

Interventional Management of Cardiogenic Stroke

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Disclosure Statement of Financial Interest

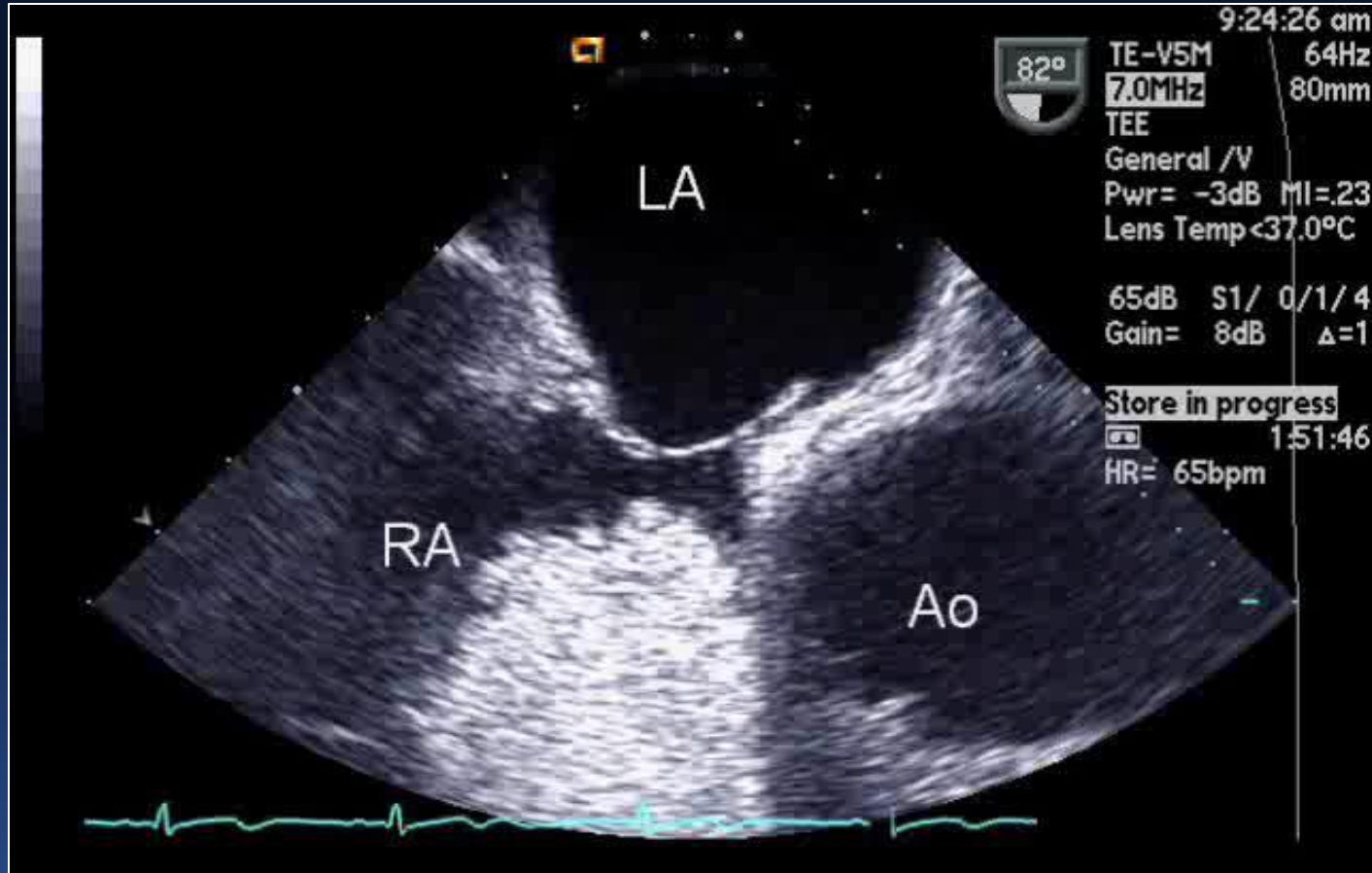
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Affiliation/Financial Relationship	Company
✓ Stock Option Holder	✓ Coherex Medical
✓ Principal Investigator – REDUCE	✓ WL Gore Medical
✓ Investigator – Cardiox 5	✓ Cardiox Medical
✓ Consultant	✓ DC Devices

What is Cardiogenic Stroke?

- ✓ Thromboembolic/ischemic cerebral infarct with origin of thrombus from the heart
 - Exclude aortic plaque, carotid disease
 - Includes:
 - Mitral or aortic valve vegetation
 - LV mural thrombus
 - Hypercoagulable conditions
 - Patent Foramen Ovale, paradoxical embolization
 - Atrial Fibrillation / Left atrial appendage thrombus

Intervention for Patent Foramen Ovale (PFO)



TEE with Agitated Saline Injection

Is PFO really the source?



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Is PFO the source?

