# Catheter-Based Approach for Prevention of Stroke in 2018: PFO, LAA closure and cerebral protection

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# Disclosure Statement of Financial Interest
## Saibal Kar, MD, FACC

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

| Affiliation/Financial Relationship | Company |
| --- | --- |
| • Grant/Research Support | • Abbott Vascular,Boston Scientific, Edwards Lifesciences, WL Gore, Mitralign |
| • Consulting Fees/Honoraria | • Abbott Vascular, Boston Scientific, WL Gore |
| • Other Financial Benefit | • Valcare |

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# *Cardioembolic stroke*

- Atrial fibrillation
- Valvular heart disease
- Cardiomyopathy
- Tumors
- Endocarditis
- Paradoxical embolism through a PFO

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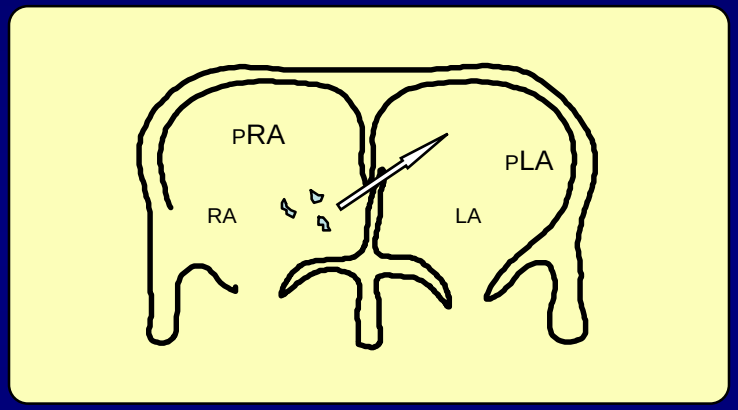
# Patent Foramen Ovale(PFO)
# Normal variant presented in 20% of population




On Valsalva, PRA > PLA

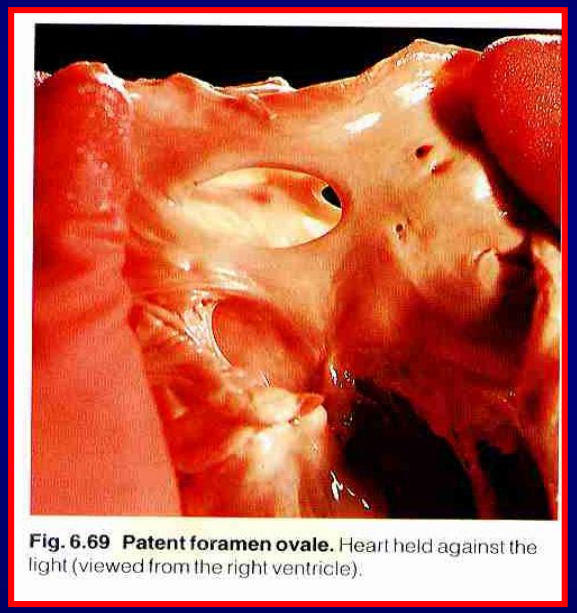
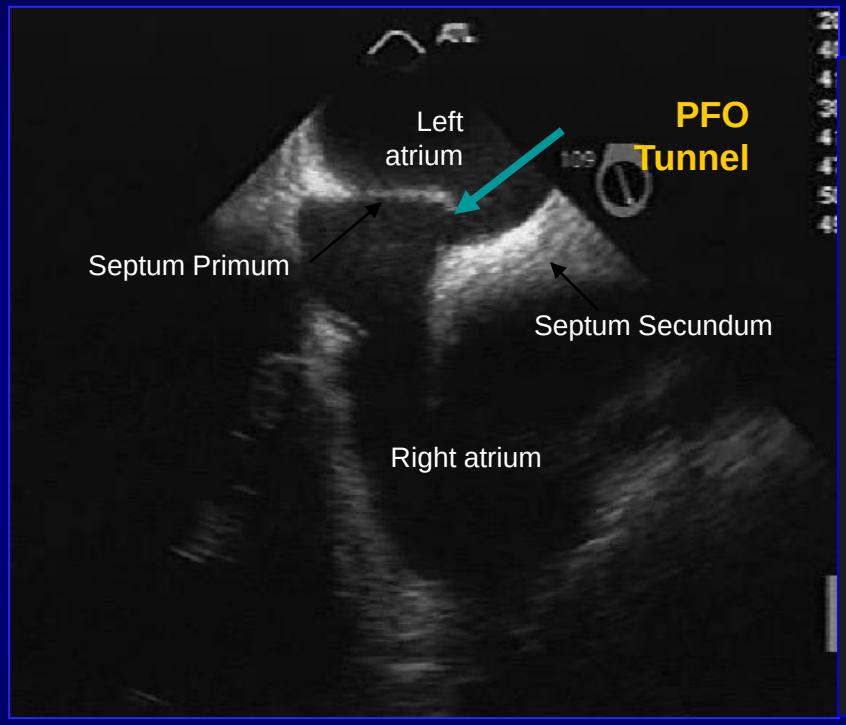


**Fig. 6.69 Patent foramen ovale.** Heart held against the light (viewed from the right ventricle).

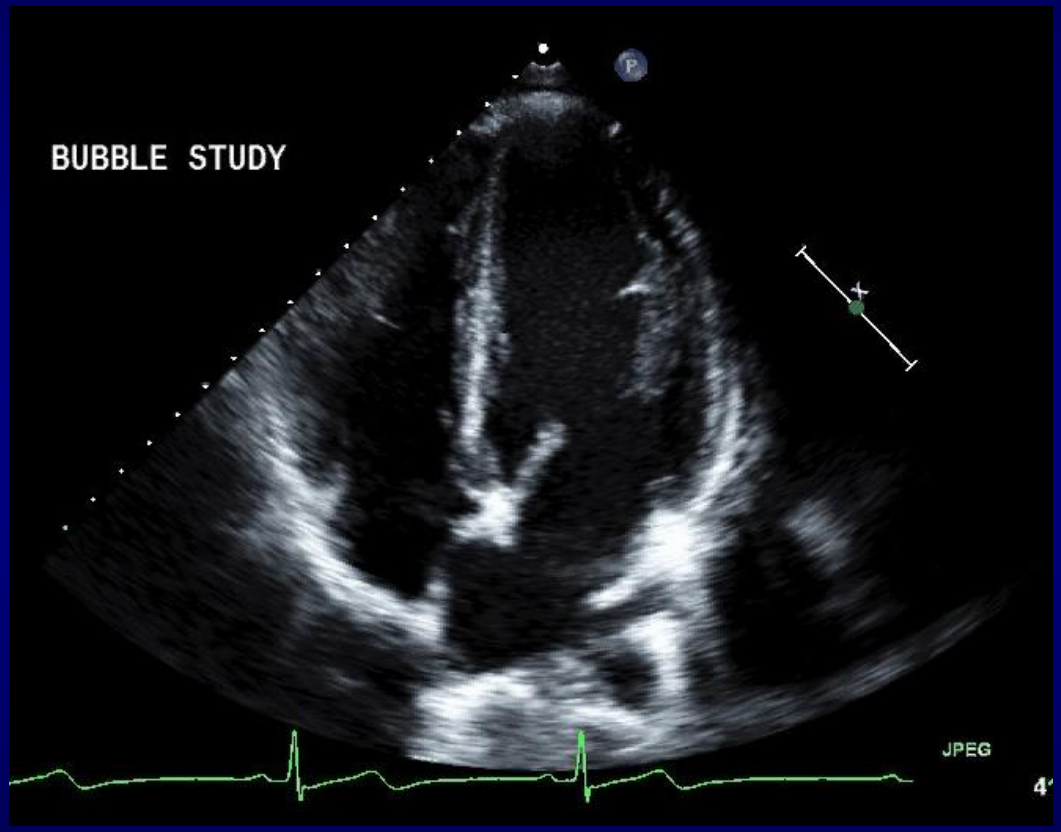
# PFO Anatomy



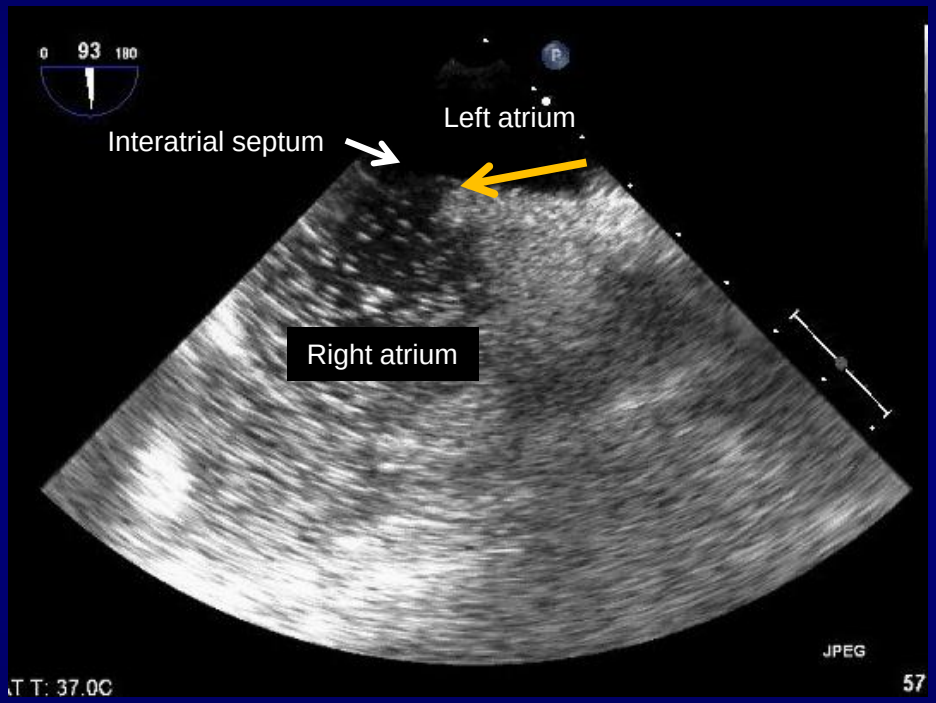

Atrial septal aneurysm: (ASA) = Hypermobile Septum primum

Size of PFO is determined By the number of bubbles Cross from right to left During agitated saline Injection in the right side

# Bubble study

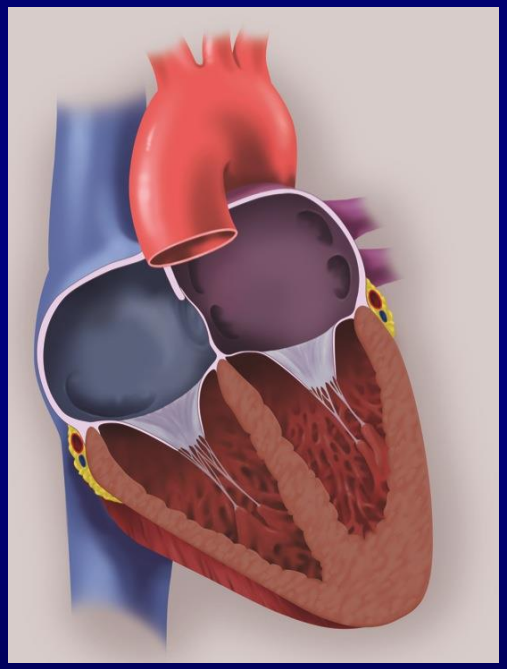


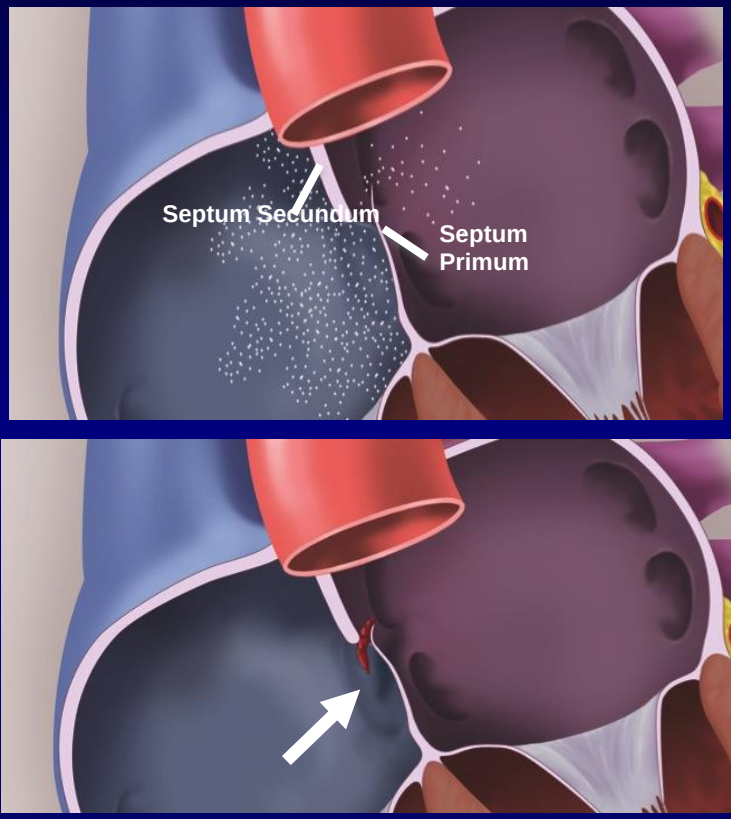
# Transesophageal Echo with bubble study



