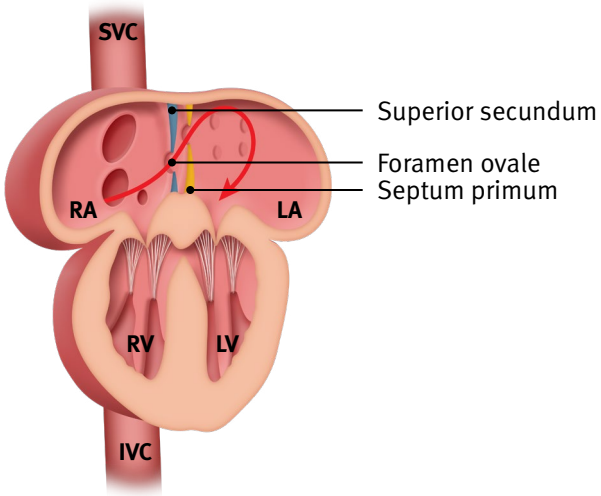
Fetal heart at six weeks

Fetal heart at seven weeks



Fetal development of the atrial septum

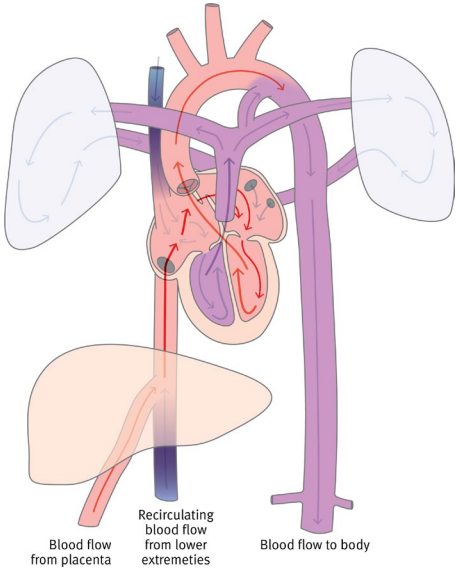
Fetal heart at three months



RA – Right Atrium
LA – Left Atrium
RV – Right Ventricle
LV – Left Ventricle

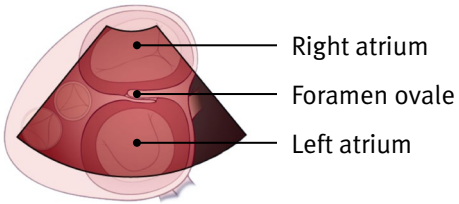
Circulation in a fetal heart

- Oxygenated blood enters the circulation from the placenta and via the ductus venosus brings it to the IVC and right atrium.
- The Eustachian valve directs blood across the patent foramen ovale into the left atrium, bypassing the lungs.
- The left ventricle pumps the oxygenated blood to the brain and body.



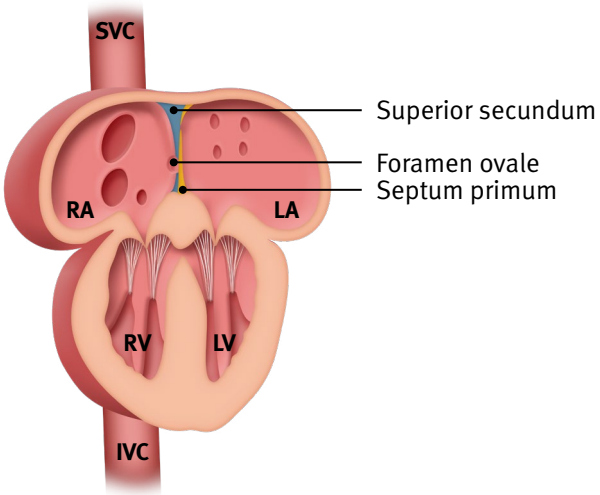
Foramen ovale closes at birth

- Lungs inflate at birth.
- Increased pumlonary blood flow elevates left atrial pressure.
- Elevated left atrial pressure causes the septum primum to seal against the foramen ovale, separating the atria.



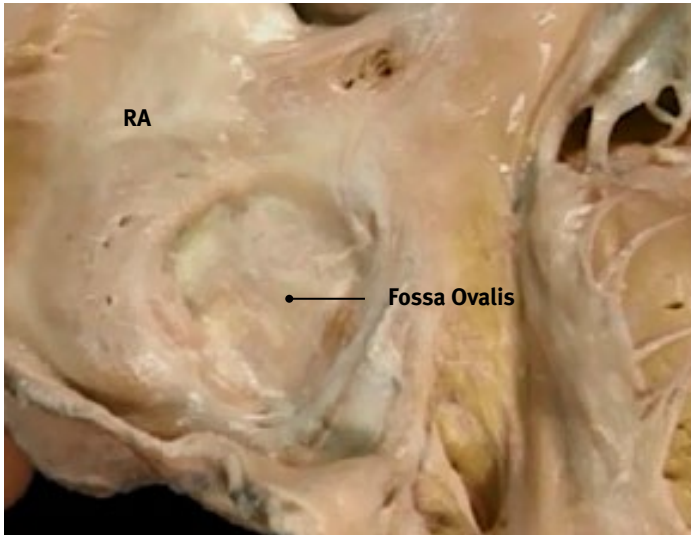
Closed foramen ovale

Heart after birth



Complete development of atrial septum

- The depression left after the septum secundum and septum primum fuse is the fossa ovalis.
- If sealing does not occur it is referred to as a patent foramen ovale or PFO.
- 25% of people have a PFO.[1]