An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke

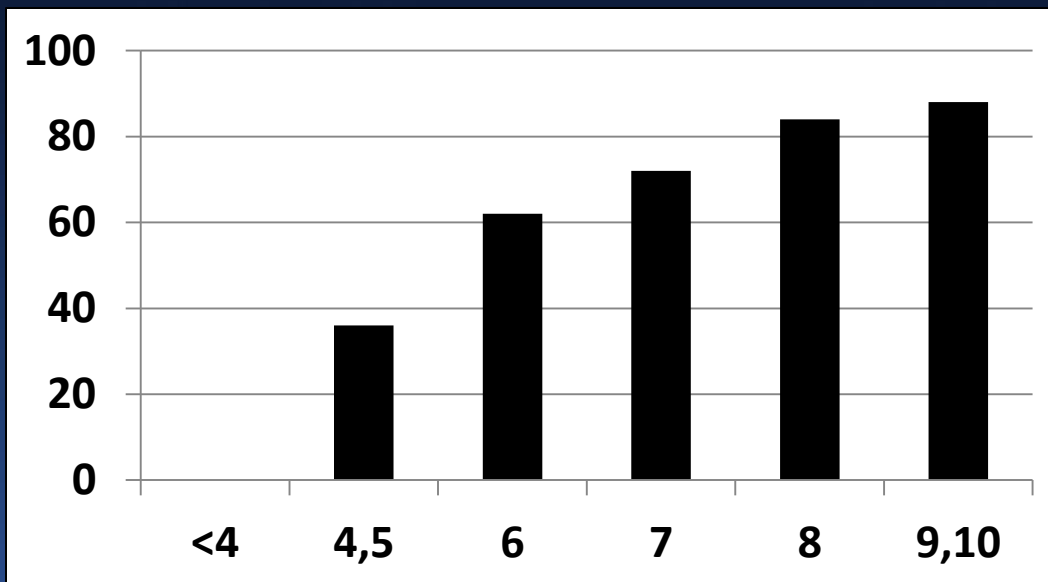
RoPE Study

- ✓ Meta-analysis using Bayes Theorem
- ✓ A risk assessment score, similar to CHADS
- ✓ Scale 0 – 10
 - Lose points for every decade of age >30 - 70
 - Lose points for known stroke risk factors (i.e. HTN, DM, smoking, prior stroke)

Is PFO the source?

An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke

RoPE Study



- ✓ In the youngest, healthiest patients, the probability that the PFO was the source is as high as 88%.

What are the options to prevent recurrence?



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Treatment of PFO After Stroke

Options?

- ✓ Surgical closure:
 - Higher complication rates
 - Closure rates not different
 - Longer hospitalization
 - Longer recovery
 - More pain, infection, transfusion
- ✓ Anti-platelet therapy
- ✓ Anti-coagulation

PFO – Stroke:

Do Blood Thinners Really Work?

Effect of Medical Treatment in Stroke Patients With Patent Foramen Ovale

Patent Foramen Ovale in Cryptogenic Stroke Study

Shunichi Homma, MD; Ralph L. Sacco, MD, MS; Marco R. Di Tullio, MD; Robert R. Sciaccia, EngScD; J.P. Mohr, MD; for the PFO in Cryptogenic Stroke Study (PICSS) Investigators*

	Warfarin	Aspirin	p-value
Recurrent event at 2 years	16.5%	13.2%	0.49

Circulation. 2002;105:2625-2631.

PFO – Stroke:

Do Blood Thinners Really Work?

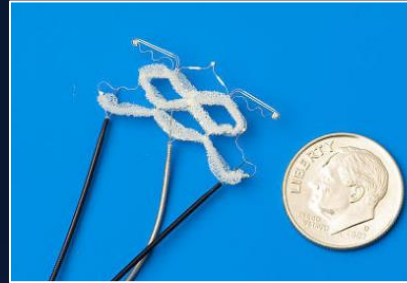


	Warfarin	Aspirin	p-value
Recurrent event at 2 years	8.1%	6.7%	0.63

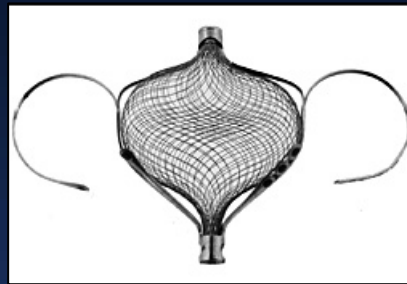
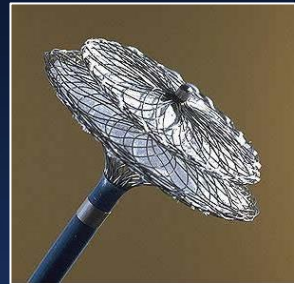
Furlan et al. N Engl J Med 2012;366:991-9.

Interventional Approach

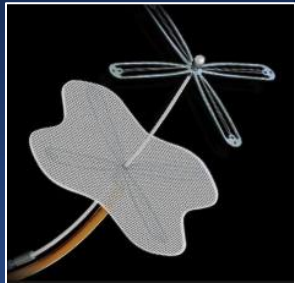
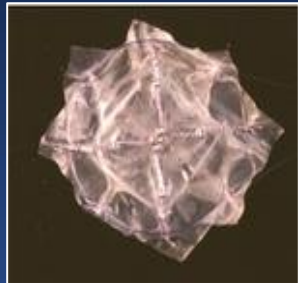
PFO Closure Devices