# Transcranial Doppler with bubble study

# Pathophysiology of PFO and Ischemic Stroke

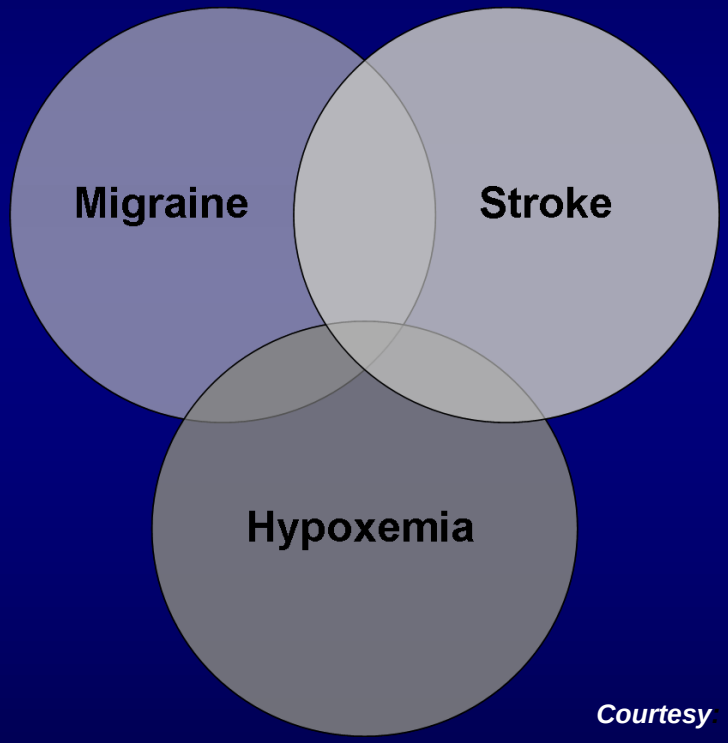





**Blood clot passing through the PFO as a paradoxical embolism *or* originating in the PFO becoming an embolism**

# PFO Syndromes:

## Isolated or Combined




*Courtesy:* ***Dr John Carroll***

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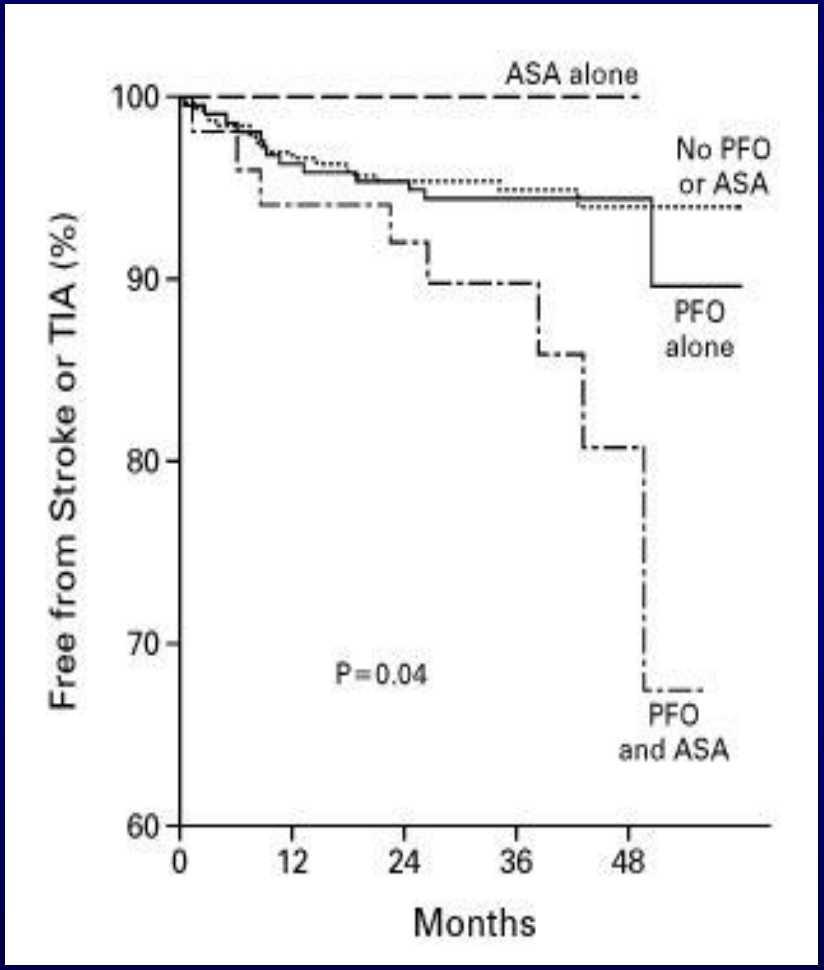
# *Recurrent Cerebrovascular Events Associated with PFO, Atrial Septal Aneurysm, or Both*

- 581 patients with cryptogenic CVA
- ASA 300 mg/day
- 4 year F/U



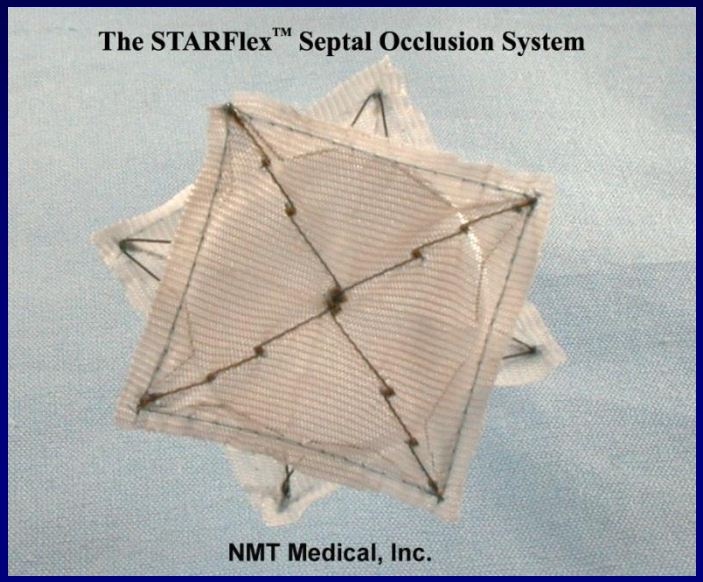

Mas, et al. NEJM Dec 13, 2001

Cedars-Sinai Medical Center

# PFO Stroke Trials

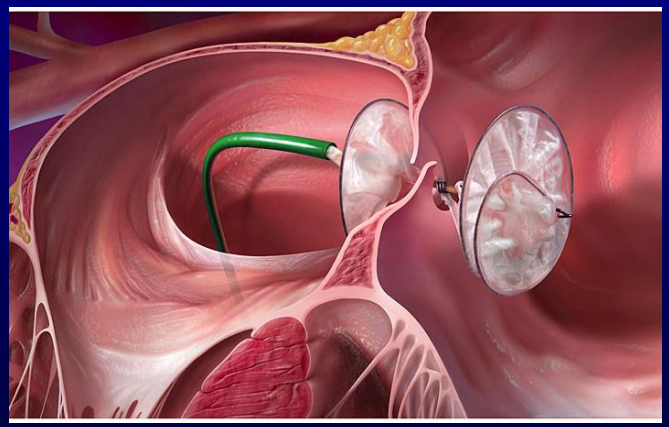
| Trial | Respect | Closure I | Reduce | PC trial | Close |
|---|---|---|---|---|---|
| N | 980 | 909 | 664 | 210 | 664 |
| Randomization | 1:! | 1:1 | 2:1 | 1:1 | 1:1:1 |
| Device (Company) | Amplatzer (AGA) | StarFlex (NMT) | Helex/Gore Septal Occluder | Amplatzer PFO | Any approved PFO device |
| Inclusion | Cryptogenic Stroke + PFO | Cryptogenic Stroke or TIA + PFO | Cryptogenic Stroke or MRI TIA + PFO | Cryptogenic Stroke of MRI TIA + PFO | Cryptogenic Stroke or retinal ischemia with a large PFO |
| Primary Endpoint | Stroke | Stroke or TIA | Stroke or MRI TIA | Composite all cause mortality, stroke, TIA, peripheral embolism | Fatal and non fatal stroke |
| Key Secondary Endpoints | ? Migraine | ? Migraine | MRI WMLs | | |

# Techniques of Closure
# PFO Occluder in Clinical Trial




STARFlex (NMT Med)

PFO occluder (AGA Med)



Helex Septal Occluder (Gore)

Gore Septal Occluder (Gore)

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# Initial data from the CLOSURE I, RESPECT, and PC trial

- Non statistically significant reduction of stroke
- No safety issues with device

# Clinical Data

- RESPECT trial  long term data
- REDUCE trial
- CLOSE Trial

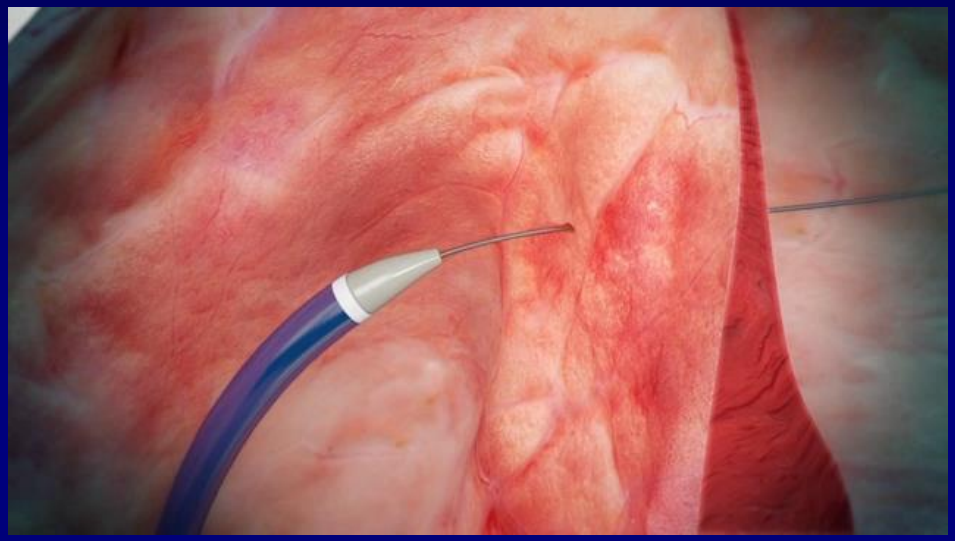
# AMPLATZER™ PFO Occluder

**Device Description:**

- Self-expandable double disc device lined with thin polyester fabric
- Linked together by a short connecting waist
- Nitinol wire mesh
- Recapturable, repositionable
- Self-centering
- Distal and proximal radiopaque marker bands
- MR conditional
- End screw to facilitate optimal handling

**Current status:**

- CE-Mark in 1998; currently available in > 80 countries worldwide
- FDA approved for PFO closure



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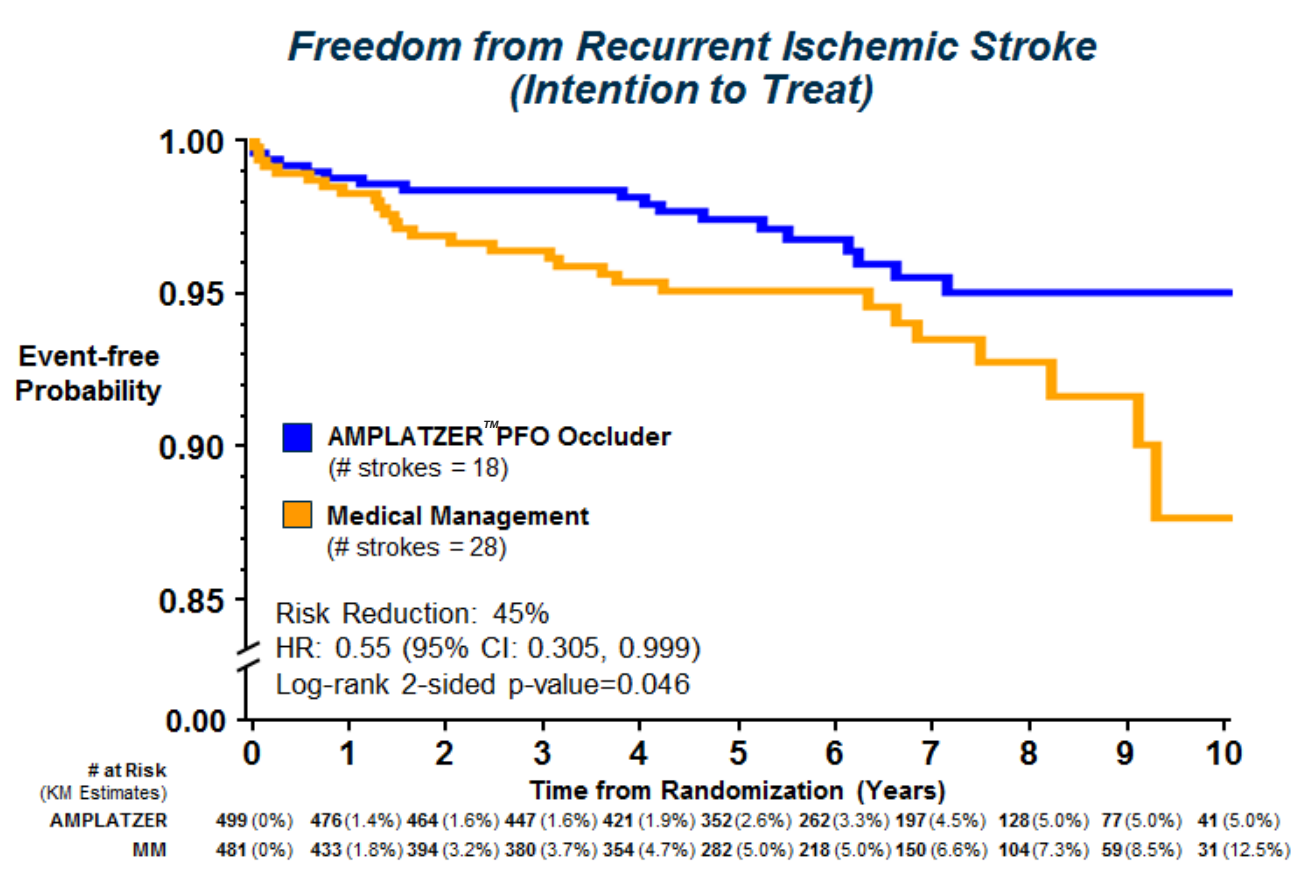
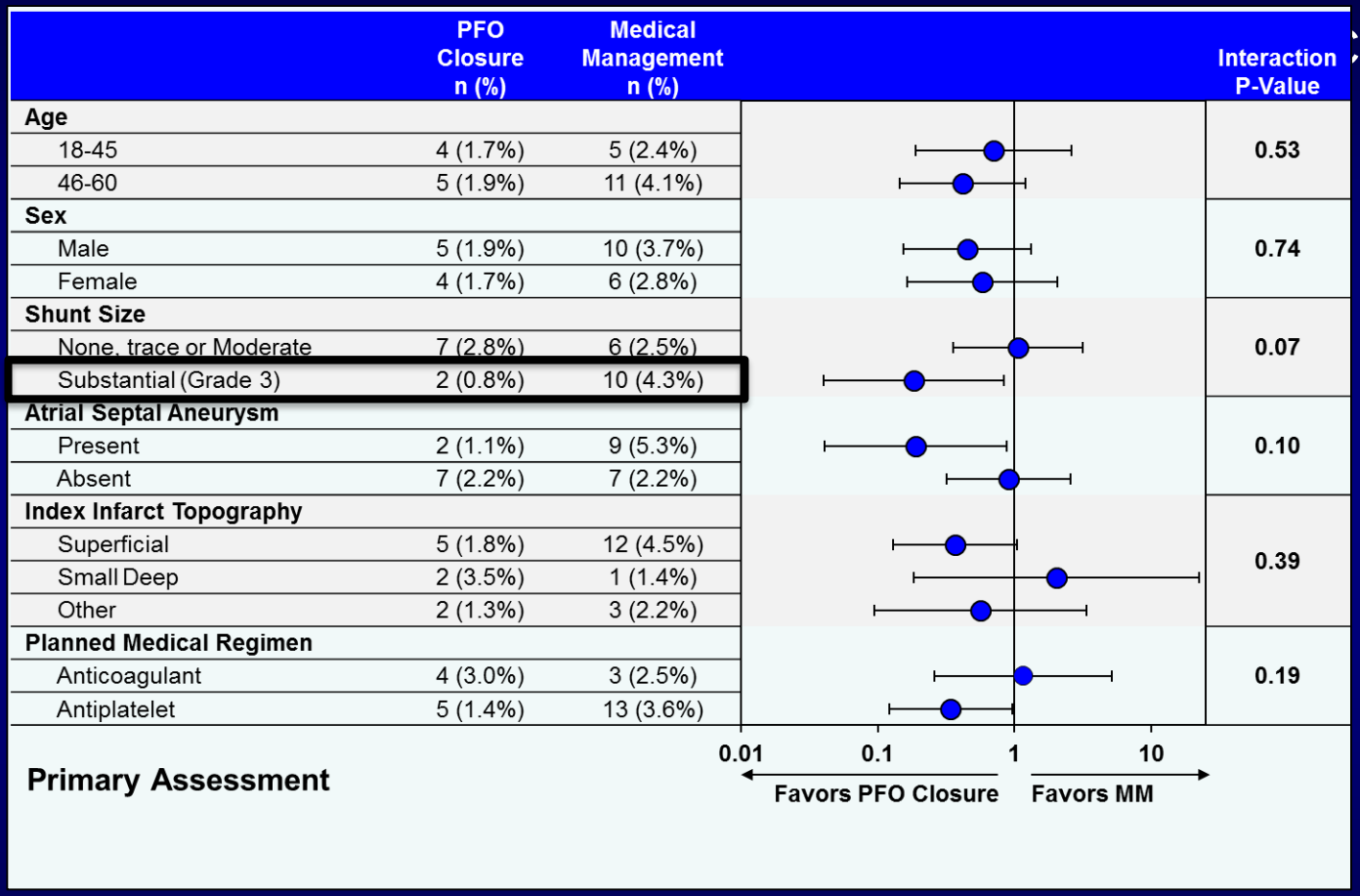
| Primary Endpoint | Stroke | | | | |
| Key Secondary Endpoints | ? Migraine | | | | |