PFO

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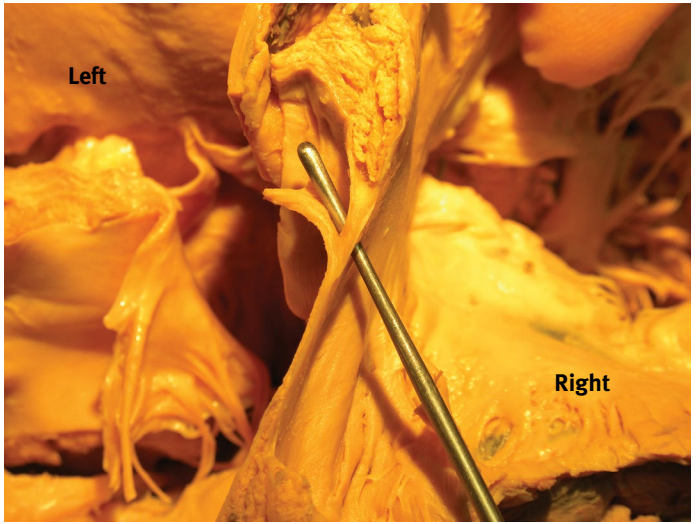
PFO — Atrial shunting

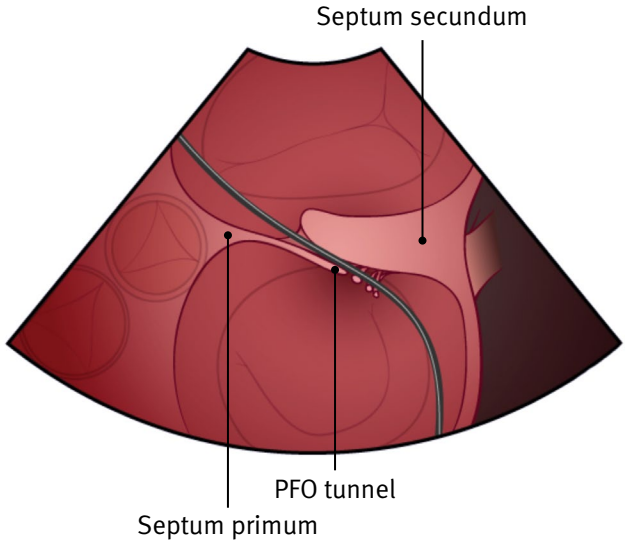
PFO can allow for atrial shunting

- A PFO occurs when the foramen ovale remains patent after birth and acts as a potential interatrial shunt.
- In 25% of the population the foramen ovale does not seal.[1]
- Shunting of blood from the right atrium to the left atrium is possible with a PFO.
- A thromboembolism from the venous circulation can pass through the PFO into the arterial circulation (paradoxical thromboembolism) leading to an ischemic stroke.[1]



PFO anatomy variations — Long tunnel

Video: Long tunnel



PFO anatomy variations — Floppy septum

Video: Floppy septum

PFO anatomy variations — Thick secundum

Video: Thick secundum

PFO anatomy variations — Multiple exits in left atrium

Video: Multiple exits

PFO and stroke

Signs of a PFO and complications

Typically someone with a PFO **does not have any symptoms.**[1]

A PFO can contribute to the following complications[1]:

- Severe migraines
- Transient ischemic attack (TIA)
- **Ischemic stroke**

PFOs do not cause these events, but can be a conduit for thrombus to pass through from the venous circulation to the arterial circulation.[1]

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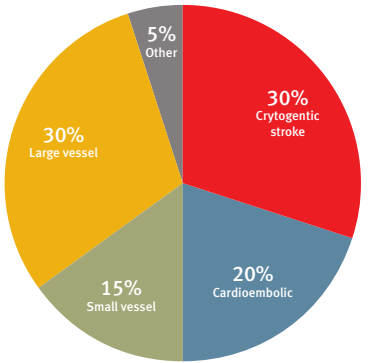
Potential complication due to a PFO — Ischemic stroke

- Stroke is the fifth leading cause of death and is the leading preventable cause of long-term severe disability.[2]
- Cryptogenic stroke or stroke of undetermined origin in TOAST terminology is defined as brain infarction that is not attributable to a source of definite cardioembolism, large artery atherosclerosis, or small artery disease despite a standard vascular, cardiac and serologic evaluation.[4]

TOAST is a classification of subtype of acute ischemic stroke[3]

1/3 of all ischemic strokes are classified as cryptogenic, or due to unknown cause[4]

Subtypes of ischemic stroke[3]