RF Energy Fusion

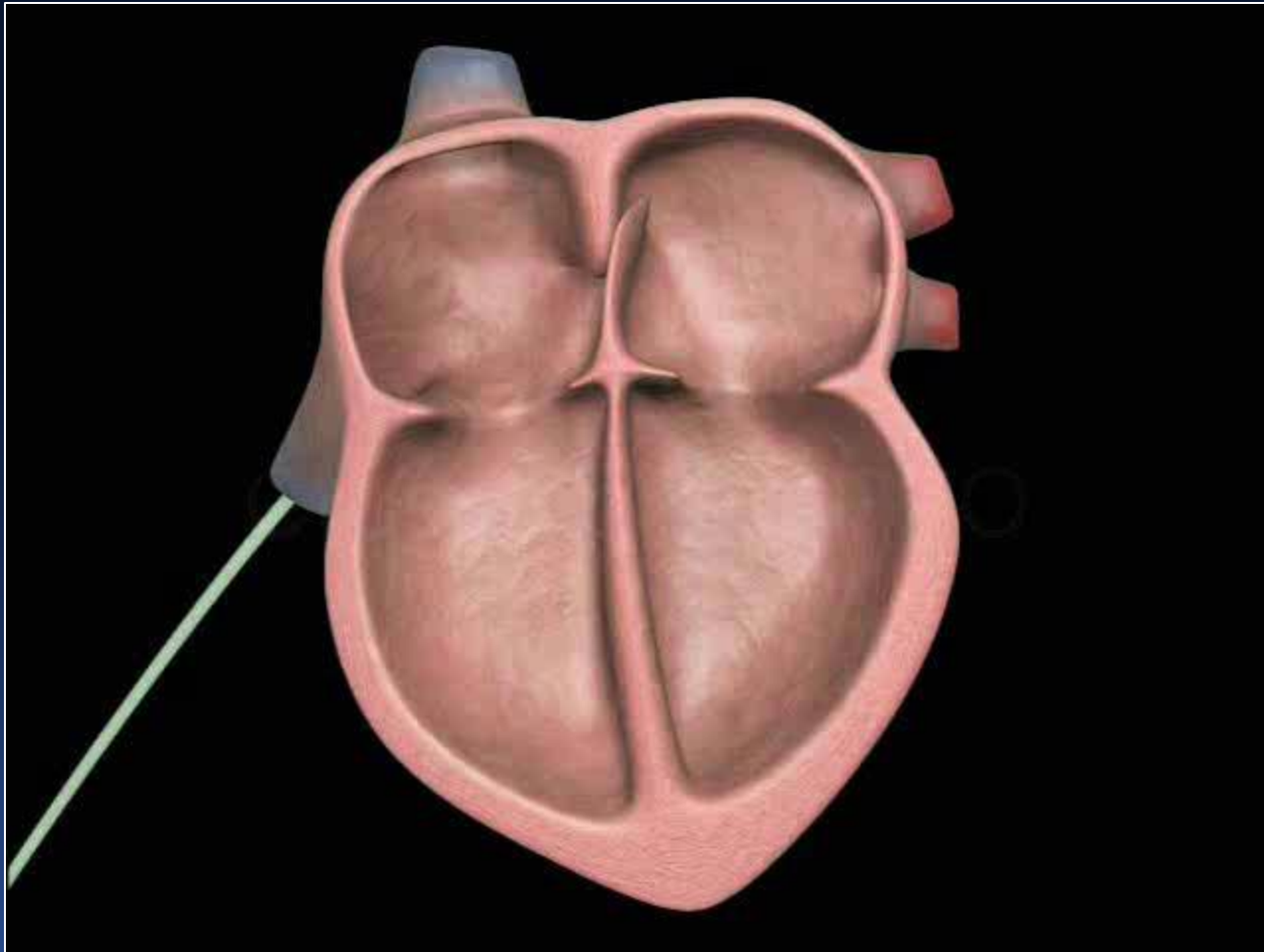


Intra-tunnel Devices



Double Disk Occluders

Transcatheter Closure of PFO



Transcatheter Closure of PFO

✓ In experienced hands:

- ~ 20 minute ambulatory procedure
- Conscious sedation
- Femoral venous access only
- 100% implantation rate
- Fewest complications of any cath lab intervention
- Dual anti-platelet therapy for 3 months
- Back in the gym in < 1 week

Does PFO Closure Work?

RESPECT Trial

✓ Randomized, controlled superiority trial:

- PFO closure with aspirin
- Medical Therapy alone

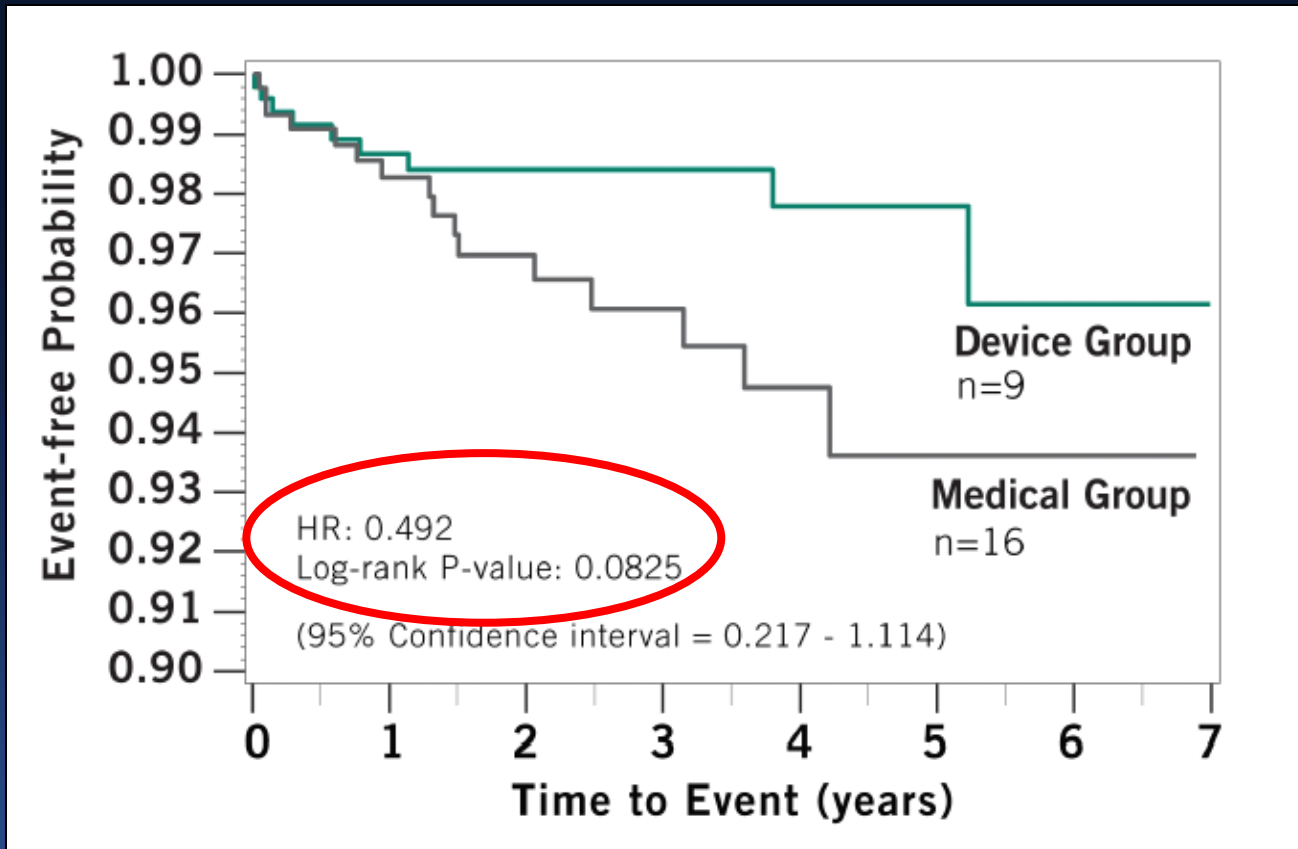


✓ Primary Endpoint: Recurrent Stroke

Carroll et al. N Engl J Med 2013;368:1092-100.

RESPECT Trial – Results

Primary Endpoint Analysis – ITT Cohort



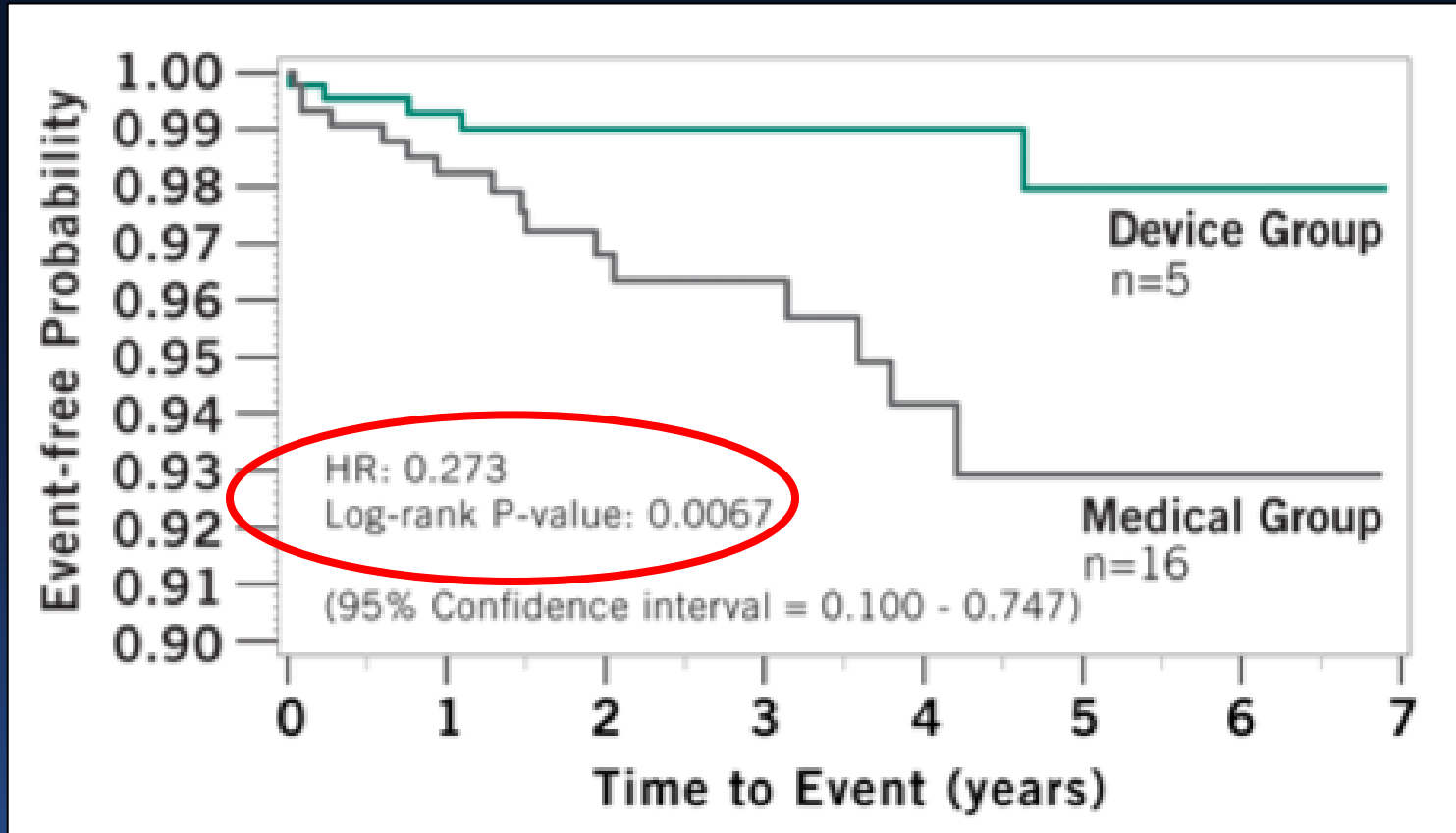
RESPECT Trial – Results

Primary Endpoint Analysis

- ✓ 3/9 pts with recurrent strokes in the closure arm had not undergone a closure procedure at the time of the endpoint event.