Long term follow up: Mean 5.9 years
Randomized to Amplatzer PFO occlude
or
Medical treatment (Antiplatelet or oral anticoagulant)

# RESPECT Final Results



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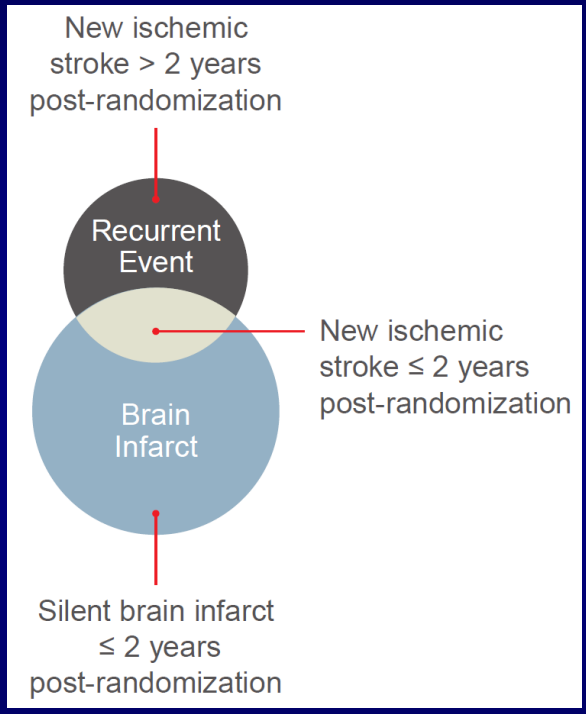
2:1 randomization
Control Arm: Antiplatelet therapy (US and EU guidelines

# Co-Primary Endpoints

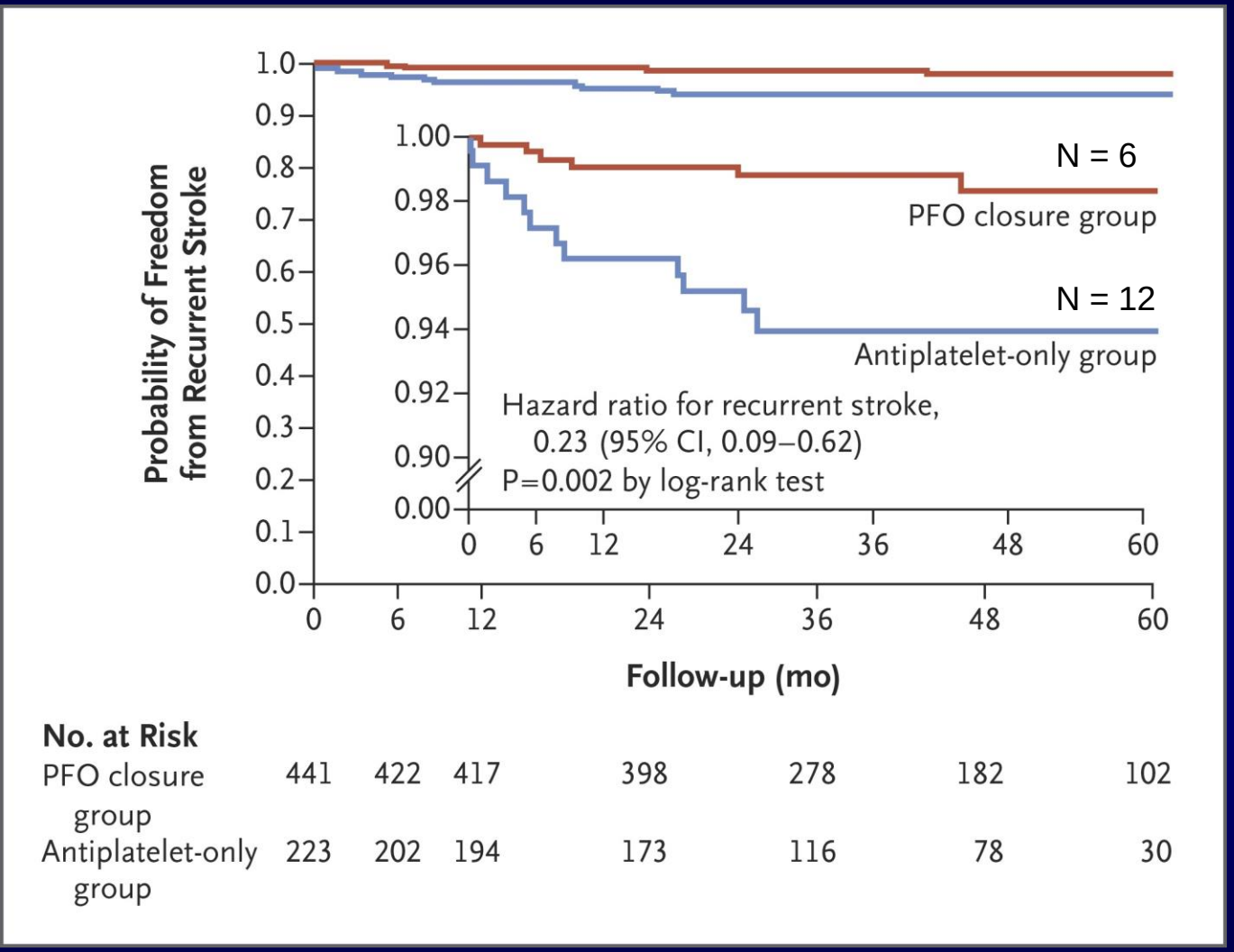
- Freedom from **recurrent clinical ischemic stroke** through at least 24 months
- Incidence of **new brain infarct** (defined as clinical ischemic stroke or silent brain infarct*) through 24 months




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

# Probability of Freedom from Clinical Evidence of Recurrent Ischemic Stroke.

## 77% reduction of risk of stroke




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| PFO closure group | 441 | 422 | 417 | 398 | 278 | 182 | 102 |
| Antiplatelet-only group | 223 | 202 | 194 | 173 | 116 | 78 | 30 |

Annualized event rates

Closure: 0.39 per 100 person-years

Medical: 1.70 per 100 person-years

Søndergaard L et al. N Engl J Med ;377:1033-1042

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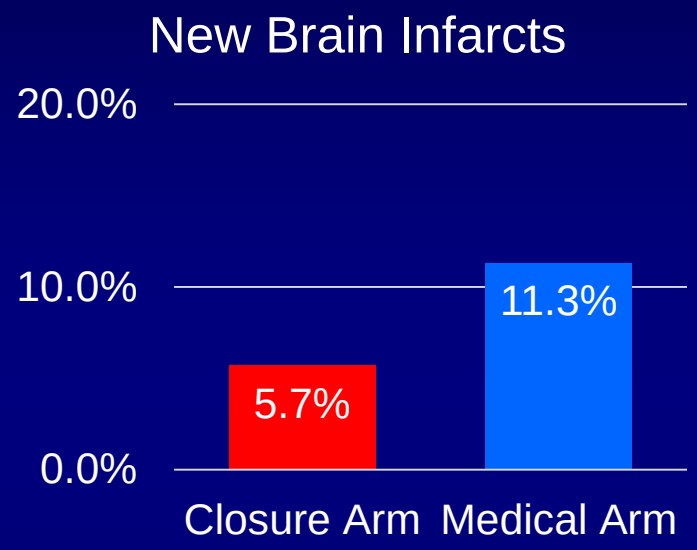
# Second co-primary endpoint: new brain infarct, intention-to-treat

| | Closure (N=441) | Medical (N=223) |
|---|---|---|
| Subjects without Evaluation | 58 | 46 |
| Brain Infarct Evaluable | 383 | 177 |
| **Brain Infarct Present** | **22 (5.7%)** | **20 (11.3%)** |
| Recurrent Stroke Only | 3 | 6 |
| Both | 2 | 6 |
| Silent Brain Infarct Only | 17 | 8 |
| Brain Infarct Absent | 361 (94.3%) | 157 (88.7%) |




- **Difference in incidence of new brain infarct of 5.6%**
- **Relative risk 0.51; 95% CI: 0.29 to 0.91**
- **p=0.024** after adjustment for multiple testing
- silent infarcts about twice as common as clinical stroke

# PFO Stroke Trials

| Trial | Respect | Closure I | Reduce | PC trial | Close |
|---|---|---|---|---|---|
| N | | | | | 664 |
| Randomization | | | | | 1:1:1 |
| Device (Company) | | | | | Any approved PFO device |
| Inclusion | | | | | Cryptogenic Stroke or retinal ischemia with a large PFO |
| Primary Endpoint | | | | | Fatal and non fatal stroke |
| Key Secondary Endpoints | | | | | |

Academically driven multicenter study
Sponsored by French Ministry of health

Mean follow up: 5.3 years

# CLOSE
## Methods

### Key inclusion criteria

- Recent (<= 6 months) ischemic stroke, confirmed by neuroimaging, mRS <= 3
- Strictly defined causes of stroke other than PFO ruled out by appropriate investigations
- PFO with ASA > 10 mm (TTE), PFO with large shunt > 30 microbubbles (TTE,TEE) confirmed by echo core lab before randomization

### Key exclusion criteria

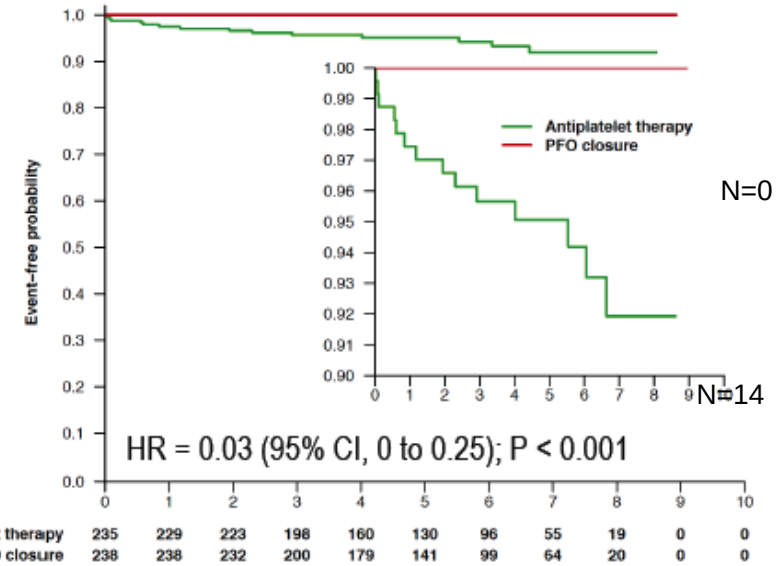
- Contraindication to oral anticoagulants and PFO closure
- Contraindication to antiplatelet therapy
- Increased bleeding risk
- Expected poor compliance or inability to attend follow-up visits
- Anatomical to device placement

### Outcomes

- **Primary** : fatal or nonfatal stroke
- **Secondary** : composite of ischemic stroke, TIA, or systemic embolism, all-cause mortality, vascular death, success of device implantation and success of PFO closure
- **Safety** : major procedural complications and major hemorrhagic complications