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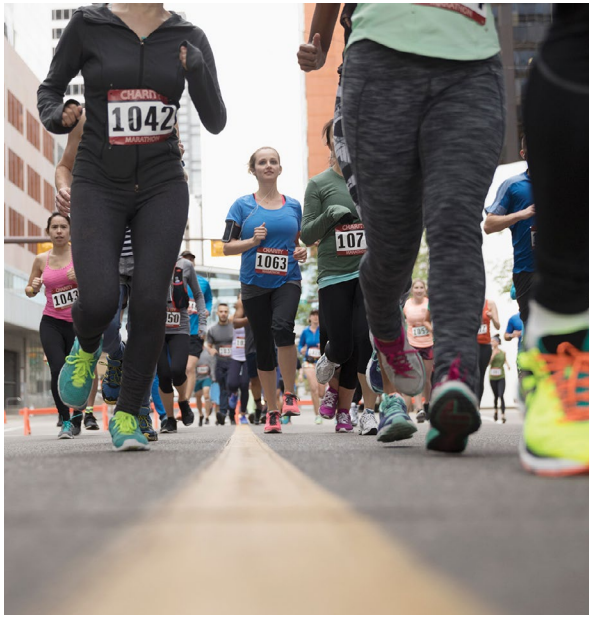
Potential complication due to a PFO — Ischemic stroke

- The category of stroke of undetermined etiology in the TOAST classification includes patients with less well-established potential causes of cardiac embolism, such as patent foramen ovale, aortic arch atheroma and mitral valve stenosis, as well as potential prothrombotic disorders; stroke of undetermined etiology also includes patients with two or more equally plausible identified causes of stroke.[4]



Potential complication due to a PFO — Ischemic stroke

- Up to 40–50% of patients who have had a cryptogenic stroke have a PFO.[1]

Video: Patient testimonial

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PFO diagnosis

How to diagnose a PFO

After traditional stroke workup has been completed and no other cause of stroke can be found, the following imaging modalities may be used to look for a PFO:

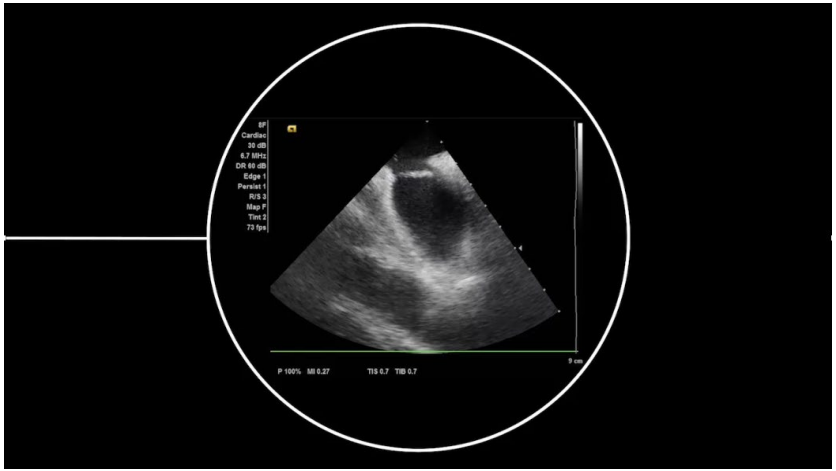
- Transesophageal echocardiogram (TEE)
  - Echocardiography with Doppler
  - Saline contrast study (bubble study)
- Transthoracic echocardiogram (TTE)
  - Echocardiography with Doppler
  - Saline contrast study (bubble study)
- Transcranial Doppler

Video: Transesophogeal echocardiography example

Bubble study — A PFO is a PFO

What to look for in a bubble study:

- Any bubbles crossing demonstrating spontaneous right-to-left shunting or right-to-left shunting during Valsalva maneuver.



PFO treatment options

Some treatment options of PFO — Mediated stroke

Open heart surgery	Percutaneous device closure	Antiplatelet therapy alone	Anticoagulant therapy
More invasive than PFO closure or medical therapy alone	Fewer procedural complications than open heart surgery	Does not require any intervention	Potentially increased stroke reduction compared with antiplatelet therapy
Longer recovery	Shorter hospital stay than open heart surgery	Patient may or may not comply	Increased bleeding complications
Can treat a wider variety of defects	Some defects are not amenable to device closure		Patient compliance challenges
May be appropriate if other surgical procedures are required	Closure rates are comparable to surgery Patient still remains on antiplatelet therapy indefinitely		Useful for patients with other conditions requiring anticoagulation (such as deep vein thrombosis [DVT])
	The Gore REDUCE Clinical Study found PFO closure plus medical therapy significantly reduces stroke over medical therapy alone*,5		
	The REDUCE Study found no significant difference in overall serious adverse event (SAE) rate between closure and medical therapy groups†,5		

* The REDUCE Study determined safety and efficacy of 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*.

† There was no statistically significant difference in the rate of serious adverse events (SAE) between the closure and medical groups. There was a significantly higher rate of atrial fibrillation or flutter in the closure group (6.6% versus 0.4%) but the majority was non-serious (66%), peri-procedural (69% had onset within 30 days of the closure procedure) and had rapid resolution (59% with resolution within two weeks of onset). Average of 3.4 years follow-up.

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Gore REDUCE Clinical Study

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Treatment options — Percutaneous closure of PFOs clinically proven to significantly reduce recurrent stroke risk

The REDUCE Study is the only U.S. IDE trial that achieved its primary endpoint and showed the largest reduction in recurrent ischemic stroke*,[5] in all PFO shunt sizes and anatomies over medical therapy alone.

Watch REDUCE Clinical Study results

* The REDUCE study determined safety and efficacy of 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*.