RESPECT Trial – Results

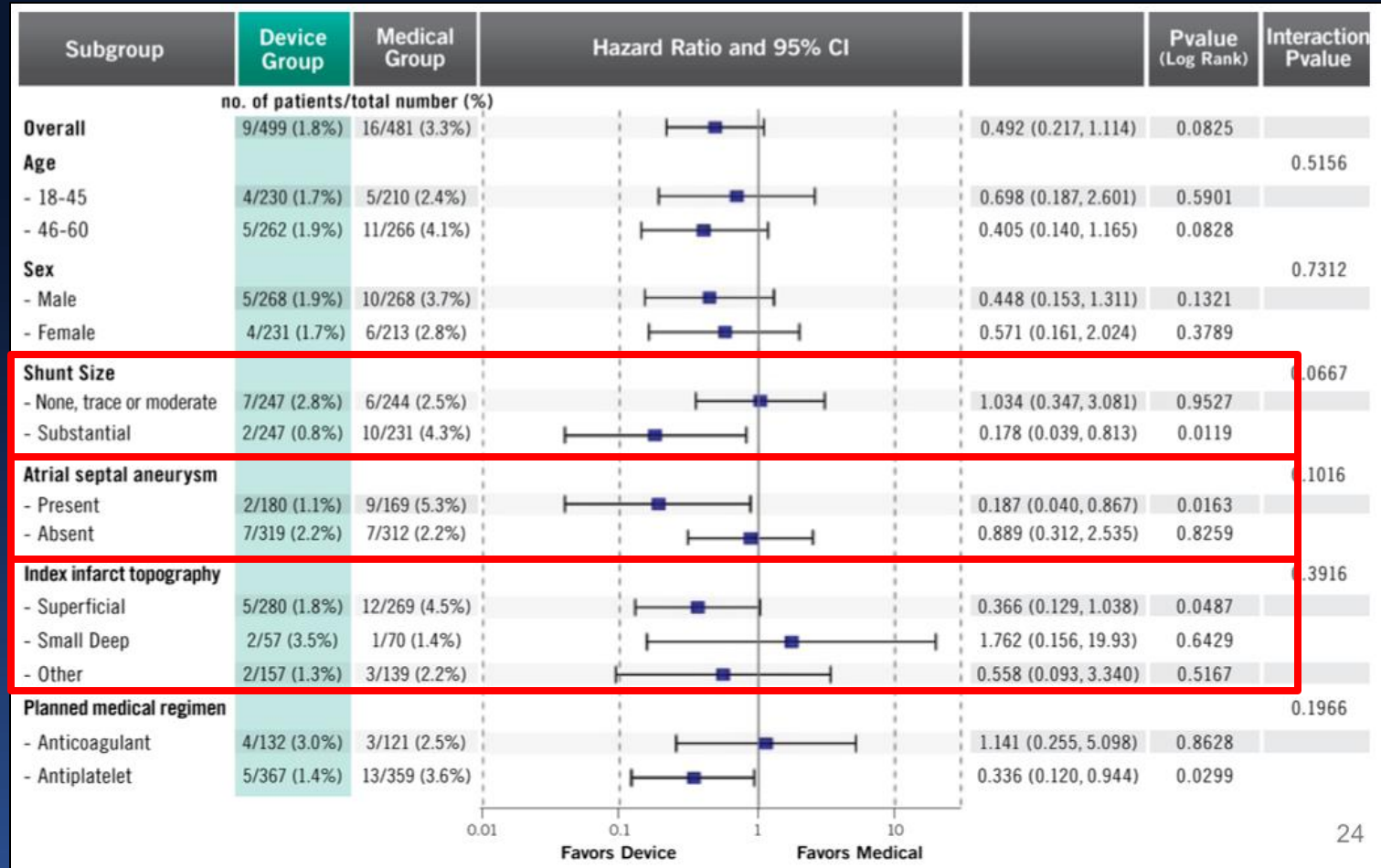
Primary Endpoint Analysis – “As Treated”



Grouped by treatment received

RESPECT Trial – Results

Multivariate Risk Analysis



Is it safe?

Transcatheter Closure of PFO

Is it Safe?

Event	Device Group N=499 n (%)	Medical Group N=481 n (%)	P-value ⁷
Thrombus on device	0 (0%)	N/A	N/A
Device embolization	0 (0%)	N/A	N/A
Atrial fibrillation ¹	3 (0.6%)	3 (0.6%)	1
Transient ischemic attack (TIA)	3 (0.6%)	3 (0.6%)	1
Major bleeding	8 (1.6%)	9 (1.9%)	0.810
Pericardial tamponade (procedure related) ²	2 (0.4%)	N/A	N/A
Major vascular complications	4 (0.8%)	0 (0%)	0.124

RESPECT Trial Results

Who should have a PFO Closure?

PFO – Stroke

Who should have interventional therapy?

- ✓ Consider after first stroke event only –
most patients with PFO will never stroke

DiTullio et al. JACC 2013;62:35-41.

Petty et al. Mayo Clin Proc. 2006;81:602-8.

- ✓ Consider for pts with large shunt/ASA after
peripheral ischemic infarct (RESPECT)

Carroll et al. N Engl J Med 2013;368:1092-100.

PFO – Stroke

Who should have interventional therapy?

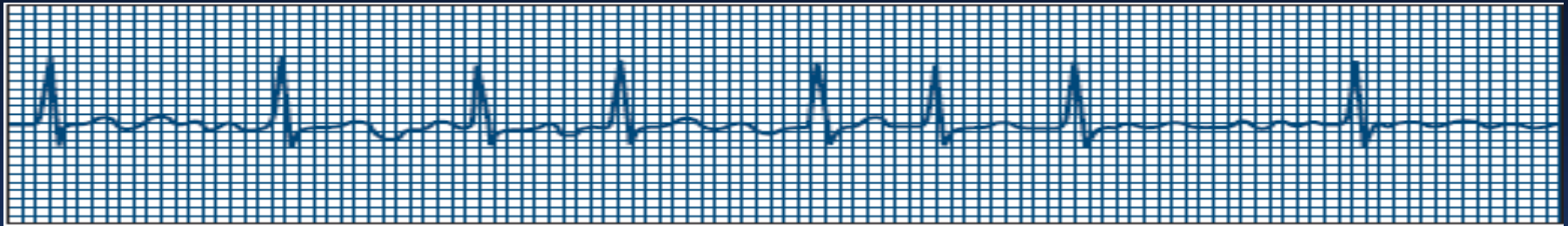
- ✓ Consider for young healthy patients without traditional stroke risks

Kent et al. *Neurology* 2013;81:619-25.