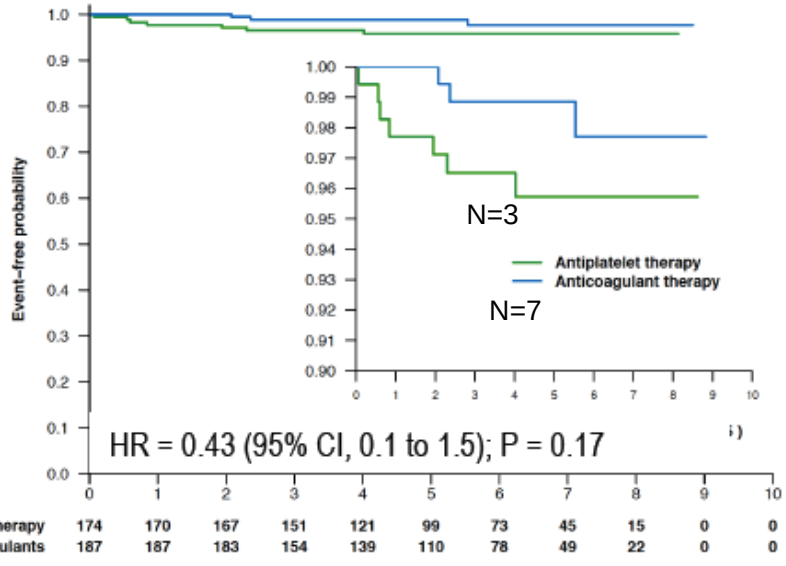
# CLOSE

## PFO closure vs. Antiplatelet therapy




| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Antiplatelet therapy | 235 | 229 | 223 | 198 | 160 | 130 | 96 | 55 | 19 | 0 | 0 |
| PFO closure | 238 | 238 | 232 | 200 | 179 | 141 | 99 | 64 | 20 | 0 | 0 |

## Oral anticoagulants vs. Antiplatelet therapy




| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Antiplatelet therapy | 174 | 170 | 167 | 151 | 121 | 99 | 73 | 45 | 15 | 0 | 0 |
| Oral anticoagulants | 187 | 187 | 183 | 154 | 139 | 110 | 78 | 49 | 22 | 0 | 0 |

5-yr absolute risk reduction = 4.9%
1 avoided stroke at 5 years for every 20 ( 17 to 25) patients treated with closure

Mas J-L et al. N Engl J Med ;377:1011-1021

# Safety issues

- Very low device or procedure related events
- No Device related deaths
- Slight increase in incidence of atrial fibrillation ( 5%) in the first few months following procedure

ORIGINAL ARTICLE

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

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

N Engl J Med 2017

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ORIGINAL ARTICLE

# Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

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

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

# Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke

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

# October 18, 2016:FDA approves first PFO device

- The AMPLAZTER PFO device is indicated for percutaneous transcatheter closure of a 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.

# March 2018

- FDA approved the Gore Septal Occluder for PFO closure for secondary prevention of cryptogenic stroke

# Summary ( All PFO trials)

- In selected patients with cryptogenic stroke, PFO closure is safe and effective in the reducing the risk of recurrent stroke compared to antiplatelet therapy /anticoagulant therapy alone
- PFO with large right to left shunt and/or atrial septal aneurysms benefit the most from closure
- Oral anticoagulants do not significantly reduce the risk of stroke recurrence in comparison to antiplatelet agents. However there is trend in favor of oral anticoagulants
- These results are likely to change clinical practice and REDUCE the risk of stroke for this population

# *Cardioembolic stroke*

- Atrial fibrillation
- Valvular heart disease
- Cardiomyopathy
- Tumors
- Endocarditis
- Paradoxical embolism through a PFO

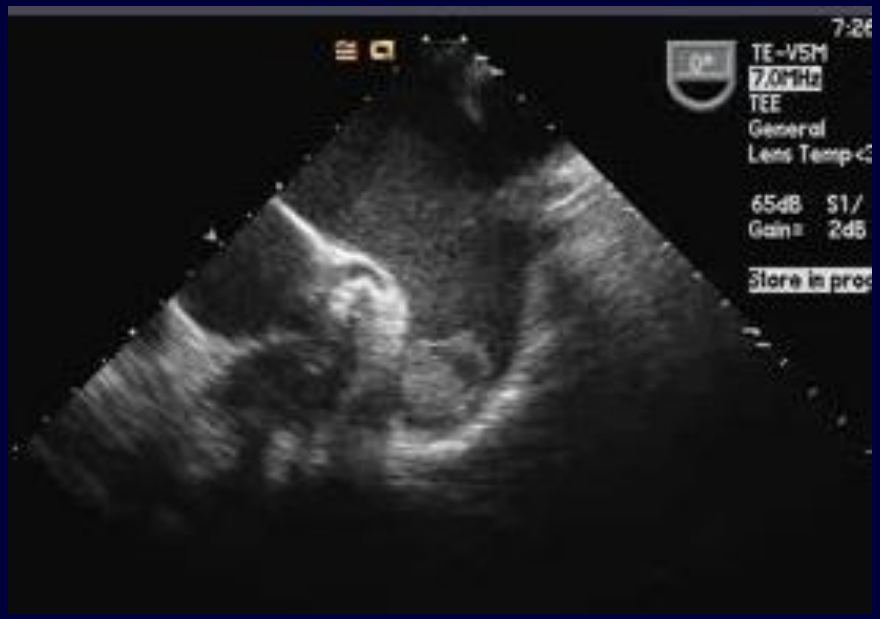
# Left atrial appendage and stroke

- Ischemic stroke is the major complication associated with atrial fibrillation (AF)
- Long term anticoagulant therapy though effective in stroke prevention, have important limitations:
  - Compliance
  - Bleeding risk
  - Drug failure

# Connection Between NVAF-Related Stroke and the Left Atrial Appendage

## AF Creates Environment for Thrombus Formation in Left Atrium

- In non-valvular AF, >90% of stroke-causing clots that come from the left atrium are formed in the LAA
- In Valvular AF stasis and clot formation can occur in any part of the left atrium [1]

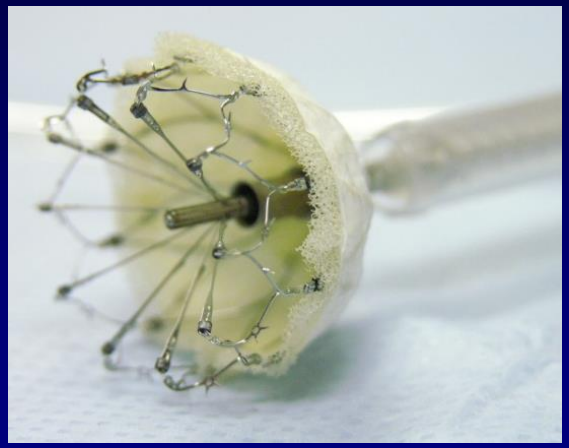



1. Blackshear JL. Odell JA., *Annals of Thoracic Surg* (1996)

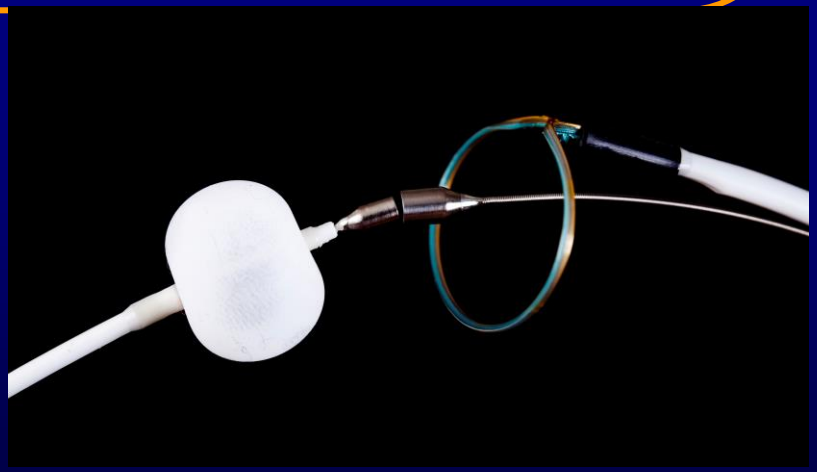
# Left atrial appendage closure(LAAC) strategies

Only FDA approved LAA closure device
For stroke prophylaxis

Watchman Device Gen II



Amulet Device Coherex Device
( Investigational in US)

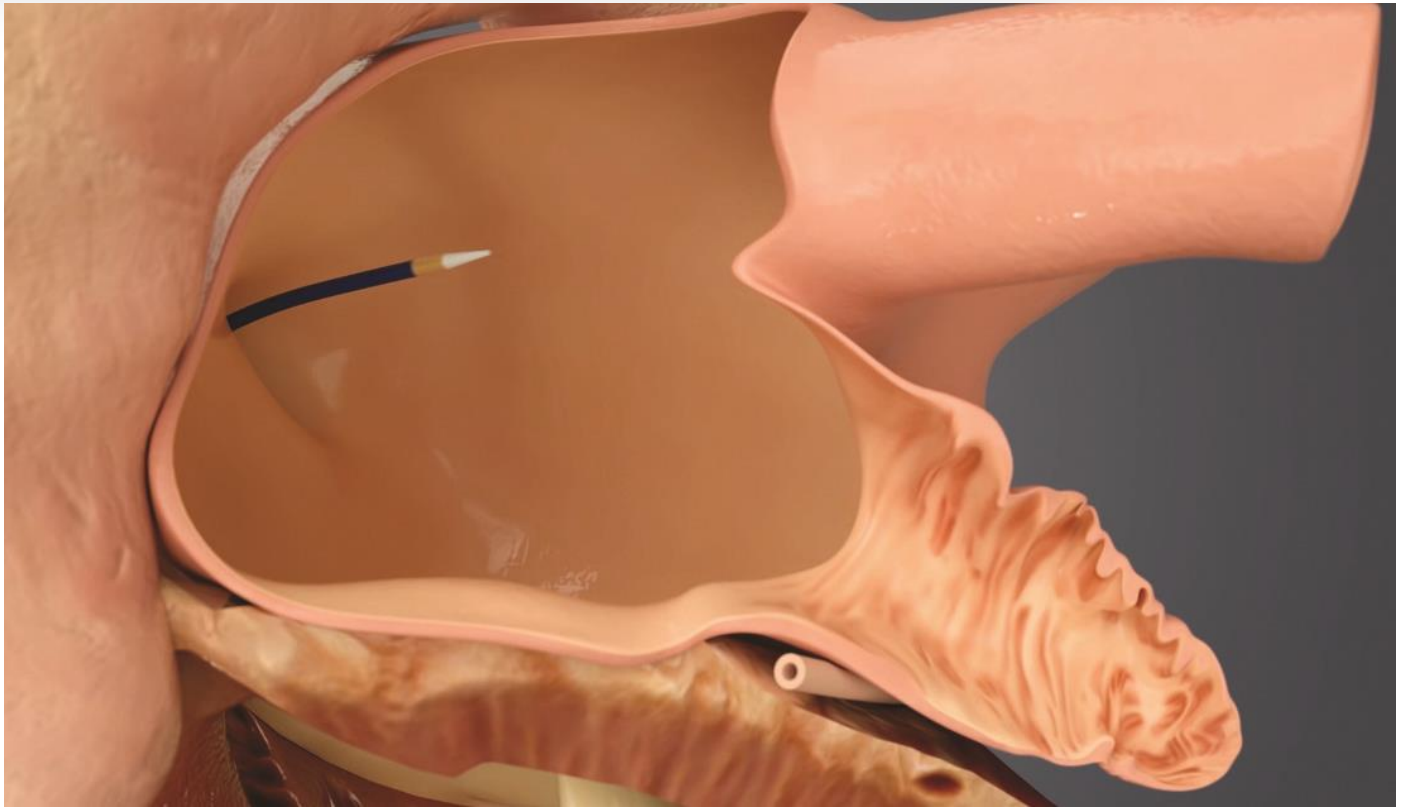


Lariat device

Atriclip device

# Procedure: Imaging and Transseptal Access

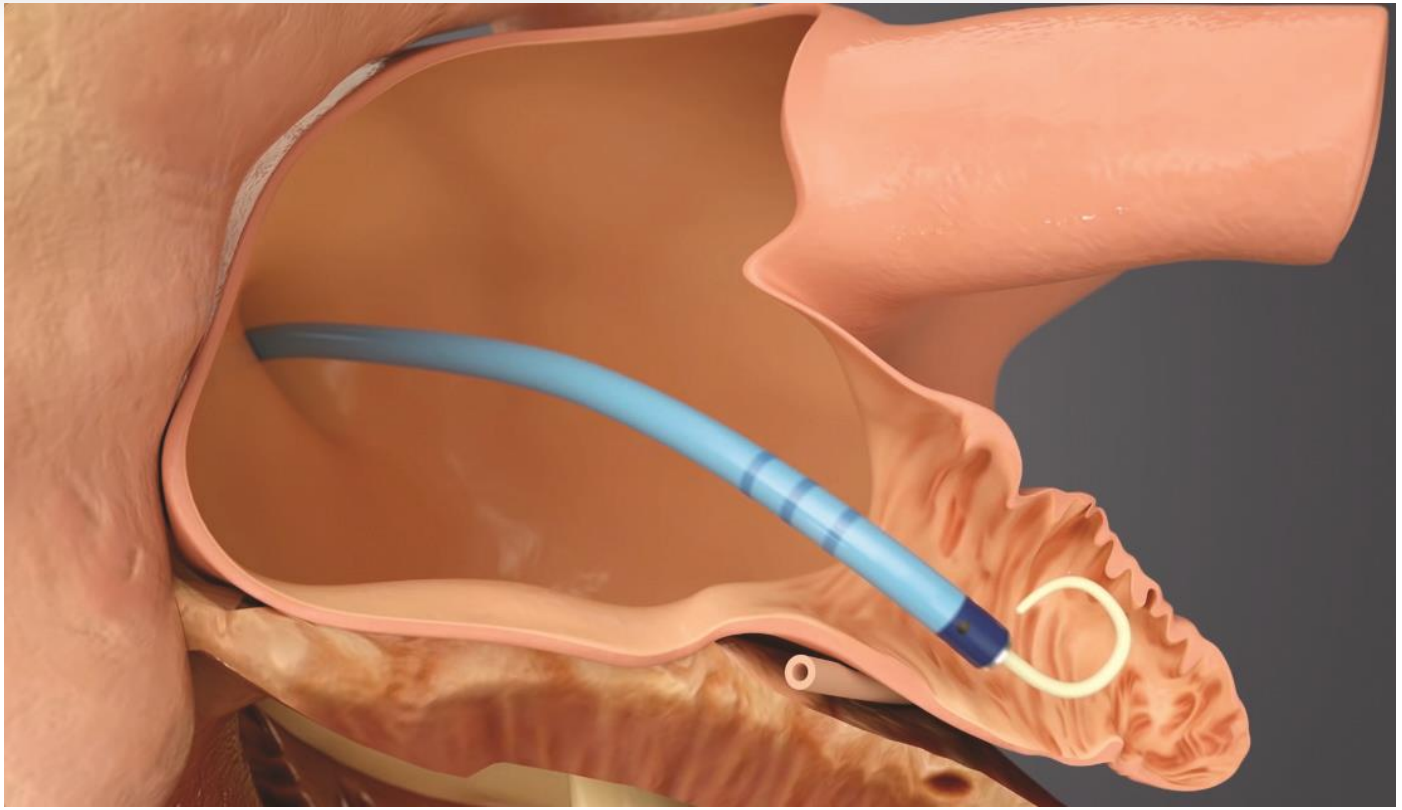




The interatrial septum is crossed using a standard transseptal access system and the procedure is performed with fluoroscopy and transesophageal echocardiography (TEE)