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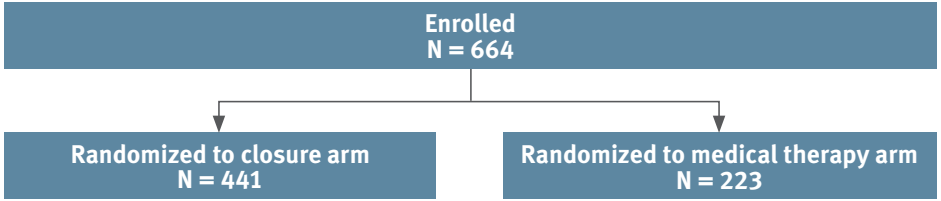
REDUCE Study overview

- Aim: Establish superiority of PFO closure in conjunction with antiplatelet therapy over antiplatelet therapy alone in reducing the risk of recurrent clinical ischemic stroke or new brain infarct.
- Randomized, controlled, open-label trial.
- 664 subjects randomized in a 2:1 ratio.*
- 63 sites in seven countries.
  - Canada, Denmark, Finland, Norway, Sweden, U.K., U.S.



GORE® CARDIOFORM Septal Occluder

* Closure: GORE® HELEX® Septal Occluder (39%) or GORE® CARDIOFORM Septal Occluder (61%) plus antiplatelet therapy. Medical therapy: antiplatelet therapy alone.

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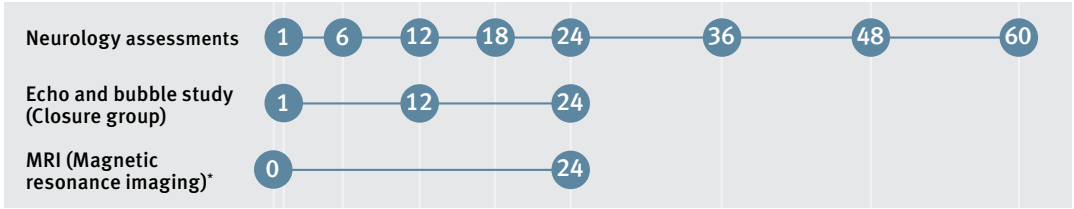
REDUCE Study design

Medical therapy

- Antiplatelet standardized options:
  - ASPIRIN Acetylsalicylic Acid alone (75–325 mg once daily).
  - Combination ASPIRIN Acetylsalicylic Acid (50–100 mg once daily). and PERSANTINE Dipyridamole (225–400 mg once daily).
  - PLAVIX® Clopidogrel Bisulfate (75 mg once daily).
  - Other combinations or the use of anticoagulants was not permitted.
- Prescribed for all subjects for the duration of the study.
- Followed for up to five years.

Follow-up



* If not already performed for an endpoint event.

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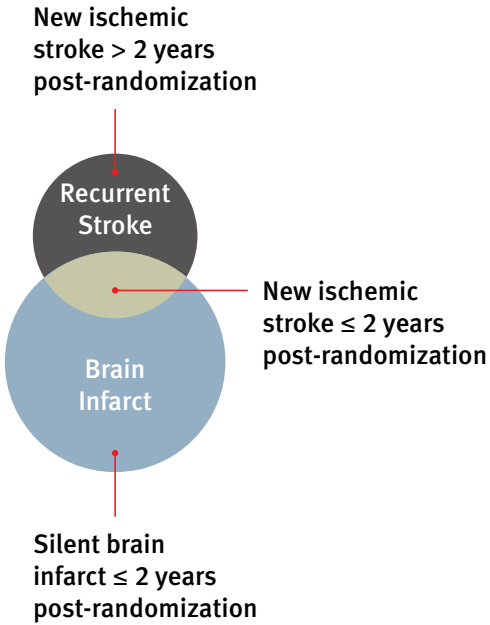
Inclusion and exclusion criteria

- Age 18–59 years
- Cryptogenic ischemic stroke within 180 days
  - Ischemic stroke = clinical symptoms ≥ 24 hours or with MRI evidence of infarction
  - Cryptogenic
    - No stenosis > 50% 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
  - Confirmed by TEE with bubble study demonstrating right-to-left shunt at rest or during Valsalva maneuver
- No indication for anticoagulation
- No uncontrolled diabetes mellitus, hypertension, autoimmune disease, alcohol or drug abuse

Co-primary endpoints

- Freedom from r*ecurrent 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.



* New T2 hyperintense MRI lesion with diameter ≥ 3 mm; adjudicated by MRI core lab.