- ✓ Consider after recurrent event while on blood thinner therapy

Italian Consensus Paper:
Pristipino et al. *Cath CV Interv* 2013;82:122-9.

Interventional Management of Chronic Atrial Fibrillation



What are the options for prevention of recurrent stroke in patients with AF?

Stroke Prevention in AF

Options?

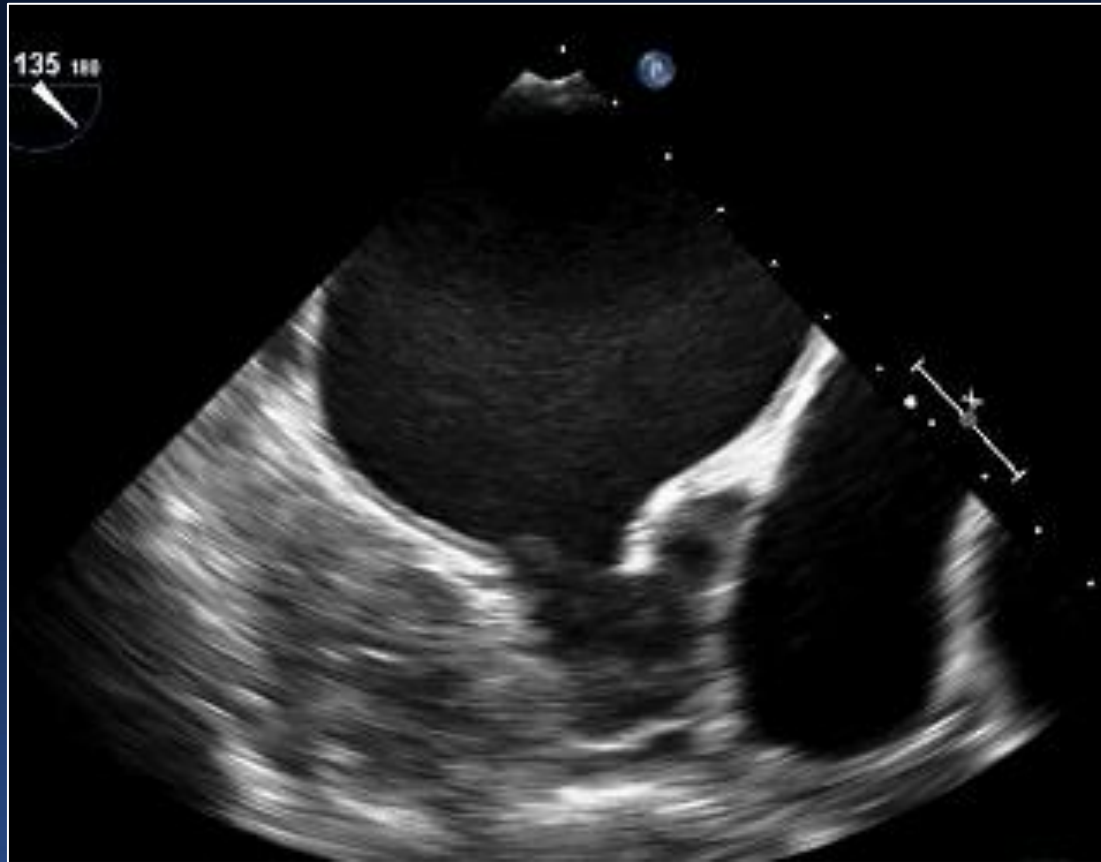
- ✓ Anti-arrhythmics:
 - Low efficacy even in the best
 - Serious potential toxicity
- ✓ Transcatheter Ablation
 - <50% success in persistent AF
 - Multiple attempts may be required
 - 2-12% complications for each try

Stroke Prevention in AF

Options?

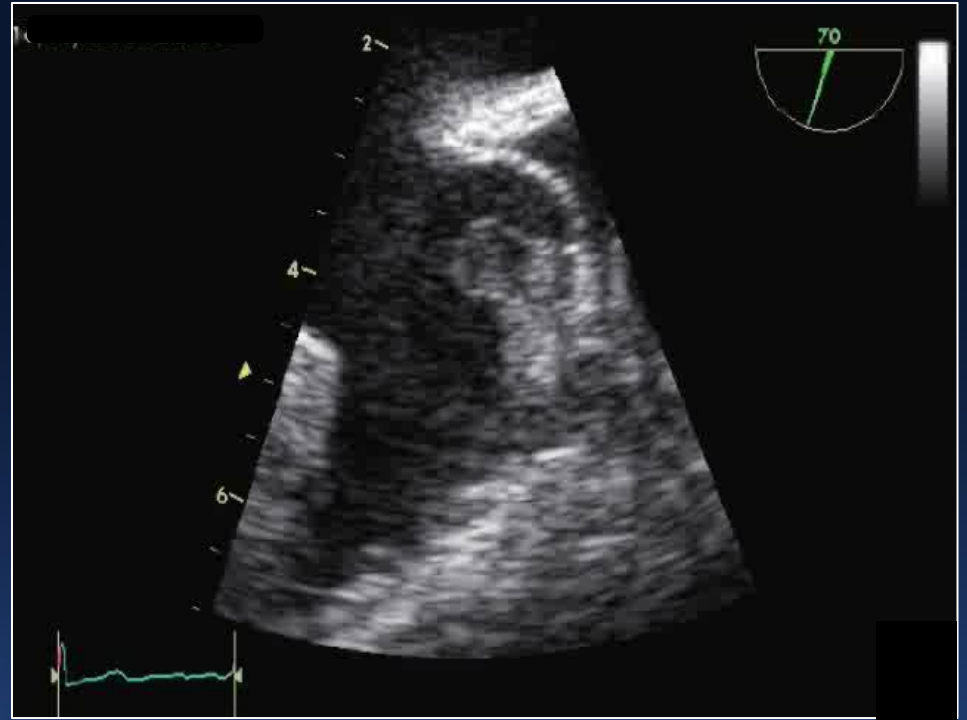
- ✓ Surgical MAZE
 - Risks, pain, recovery of open heart surgery
 - Potential recurrence
- ✓ Oral anti-coagulation (GOLD STANDARD)
 - ✓ Risks of bleeding
 - ✓ Dietary restrictions (warfarin)
 - ✓ Blood testing (warfarin)