# Procedure: Navigating to the LAA

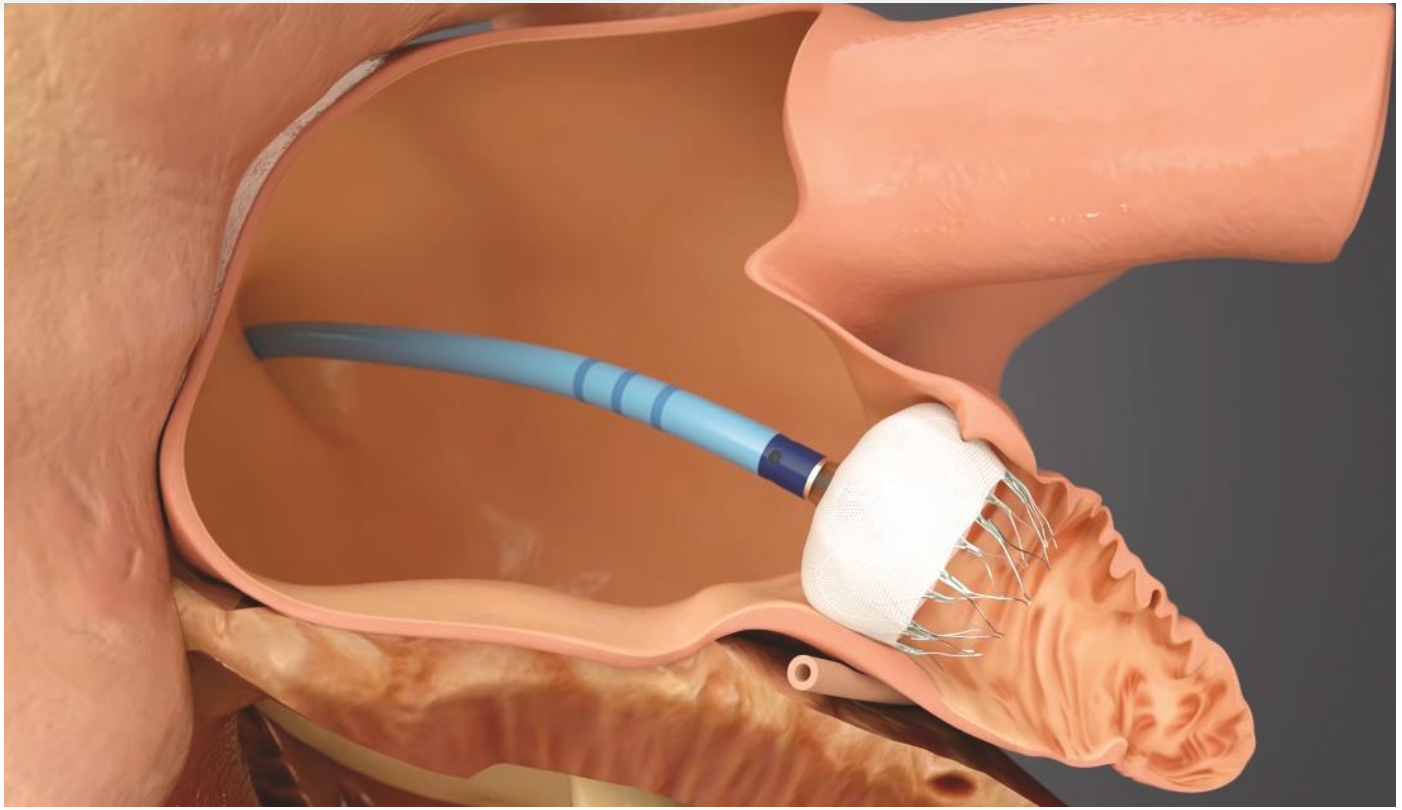




Access sheath is advanced over the guidewire into the left atrium and then navigated into the distal portion of the LAA over a pigtail catheter.

# Procedure: Navigating to the LAA

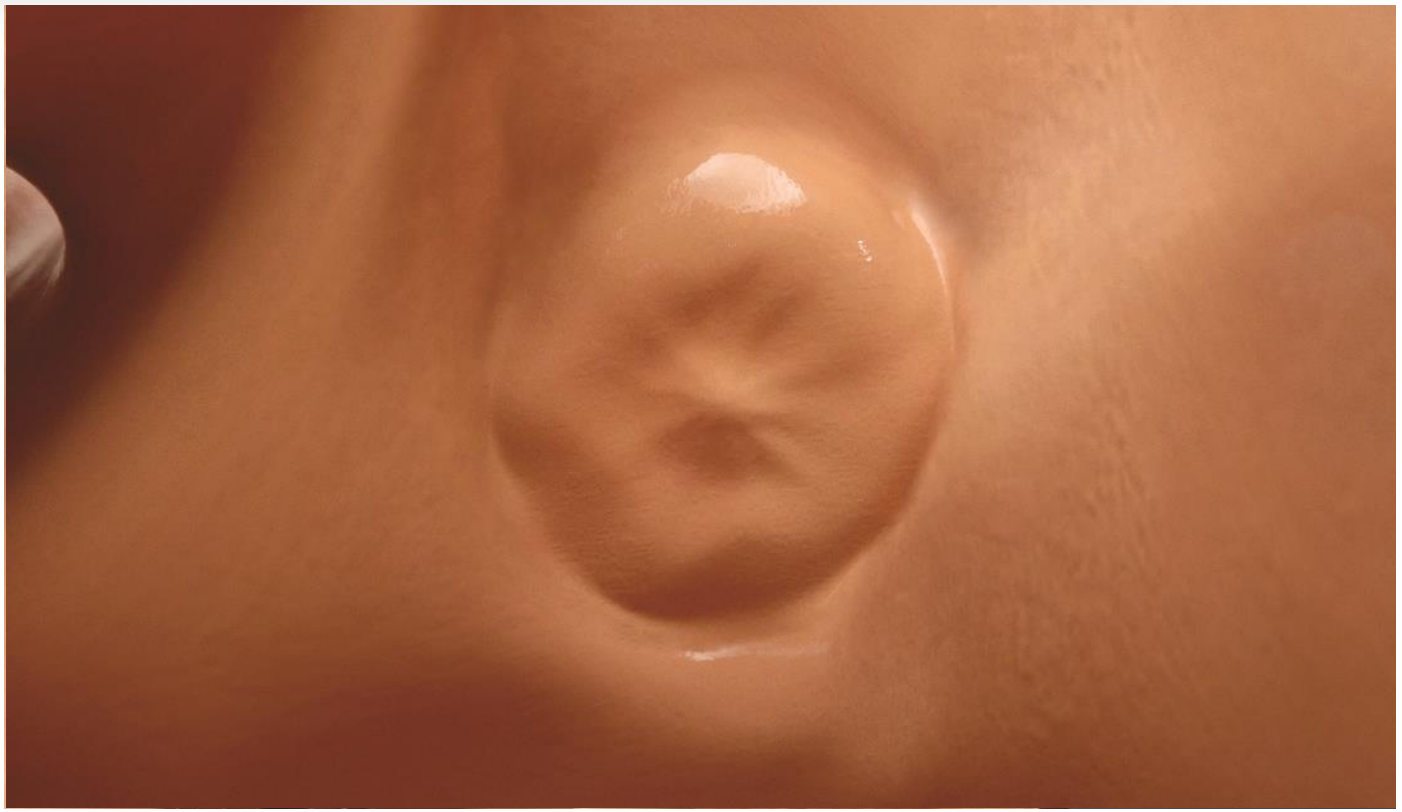




WATCHMAN is then deployed and released in the LAA.

# Procedure:
# Healing after ~45 days

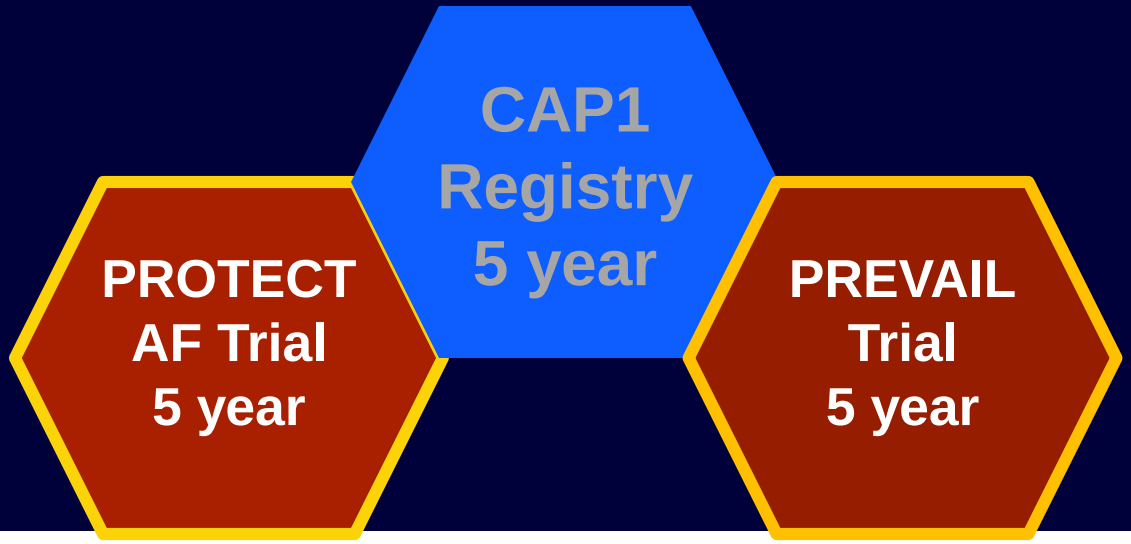
WATCHMAN™
LEFT ATRIAL APPENDAGE
CLOSURE DEVICE



Heart tissue grows over the WATCHMAN Implant, and the LAA is permanently sealed after approximately 45 days

# Clinical Evidence

- Randomized studies (Watchman device)
  - Two clinical trials
- Registries
- Post market registries