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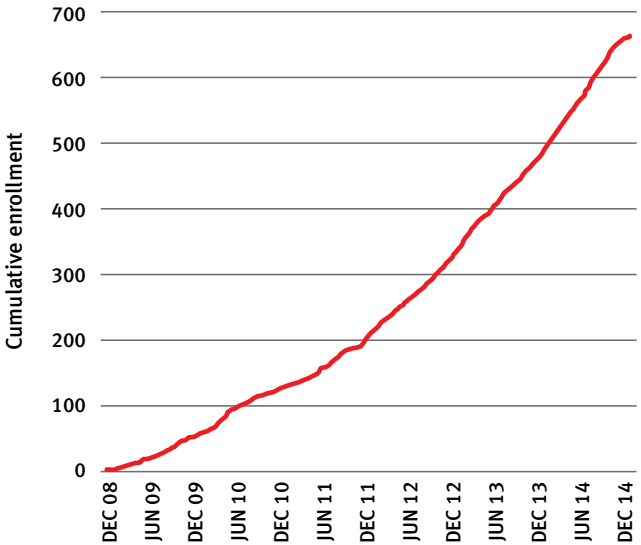
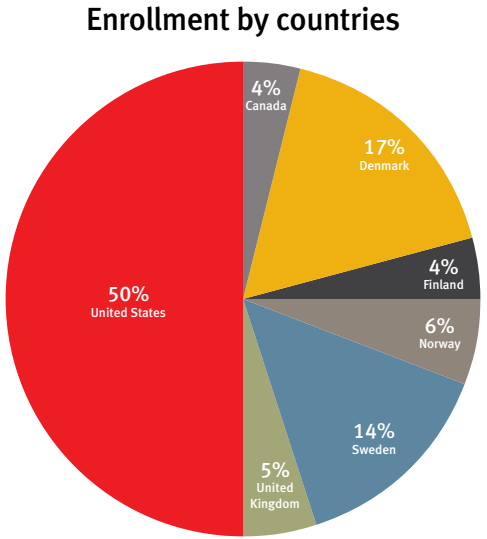
Secondary endpoints

- Safety assessments
  - All adverse events
    - Evaluated by site investigators for relatedness and seriousness
  - SAEs
    - SAEs of special interest: bleeding, atrial fibrillation, DVT / PE
- Performance assessments
  - Technical success
  - PFO closure success measured by assessing the degree of residual right-to-left shunt after device implant

Logistics and timeline





Enrollment: December 2008 to February 2015

Last subject completed 24-month evaluation: March 2017

Final CEC adjudication of clinical events: April 17, 2017

Final MRI core lab review of new brain infarction: April 24, 2017

Data freeze and analysis: April 24, 2017

Public presentation at ESOC: May 16, 2017

Results published in *New England Journal of Medicine*: September 14, 2017

Baseline characteristics

No significant differences between closure and medical therapy*

Demographic / characteristic	Closure (N = 441)	Medical therapy (N = 223)
Age (SD), years	45.4 (± 9.3)	44.8 (± 9.6)
Days (SD) from qualifying event to randomization	100 ± 52	101 ± 53
Sex, male	59.2%	61.9%
Current smoker	14.3%	11.2%
Diabetes mellitus	4.1%	4.5%
Hypertension	25.4%	26.0%
Previous cerebrovascular event	14.1%	10.3%
Maximal baseline shunt grade	N = 425	N = 216
Moderate or large	81.9%	80.1%
Atrial septal aneurysm	20.4%	Did not collect

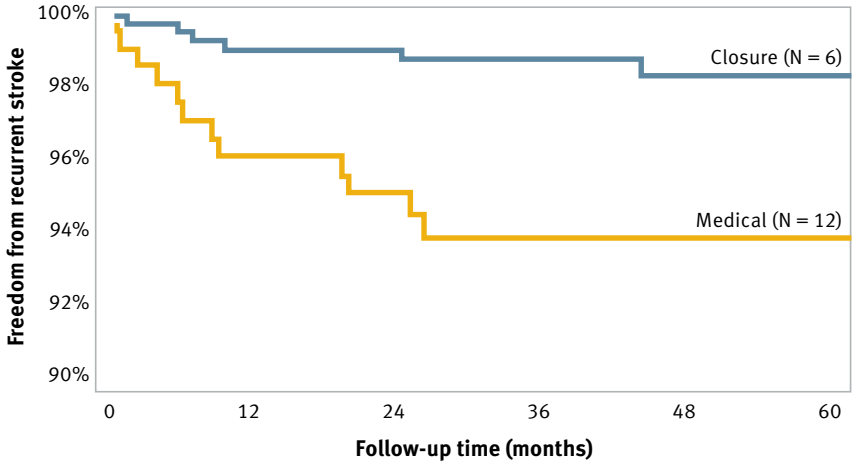
* All *P*-values > .2.

Duration of follow-up

	Closure (N = 441)	Medical therapy (N = 223)	Total (N = 664)
Mean (SD), years	3.5 (1.4)	3.2 (1.5)	3.4 (1.4)
Total exposure, patient-years	1,529	703	2,232

Primary endpoint result: Recurrent clinical ischemic stroke

77% reduction in clinical stroke with PFO closure (intention-to-treat analysis)



Annualized event rates
Closure: 0.39 per 100 person-years
Medical: 1.71 per 100 person-years

- PFO closure effect similar across subgroups based on age, sex, region and baseline shunt size.
- Number needed to treat (NNT) = 28 at two years.