TEE in Atrial Fibrillation



LAA "Smoke"

LAA as a Source in AF



✓ 91% of identified thrombus found in the LAA

Exclusion of the LAA becomes
an attractive therapeutic
strategy.

Endocardial LAA Plugs

PLAATO



Watchman



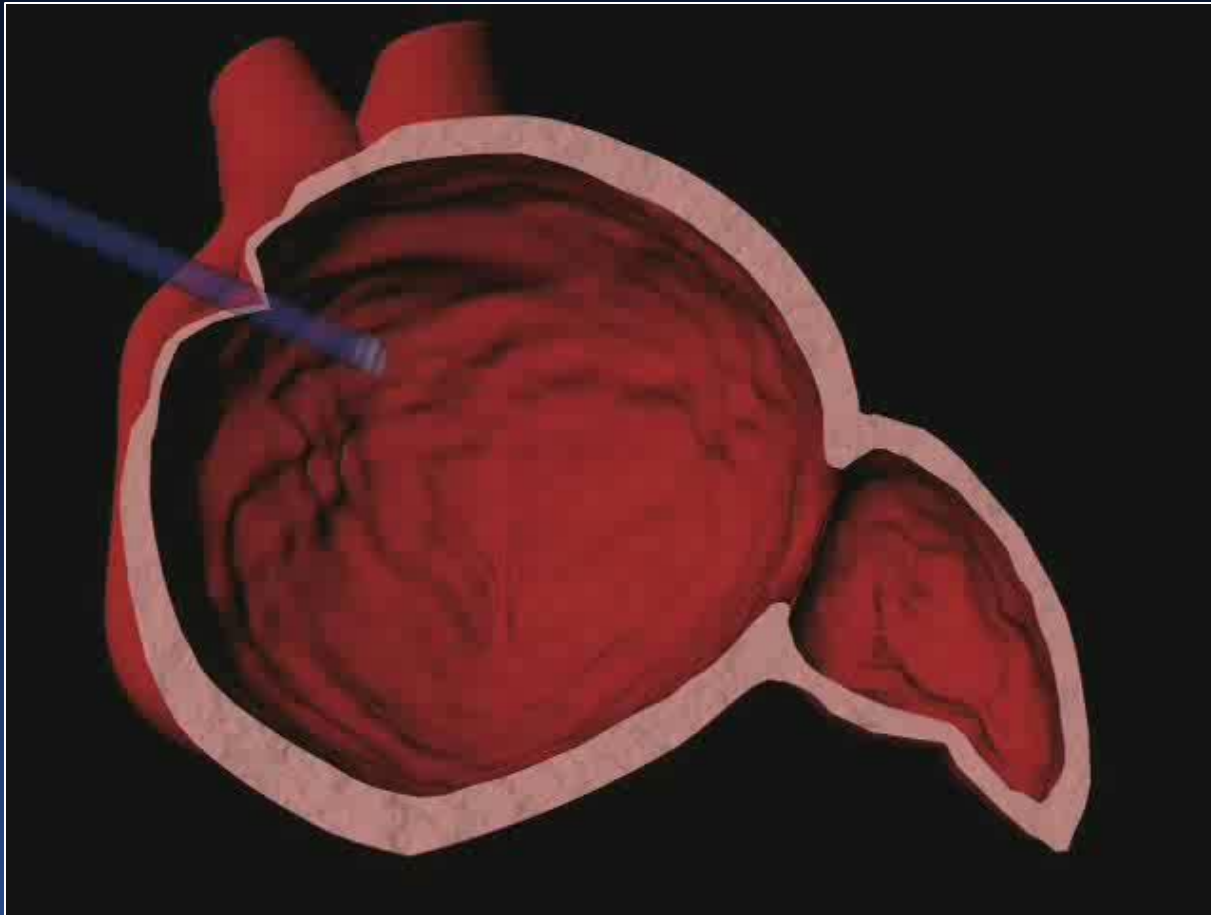
ACP



WaveCrest



Watchman Implantation

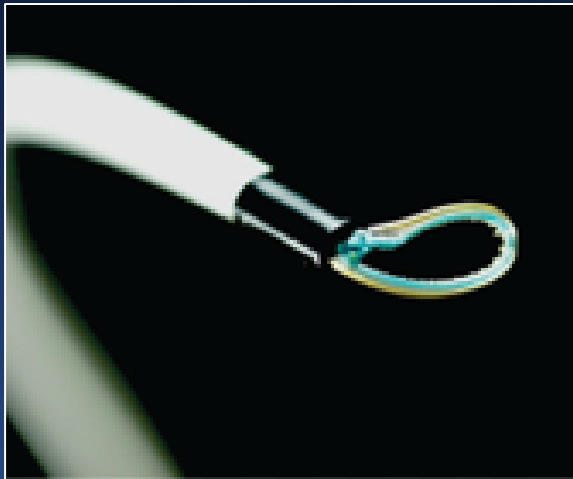


Epicardial Approach

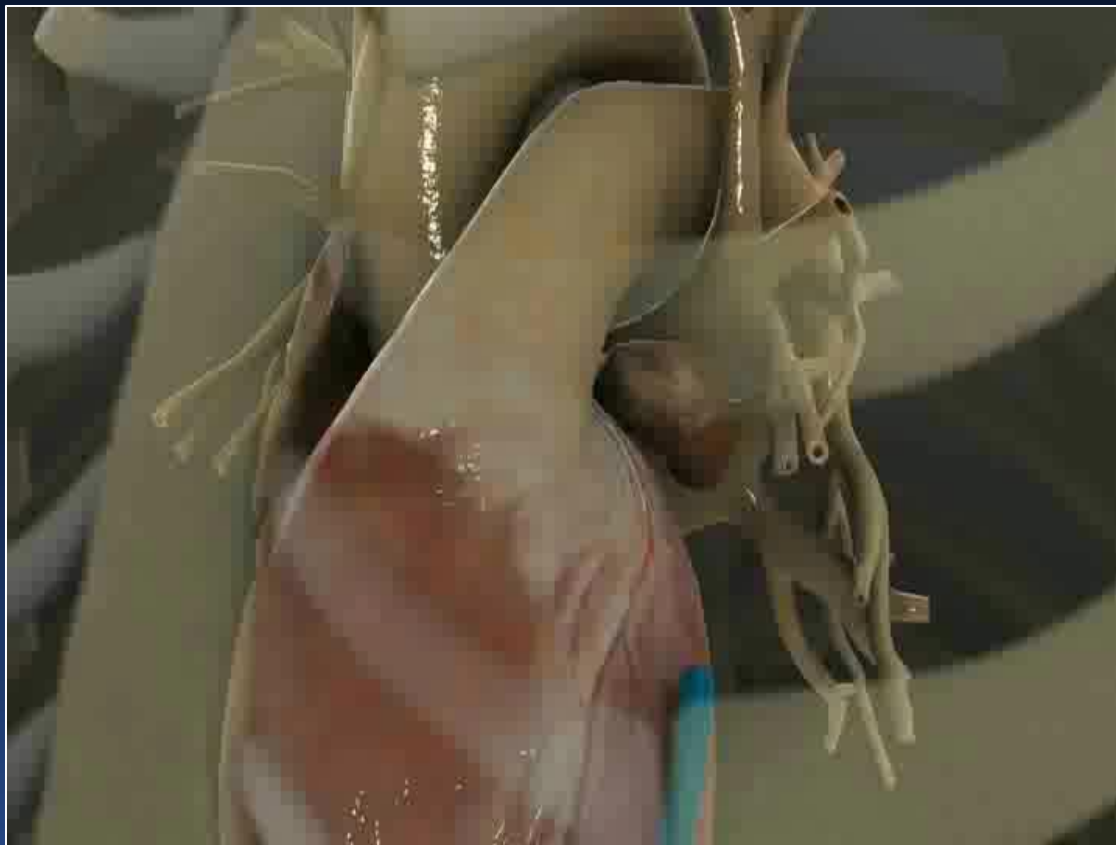


SentreHeart Lariat Device

Transcatheter Approach



Lariat Device Movie

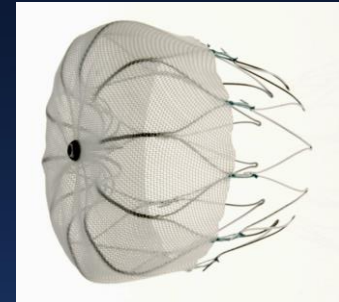


Does LAA Exclusion Work?

PROTECT AF Trial

✓ Randomized, controlled trial, non-inferiority and superiority analysis:

- LAA Exclusion with aspirin therapy
- On-going Warfarin



✓ Primary Efficacy Endpoint: Recurrent Stroke, CV Death, Systemic Embolization

PROTECT AF – 4 Year Data Results

✓ Efficacy Endpoints:

- 39/1720.2 pt-yrs Watchman
- 34/900.8 pt-yrs Warfarin
- Hazard Ratio 0.60 [95% CL 0.41 – 1.05]
- Non-inferiority > 0.999, Superiority >0.960

✓ Hemorrhagic Stroke:

- Hazard Ratio = 0.15 [95% CL 0.03 – 0.49]

PROTECT AF – 4 Year Data Results

✓ CV Mortality:

- Hazard Ratio 0.40 [95% CL 0.23 – 0.82]

✓ All Cause Mortality:

- Hazard Ratio 0.66 [95% CL 0.45 – 0.98]

Watchman is superior to Warfarin.

SentreHeart Lariat

- ✓ Closure rates are good
- ✓ No stroke prevention data to date

Who should have LAA Exclusion?

Interventional Exclusion/Closure of LAA

Who should have it?



Blood
thinners for
me?
Really?

- ✓ Active young AF patients with $CHADS_2 > 2$, who would otherwise need OAC

Interventional Exclusion/Closure of LAA

Who should have it?

Blood
thinners for
me?
Really?



- ✓ Patients with high risk of bleeding, or history of hemorrhage on OAC

Conclusions

- ✓ AF exists in 35 million people in the US and will increase as the population ages.
- ✓ PFO exists in twice as many.
- ✓ Cardiogenic stroke prevention is an important health care priority.