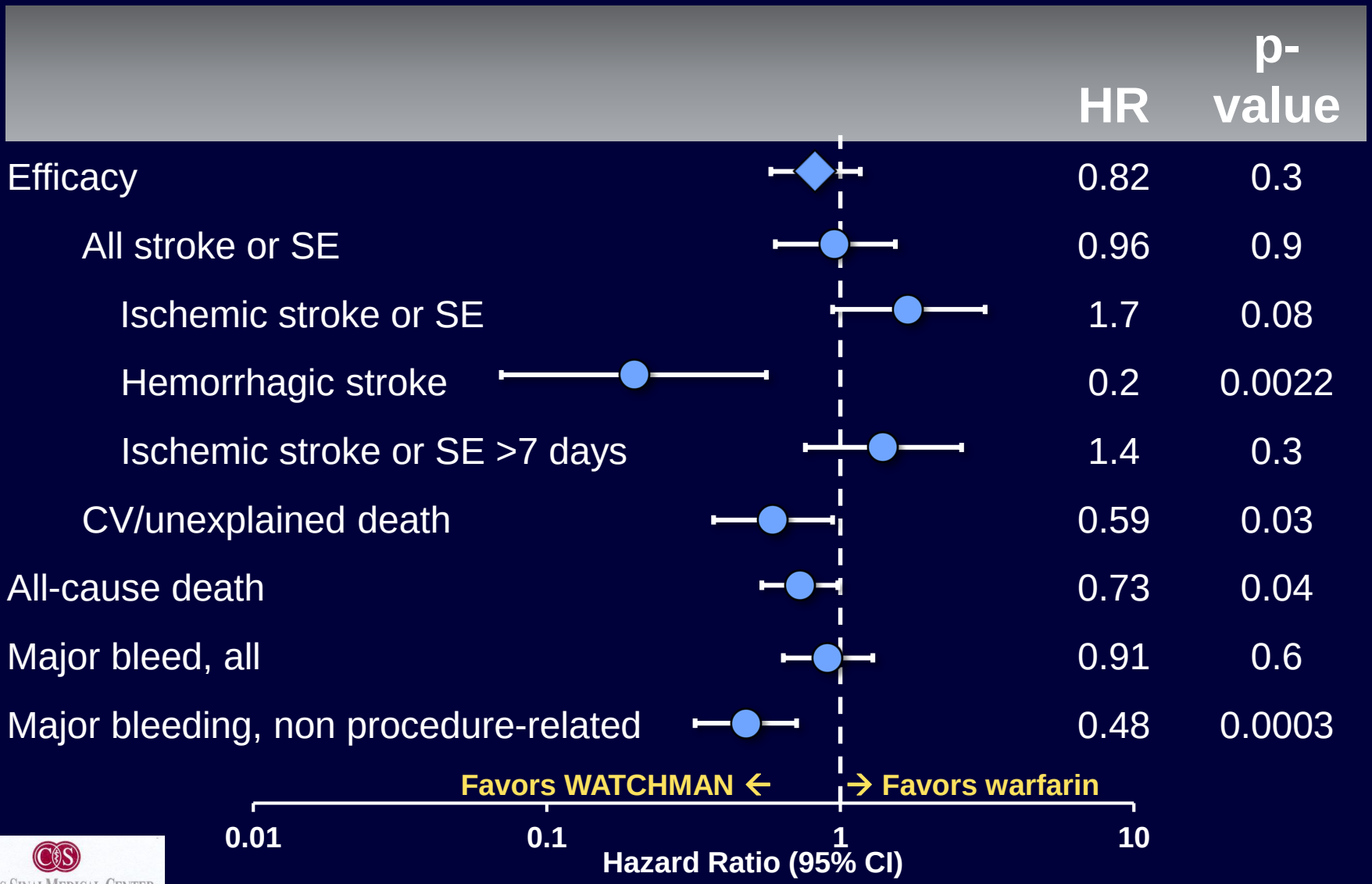

# 5-Year Outcomes After Left Atrial Appendage Closure

## From the PREVAIL and PROTECT AF Trials

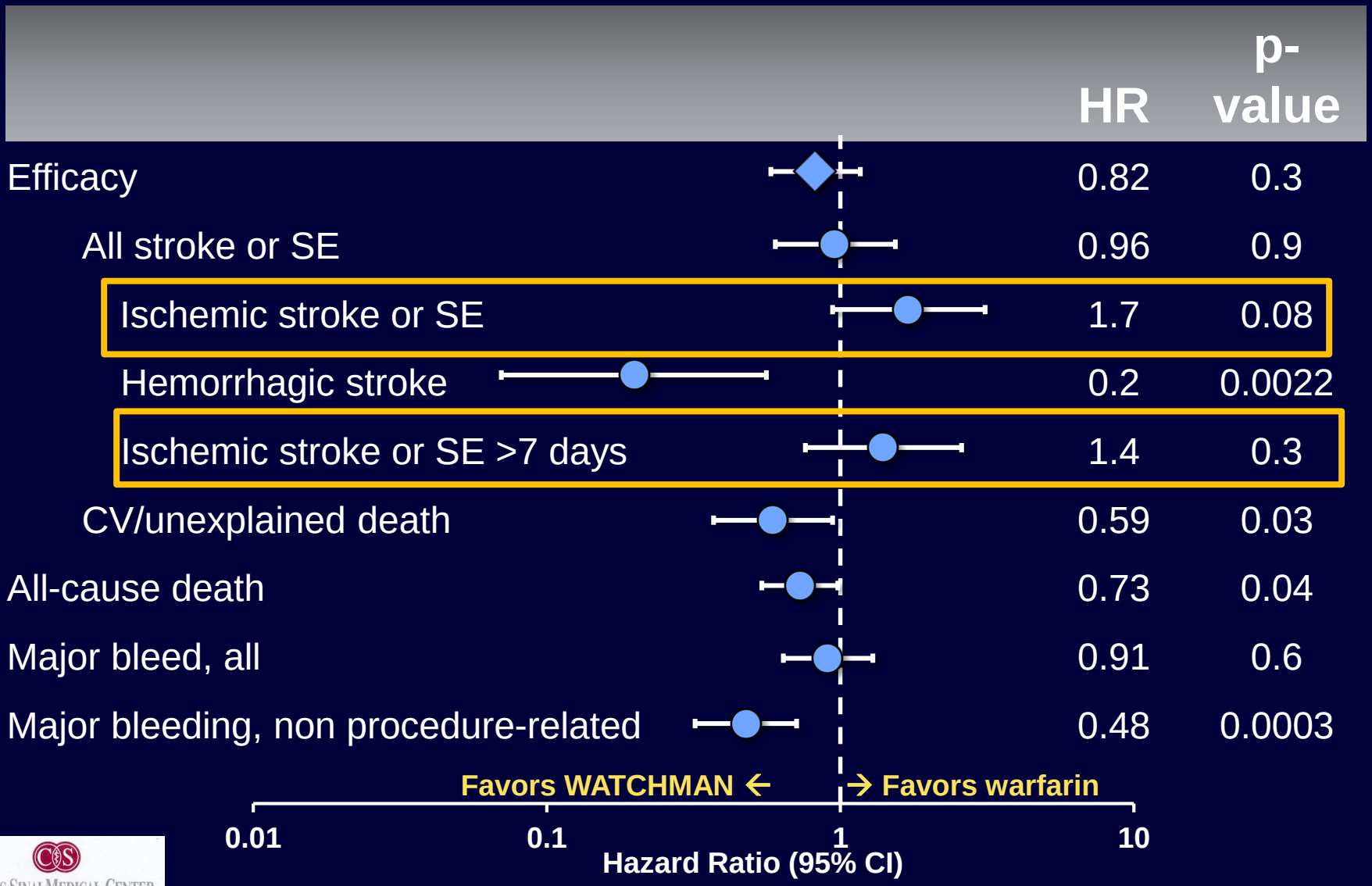
Vivek Y. Reddy, MD,[a,b] Shephal K. Doshi, MD,[c] Saibal Kar, MD,[d] Douglas N. Gibson, MD,[e] Matthew J. Price, MD,[e] Kenneth Huber, MD,[f] Rodney P. Horton, MD,[g] Maurice Buchbinder, MD,[h] Petr Neuzil, MD, PhD,[b] Nicole T. Gordon, BSEE,[i] David R. Holmes, Jr, MD,[j] on behalf of the PREVAIL and PROTECT AF Investigators

J Am Coll Cardiol 2017

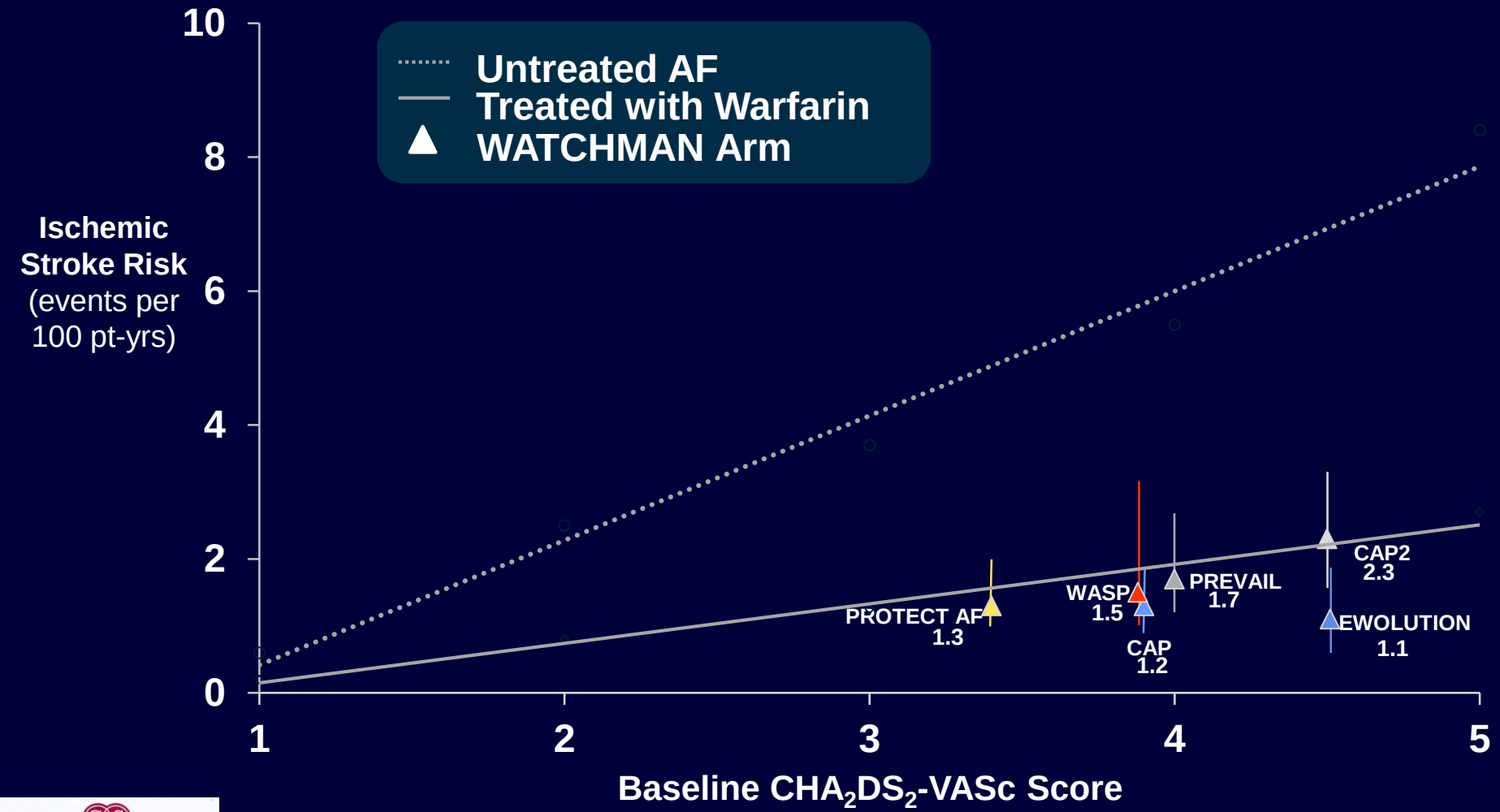
# Patient-Level Meta-Analysis PROTECT AF and PREVAIL 5 years



# Patient-Level Meta-Analysis
## WATCHMAN Comparable To Warfarin For Ischemic Stroke



# Results
# WATCHMAN Comparable to Warfarin for Ischemic Stroke

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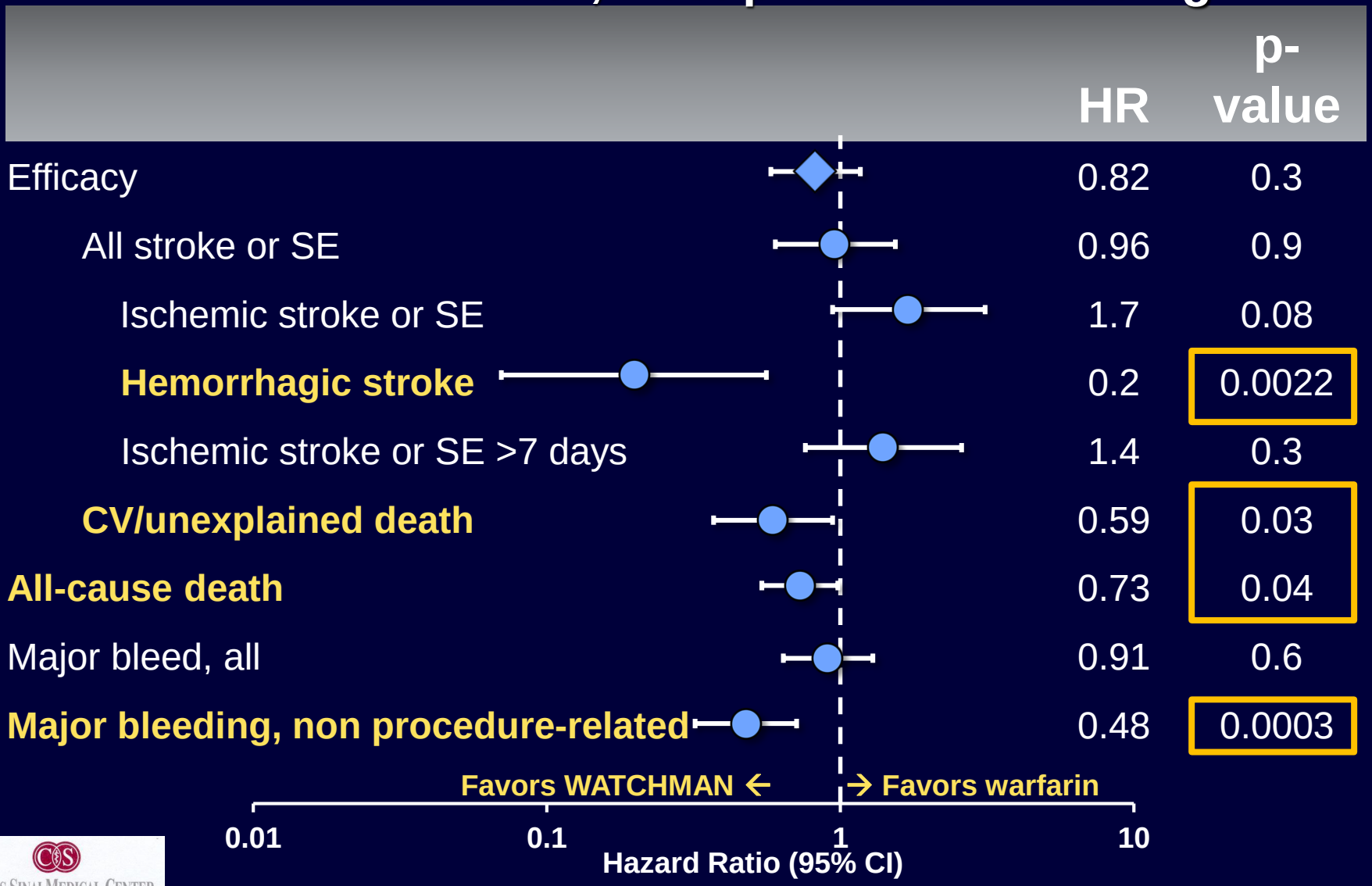
EWOLUTION: Boersma Lva et al Heart Rhythm 2017;doi-10.1016/j.hrthm.2017.05.038; WASP: Philips K, et al.Journal of Arrhythmia (in press).