Hazard ratio: 0.23
95% CI: 0.09 to 0.62
One-sided *P* = .001
Adjusted for multiple testing

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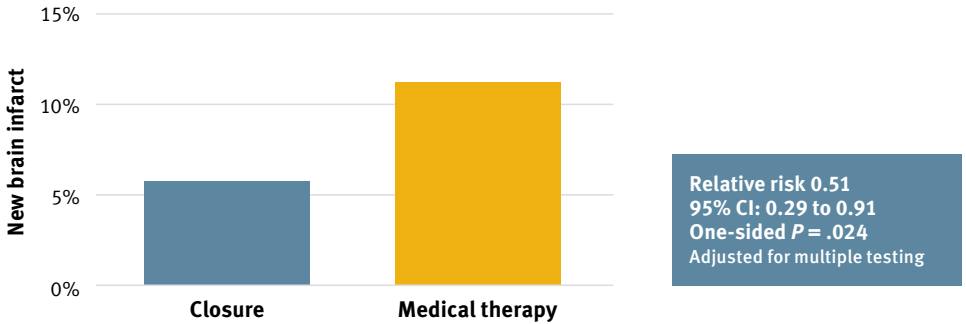
Primary endpoint result: New brain infarct

- 49% relative risk reduction for PFO closure on new brain infarct at two years.
- Difference in incidence of new brain infarct of 5.6%.



The REDUCE Study is the first to assess the relationship between PFO closure and the reduction of new brain infarct.

Technical and PFO closure success

Performance outcome*	
Technical success†	98.8%
Effective closure‡ at 12 months (GORE® CARDIOFORM Septal Occluder)	98.0%

* Closure arm comprised of GORE® HELEX® Septal Occluder (39%) or GORE® CARDIOFORM Septal Occluder (61%). No significant differences in safety, performance, or efficacy between the two test devices.

† The proportion of closure subjects with successful implant and retention of study device after implant attempt with study device.

‡ Freedom from large shunt (> 25 bubbles) in subjects with retained study device as detected by transthoracic echocardiography adjudicated by Echo Core Lab. 75.6% complete closure at 12 months.

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Adverse events

- No significant difference in overall SAE rate
- Low risk of device or procedure-related SAEs
- Deaths were uncommon and unrelated to study
  - Depression leading to suicide
  - Prior cardiovascular disease leading to an acute cardiovascular event

All enrolled subjects (N = 664)	Closure (N = 441)	Medical (N = 223)
Any serious adverse events (SAE)*	**102 (23.1%)**	**62 (27.8%)**
Device-related SAE	6 (1.4%)	–
Procedure-related SAE	11 (2.5%)	–
Death*	**2 (.5%)**	**0 (0%)**

* All *P*-values > .2.

Adverse events

- The risks of serious bleeding, deep-vein thrombosis and pulmonary embolism did not differ significantly between study groups.
- Atrial fibrillation (AF) / flutter was higher in the closure group, but it was usually transient.
  - Onset in first 45 days: 83%
  - Resolved within two weeks: 59%
  - 1 / 29 with AF after closure had a stroke
- No significant difference in serious AF / flutter rates.

All enrolled subjects (N = 664)	Closure (N = 441)	Medical (N = 223)	P-value
Serious bleeding adverse events	**8 (1.8%)**	**6 (2.7%)**	**.57**
Any AF / flutter adverse events	**29 (6.6%)**	**1 (0.4%)**	**< .001**
Serious AF / flutter	10 (2.3%)	1 (0.4%)	.11
Serious device adverse events*	**6 (1.4%)**	**–**	**–**
Any DVT or pulmonary embolism (PE) adverse events	**3 (0.7%)**	**2 (0.9%)**	**1.0**

* Serious device events included device embolization (0.7%), device thrombosis (0.5%), and aortic dissection (0.2%).

Global REDUCE Study sites

Study sites		
Karolinska Hospitals, Huddinge and Solna	Tufts Medical Center	The Methodist Hospital
Aarhus University Hospital	University of Kentucky	Lawson Health Research Institute
Glostrup Hospital	Riverside Methodist Hospital	Montreal Heart Institute
Haukeland University Hospital	South Denver Cardiology Associates	NorthShore University HealthSystem
Turku University Central Hospital	University of Alberta	University of Pittsburgh Medical Center
Sahlgrenska University Ostra Hospital	Guilford Neurologic Associates	Moffitt Heart & Vascular Group
Lund University Hospital	Santa Barbara Cottage Hospital	Saint Joseph's Hospital
Royal Sussex County Hospital	Columbia University Medical Center	Medical Center of the Rockies
Bispebjerg Hospital	Millard Fillmore Gates Circle Hospital	University of Tennessee
Royal Victoria Hospital	Medical College of Wisconsin	Aventura Hospital and Medical Center
Oslo University Hospital	The Christ Hospital	Emory University
Nottingham University Hospitals	Carolinas Medical Center	Morristown Memorial Hospital
Birmingham University Hospital	Cox Health	Intermountain Medical Center
Rigshospitalet	Cleveland Clinic	Beaumont Hospital
Hillerød Hospital	Loyola University	Neurology Associates
St. Luke's Medical Center	Vancouver General Hospital	Nationwide Children's Hospital
Rush University Medical Center	Oklahoma Heart Institute	University of Wisconsin
Cedars Sinai Medical Center	Carilion Clinic Hospitals	Centennial Medical Center
University of Pennsylvania	Sentara Cardiovascular Research Institute	University of Utah
Appleton Medical Center / Theda Clark Hospital	Henry Ford Health System	Black Hills Cardiovascular
University of Virginia Medical Center	Winthrop University Hospital	University of Colorado