# Patient-Level Meta-Analysis

## WATCHMAN Superior for Hemorrhagic Stroke, CV Death, All-Cause Death, Post-procedure Bleeding

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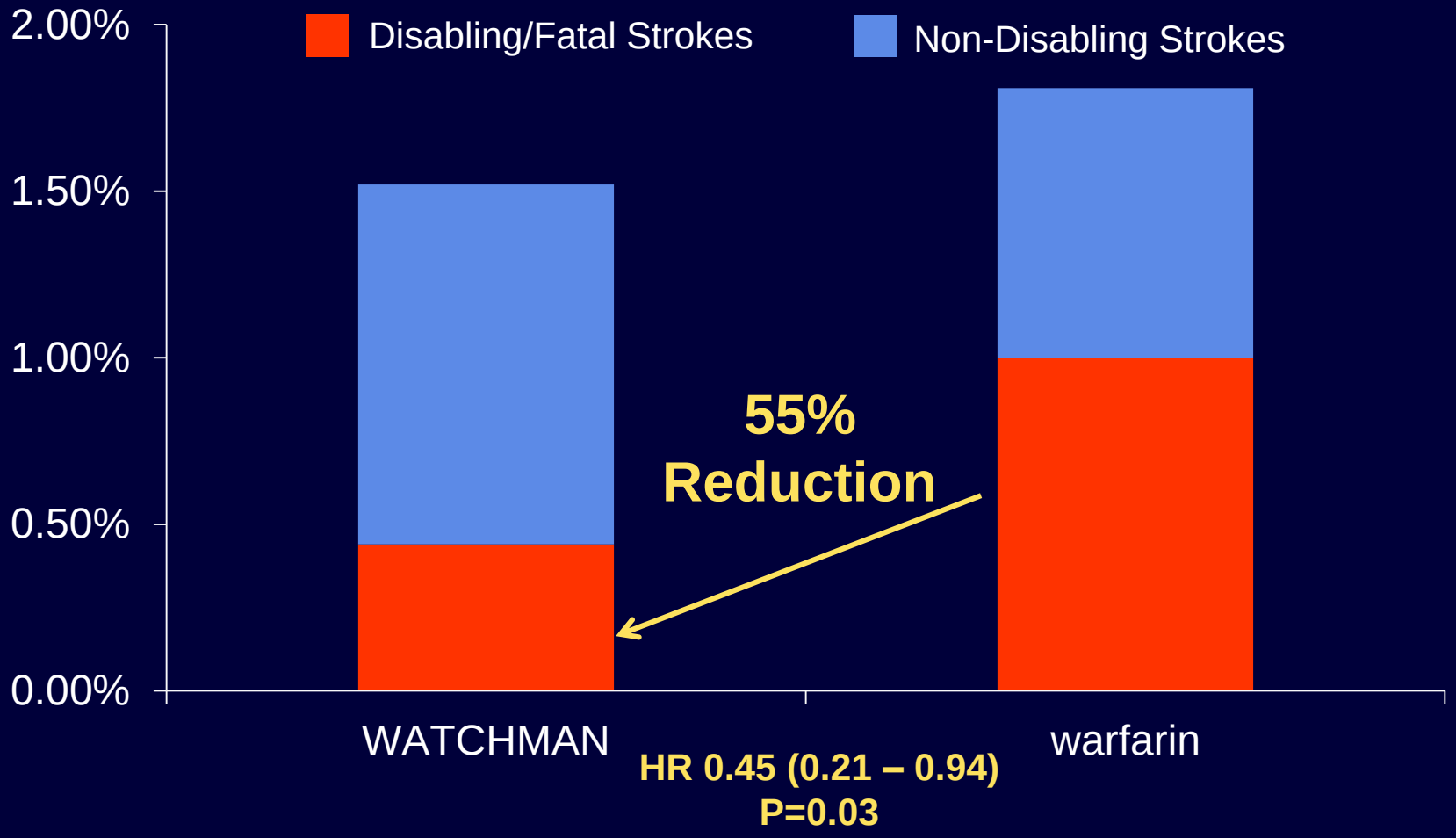
# Patient-Level Meta-Analysis
# WATCHMAN Superior Reduction in Disabling Strokes




Disabling Stroke defined as MRS ≥2

Two strokes in PREVAIL are excluded because the baseline MRS score was unavailable

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# Summary: 5 year follow up

- LAAC with the Watchman device provides stroke prevention in NVAF patients to a similar degree as oral anticoagulation
- By minimizing major bleeding, particularly hemorrhagic stroke, LAAC results in less disability or death than warfarin

Reddy V, Doshi S, Kar S et al. J Am Coll Cardiol 2017;70:2964-2975

# Watchman Clinical Experience

- > 45,000 implants worldwide
- > 3500 cases performed in China
- Approved in US since March 2015
- Approved in most countries in Asia
- SALUTE trial completed in Japan
  - (Expected approval in 2019)
- Most well studied device :
  - 2000 patients with 6000 pt-year follow up

# Who is the ideal patient with non-valvular AF for LAA closure: be a good clinician

*Ideal for patients who are at risk for stroke, but :*

- *Cannot not*
- *Should not*
- *Will not*

Take long term anticoagulants

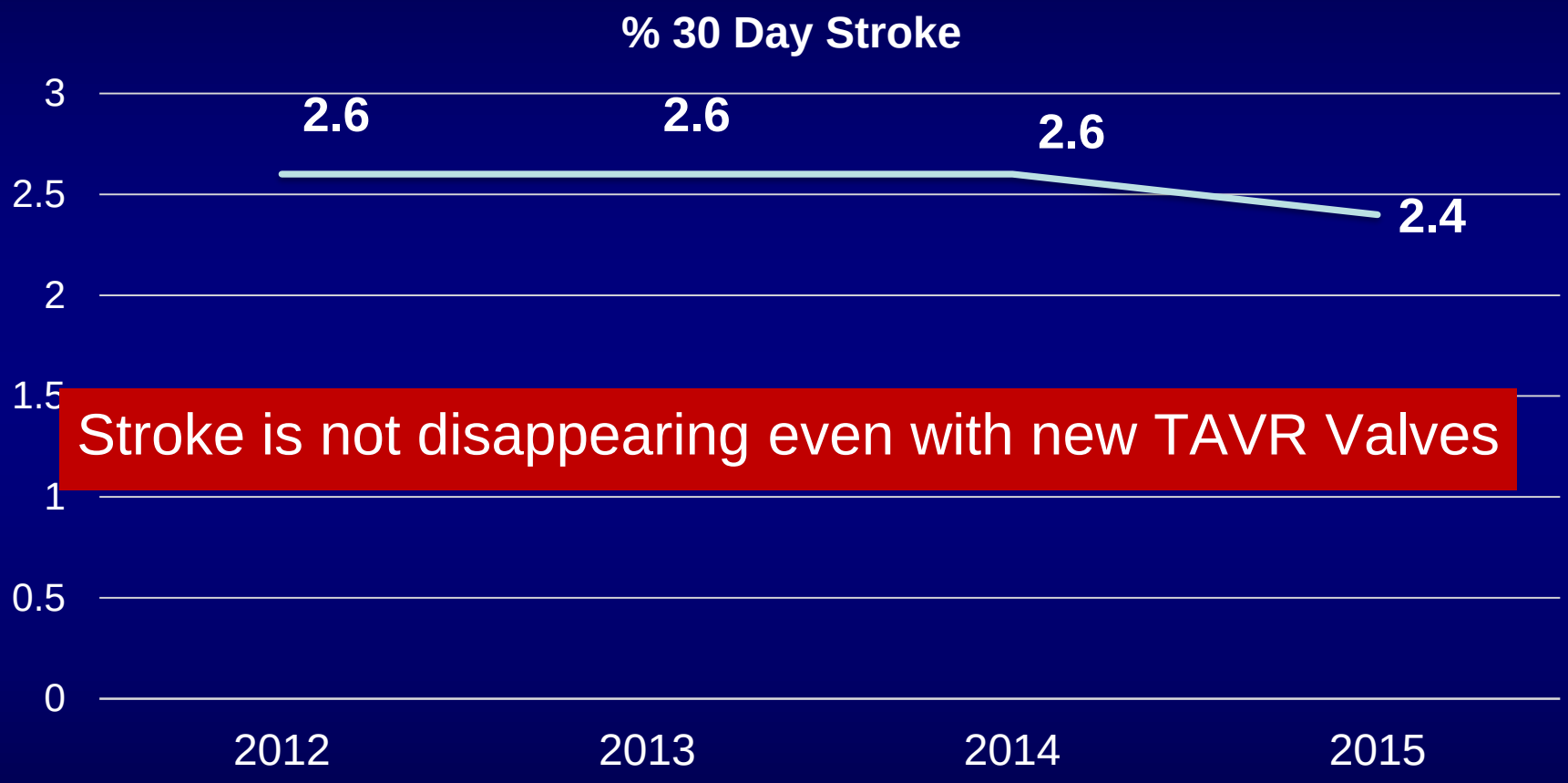
# *Cardioembolic stroke*

- Atrial fibrillation
- Valvular heart disease
- Cardiomyopathy

**Cerebral Protection during TAVR**

- Endocarditis
- Paradoxical embolism through a PFO

# US TVT Registry Stroke Rate




Stroke is not disappearing even with new TAVR Valves

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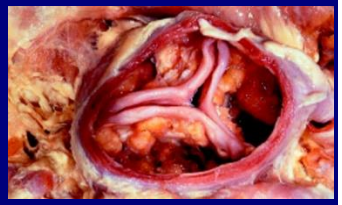
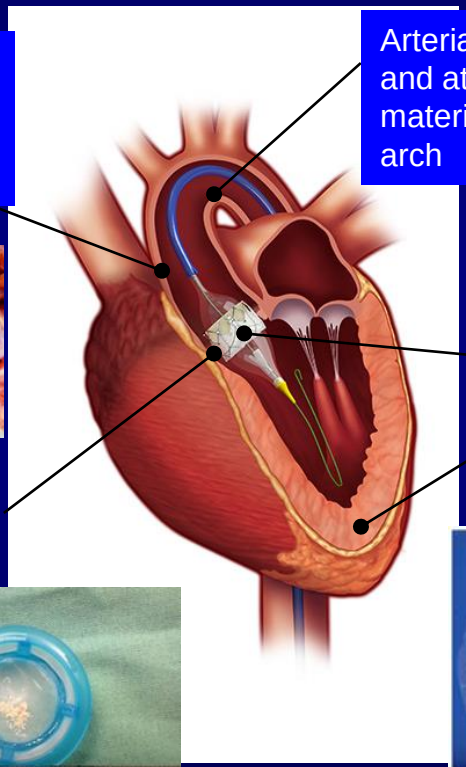
# Embolic Debris is Derived from a Variety of Sources During TAVR

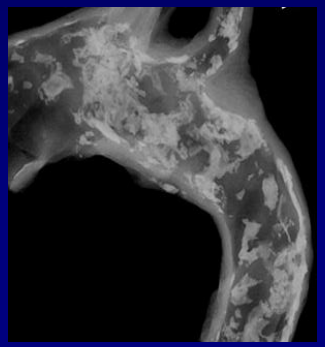
Arterial wall and calcific and atherosclerotic material from ascending arch



Valve leaflet tissue and calcific deposits from stenotic valve



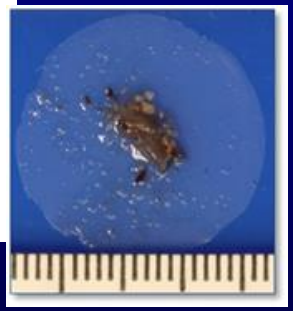
Arterial wall and calcific and atherosclerotic material from transverse arch

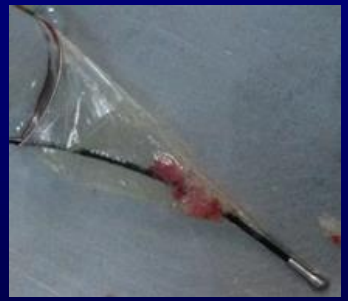


Foreign material from TAVR devices

Myocardium



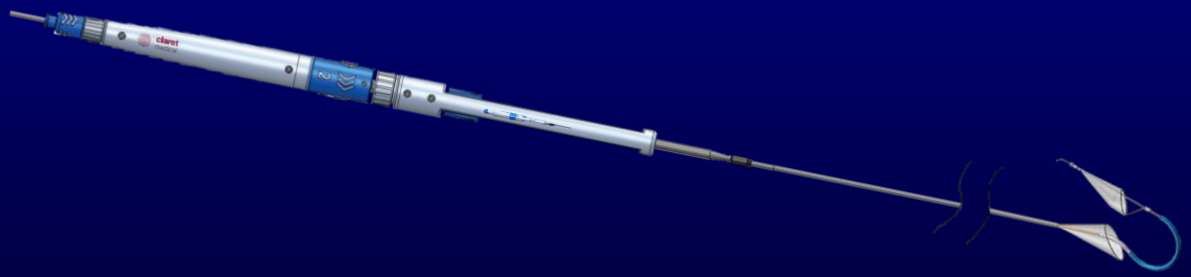




Courtesy: Dr Makkar

# Claret Medical® Sentinel® Cerebral Protection System

- Dual independent filters for embolic debris capture and removal
- Right transradial 6F sheath
- access
- Deflectable sheath facilitates cannulation of LCC
- Low profile in aortic arch to minimize interaction with TAVR delivery catheter



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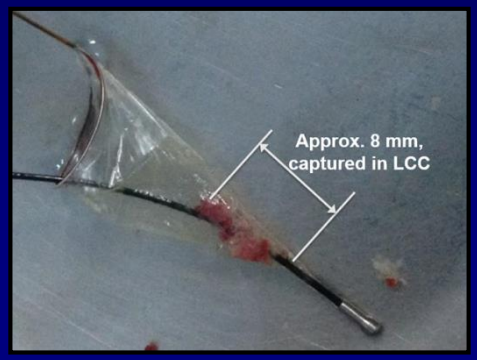
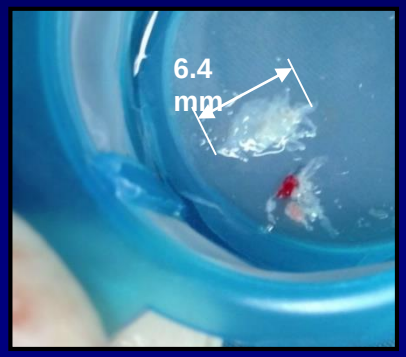
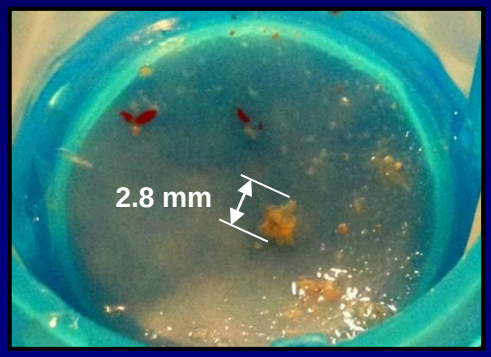
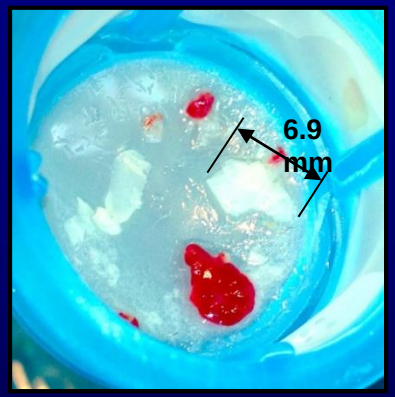
# Claret Medical™ Sentinel™ Cerebral Protection System

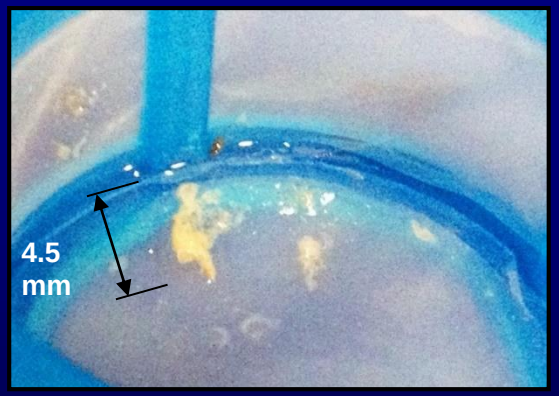
Embolic Debris Captured from TAVI Procedures