PFO closure with GORE® CARDIOFORM Septal Occluder

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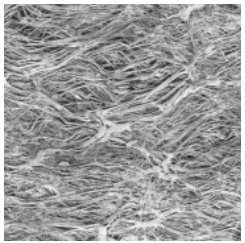
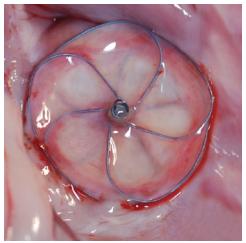
Material properties

Proprietary ePTFE

- Low thrombogenicity[6,7]
- Rapid endothelialization



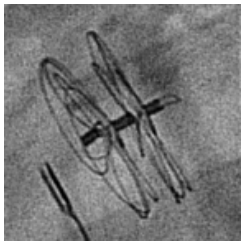
ePTFE 250x magnification



After 30 days in canine model

Platinum-filled nitinol

- Engineered for enhanced fluoroscopic visibility



Fluoro from IDE study subject taken at time of implant

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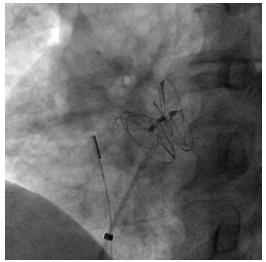
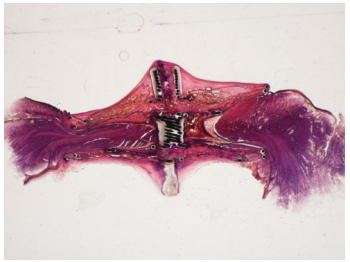
Design features

- Two soft conformable discs to span and cover the anatomy.
- Each disc has a five wire, independent petal design, providing optimal apposition and rapid endothelialization.
- Low thrombogenicity.[6,7]





After 90 days in canine model

* ePTFE – expanded polytetrafluoroethylene.

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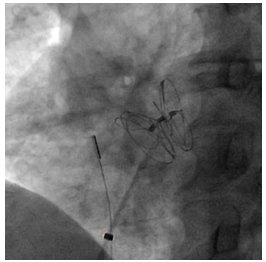
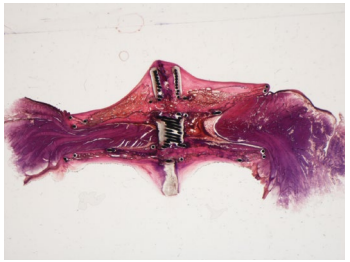
Occluder benefits — Soft, conformable and rapid occlusion

- Device design and material properties combine to optimize septal conformability and tissue ingrowth for short-term and long-term performance.
  - Rapid occlusion*
  - Conforms to surrounding anatomy
  - Optimal apposition
  - Low thrombogenicity[6,7]
  - Rapid endothelialization





After 90 days in canine model

* Rapid occlusion defined as Technical Success with completely occluded defect or residual shunt ≤ 2 mm at the completion of the implant procedure.

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Percutaneous PFO closure with GORE® CARDIOFORM Septal Occluder

Video: GORE® CARDIOFORM Septal Occluder

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PFO procedural equipment

Equipment considerations

High resolution fluoroscopy

- TEE or Intracardiac Echo (ICE) with color flow doppler
- Required accessories
  - 10 Fr introducer sheath
  - Heparinized saline
  - Flushing syringe
  - Stopcock
  - Sizing balloon
  - Sterile bowl for flushing catheter
- Optional accessories
  - 0.035" guidewire or smaller
  - 12 Fr introducer sheath when a guidewire is utilized

Post-procedural care

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Post-procedural care per REDUCE Study protocol

Post-procedural follow-up visit protocol

Discharge	1 month	6 months	12 months
Physical exam, ECG, TTE	Physical exam, ECG, TTE	Physical exam, ECG, TTE	Physical exam, ECG, TTE

Fluoroscopic examination should be considered in instances where device stability is questionable.

Post-procedural medical therapy protocol

Patients should take appropriate prophylactic antibiotic therapy consistent with the physician's routine procedures following device implantation.

First three days post implant	Fourth day plus — options: ASPIRIN Acetylsalicylic Acid (81–325 mg daily), combination ASPIRIN Acetylsalicylic Acid (50–100 mg daily) and PERSANTINE Dipyridamole (225–400 mg once daily) or PLAVIX® Clopidogrel Bisulfate (75 mg daily) antiplatelet therapy should be used indefinitely
75 mg clopidogrel	

Post-procedural activity

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

Hospital rest for up to one day	One to two days light to moderate activity	Two weeks plus — strenuous physical routine

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Adverse events

Adverse events associated with the use of the GORE® CARDIOFORM Septal Occluder may include, but are not limited to:

Most common

- A noticed or unnoticed rapid or irregular heartbeat
- Headache or migraine
- Dizziness or abnormal sensation
- Chest pain or discomfort
- Upper respiratory infection
- Back pain
- Nausea
- High or low blood pressure
- Pain at the incision site
- Difficulty breathing
- Bleeding
- Fatigue
- Anxiety

Most serious

- Death
- Stroke (major or minor)
- Heart attack
- Kidney failure
- Clot formation or blood vessel blockage due to clots or air
- Injury to the heart or blood vessels
- Perforation of the heart muscle or blood vessels
- Blood or fluid build-up between the heart and the sac covering the heart
- Infection

Other

- Movement of the device from its position in the PFO to other parts of the body
- A second surgical or interventional procedure

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Imaging examples of percutaneous PFO closure with GORE® CARDIOFORM Septal Occluder

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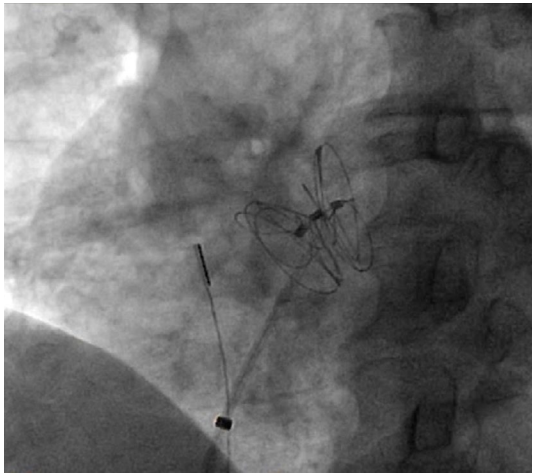
Imaging examples of percutaneous PFO closure with GORE® CARDIOFORM Septal Occluder

Closure of a PFO with a long tunnel and atrial septal aneuruysm



Video: Defect interrogation of long tunnel and ASA

Video: Occluder release in long tunnel and ASA

Imaging examples of percutaneous PFO closure with GORE® CARDIOFORM Septal Occluder

Closure of a PFO with a thick secundum

Video: Defect interrogation of thick secundum

Video: Occluder release in thick secundum

Video: Occluder deployment in thick secundum

PFO closure — Step by step

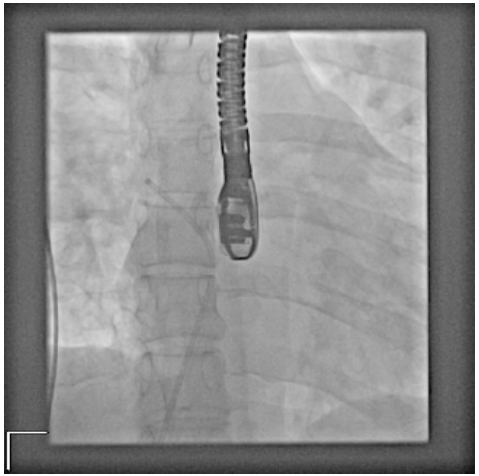
Assess the PFO anatomy with TEE / ICE

Video: Defect interrogation in TEE bicaval

Video: Defect interrogation in TEE aortic short axis

PFO closure — Step by step

Femoral vein access



- Local anesthesia with lidocaine at the right groin
- Echo-guided puncture of the right femoral vein below the inguinal ligament
- Insertion of a 7 Fr introducer in the femoral vein
- Insertion of a multipurpose catheter in the right atrium

PFO closure — Step by step

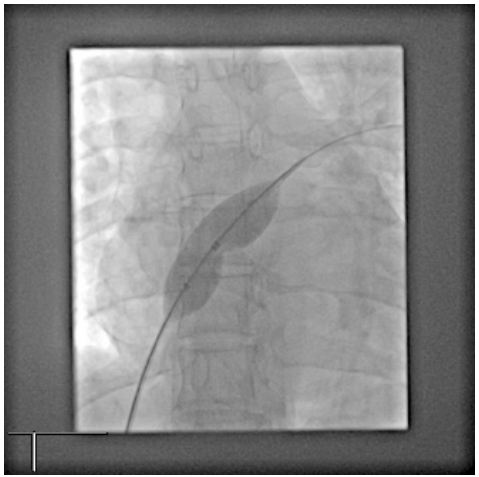
Access the PFO

Video: Guidewire placement

- Insertion of a J-tipped 0.035" guidewire through the PFO with multipurpose catheter
- Advanced the guidewire and multipurpose catheter into the left superior pulmonary vein
- Exchange the standard 0.035" guidewire for a stiff 0.035" guidewire
- Exchange the femoral introducer for a 12 Fr introducer

PFO closure — Step by step

Sizing the PFO



- The stiff 0.035" guidewire across the PFO will provide information about the PFO anatomy.
- Additional information should be obtained from stop flow balloon sizing.
- Place a contrast filled, compliant balloon (14 mm) across the defect and gently inflate until shunting through the defect has stopped.
- Measure the diameter of the defect using either TEE / ICE or calibrated fluoroscopy.
- Remove the sizing balloon.

PFO closure — Step by step

Delivering the GORE® CARDIOFORM Septal Occluder

Video: Advancing the delivery system

- Advance the delivery catheter over the wire across the atrial septum until the tip is positioned within the left atrium under fluoroscopic and echo guidance.

PFO closure — Step by step

Deploy, lock and release the GORE® CARDIOFORM Septal Occluder

Video: Occluder deployment in fluroscopy

Video: Occluder deployment in echo

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INDICATIONS/INTENDED USE: 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

Products listed may not be available in all markets.

W. L. Gore & Associates, Inc.
Flagstaff, AZ 86004

+65 67332882 (Asia Pacific)
1800 680 424 (Australia / New Zealand)
00800 6334 4673 (Europe)
800 437 8181 (United States)
928 779 2771 (United States)

goremedical.com