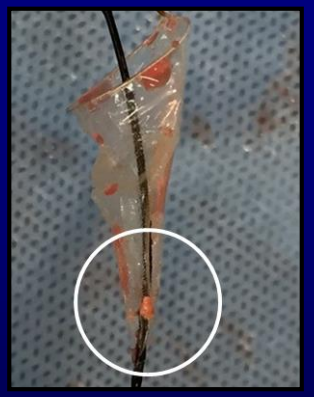


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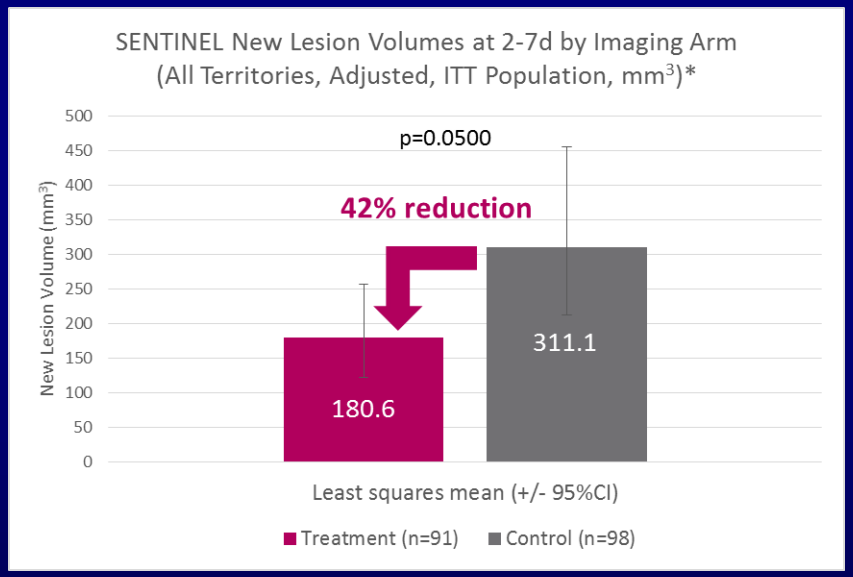
# Average STS score was 6.0% for SENTINEL subjects

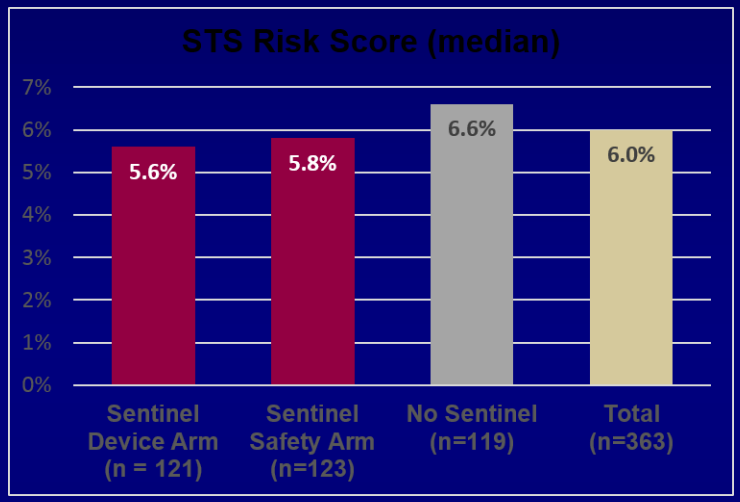
## Cerebral protection captured debris in 99% of patients and reduced cerebral damage by >42%

SENTINEL

- Average STS score 6.0% (SD 3.2%)
- Cerebral embolic debris was captured in 99% of SENTINEL patients treated with Claret (n=103)




*Adjusted for baseline FLAIR lesion volume and valve type
ITT= Intention to Treat Population




Kapadia, et al. Cerebral embolic protection during transcatheter aortic valve replacement. *JACC*. doi: 10.1016/j.jacc.2016.10.023.

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# SENTINEL study shows neurologist adjudicated stroke rate for the control arm (unprotected TAVR) of 9.1%

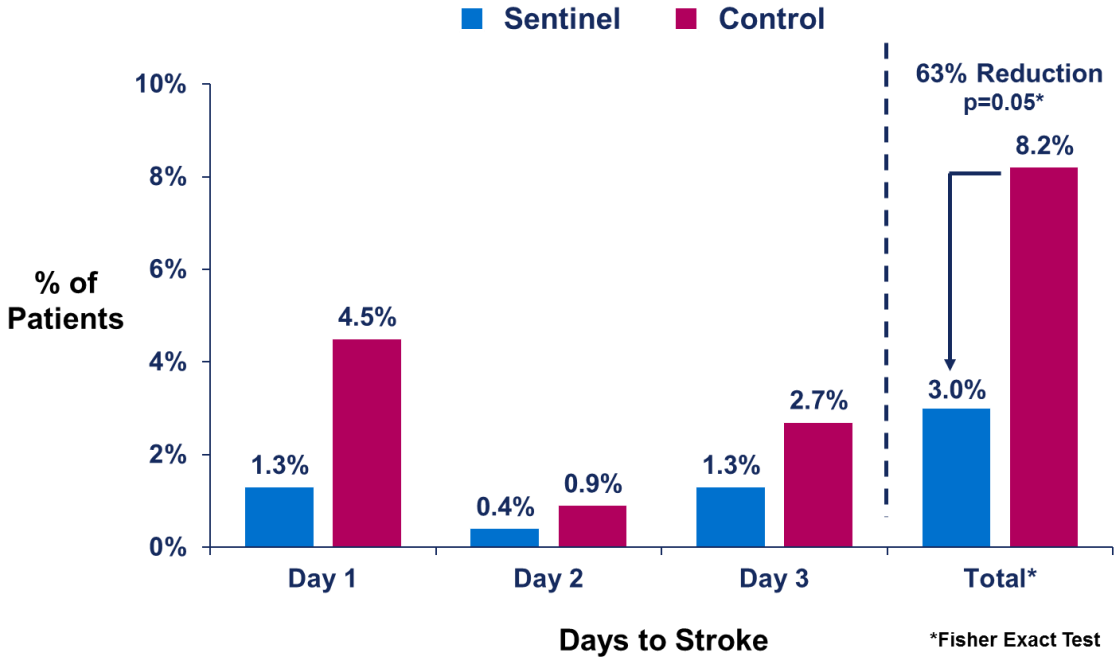
| | Device Arm (n=234) | Control Arm (n=111) | p-value |
|---|---|---|---|
| **30-day Clinical Outcomes** | | | |
| **Any MACCE†** | 7.3% (17/234) | 9.9% (11/111) | 0.40 |
| **Death (all-cause)** | 1.3% (3/234) | 1.8% (2/111) | 0.65 |
| **Stroke** | 5.6% (13/231) | 9.1% (10/110) | 0.25 |
| **Disabling** | 0.9% (2/231) | 0.9% (1/109) | 1.00 |
| **Non-disabling** | 4.8% (11/231) | 8.2% (9/110) | 0.22 |
| **AKI (Stage 3)** | 0.4% (1/231) | 0% | 1.00 |
| **TIA** | 0.4% (1/231) | 0% | 1.00 |
| **Sentinel Access Site Complications** | 0.4% (1/244) | N/A | 0.53 |

†MACCE defined as All Death, All Stroke, Acute Kidney Injury (Stage 3) as 72 hours or discharge, whichever occurs first

Kapadia, et al. Cerebral embolic protection during transcatheter aortic valve replacement. *JACC.* doi: 10.1016/j.jacc.2016.10.023.

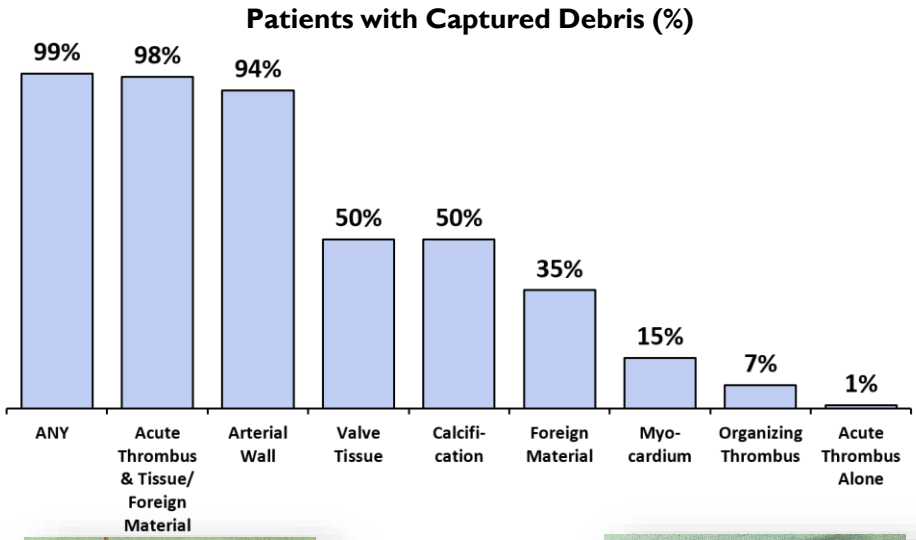
# SENTINEL study shows significant procedural stroke reduction

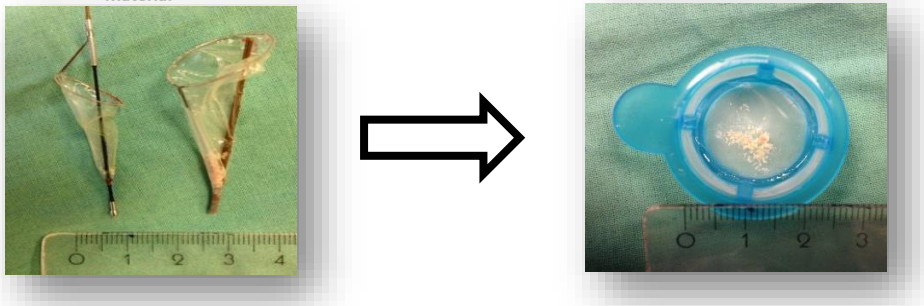
Results from SENTINEL multi-national randomized trial of n=363 TAVI patients with vs. without protection using Sentinel™ cerebral embolic protection system shows a significant reduction in procedural stroke (63%)

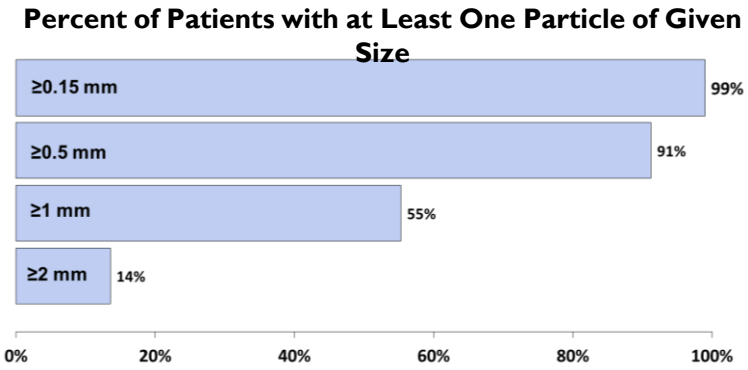


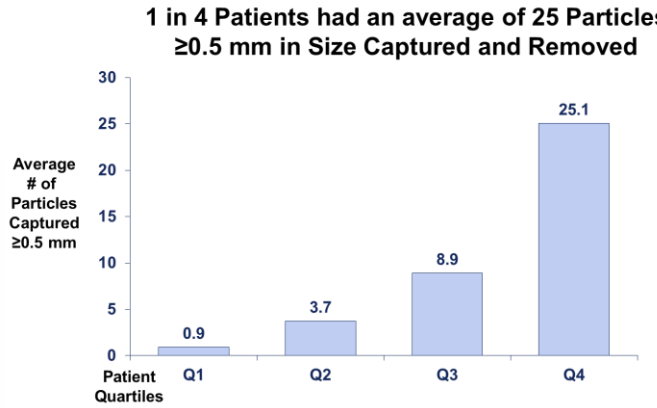

SENTINEL trial. Data presented at Sentinel FDA Advisory Panel, February 23, 2017

# Sentinel™ CPS captured debris in 99% of TAVI patients in SENTINEL






Virmani R, et al. CVPath. SENTINEL trial. Data presented at Sentinel FDA Advisory Panel, February 23, 2017

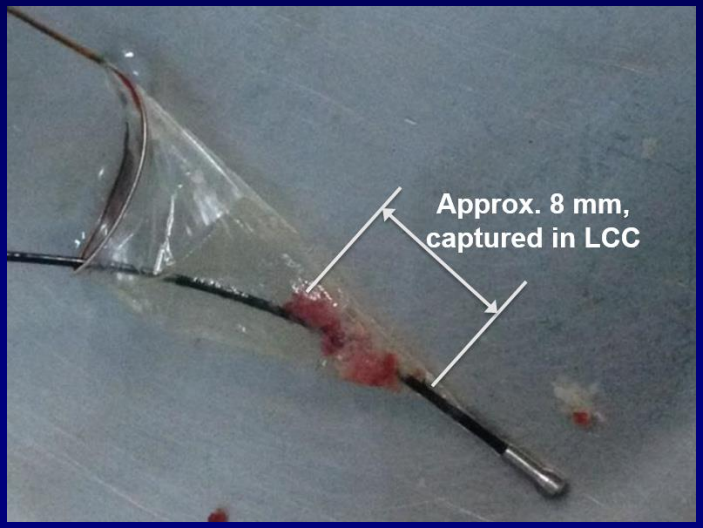
# Clinical summary

- Transcatheter cerebral embolic protection(TCEP) is safe
- Embolic debris was captured in 99% of patients
- No significant reduction of new lesion volume by MRI

Kapadia S et al. J Am Coll Cardiol 2017;69:367-77

- Jun 5, 2017:
- **FDA clears Claret Medical's Sentinel TAVR stroke protection device for U.S. market**

# Is Cerebral Protection Necessary?


Would you take a chance and drive without a seatbelt?

You never know when you'll need protection

# Conclusions

- Cardioembolic stroke is a serious medical condition
- Device based therapies are available in prevention of stroke in a vulnerable population.
- Ongoing clinical trials will expand the indication and availability of new devices