Interventional Management of Cardiogenic Stroke

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Disclosure Statement of Financial Interest

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

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
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<tbody>
<tr>
<td>Stock Option Holder</td>
<td>Coherex Medical</td>
</tr>
<tr>
<td>Principal Investigator – REDUCE</td>
<td>WL Gore Medical</td>
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<tr>
<td>Investigator – Cardiox 5</td>
<td>Cardiox Medical</td>
</tr>
<tr>
<td>Consultant</td>
<td>DC Devices</td>
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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?
Is PFO the source?

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?

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

RoPE Study

What are the options to prevent recurrence?
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. Sciacca, EngScD; J.P. Mohr, MD; for the PFO in Cryptogenic Stroke Study (PICSS) Investigators*

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Aspirin</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>Recurrent event at 2 years</td>
<td>16.5%</td>
<td>13.2%</td>
<td>0.49</td>
</tr>
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</table>

## PFO – Stroke:
**Do Blood Thinners Really Work?**

![Closure I logo](image)

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<tr>
<td>Recurrent event at 2 years</td>
<td>8.1%</td>
<td>6.7%</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Interventional Approach
PFO Closure Devices

Double Disk Occluders

Intra-tunnel Devices

RF Energy Fusion
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

RESPECT Trial – Results
Primary Endpoint Analysis – ITT Cohort

Event-free Probability

Time to Event (years)

HR: 0.492
Log-rank P-value: 0.0825
(95% Confidence interval = 0.217 - 1.114)

Device Group
n=9

Medical Group
n=16
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

<table>
<thead>
<tr>
<th>Time to Event (years)</th>
<th>Event-free Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>0.95</td>
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<tr>
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<td>0.94</td>
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<td></td>
<td>0.93</td>
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<tr>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>0.90</td>
</tr>
<tr>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>0.99</td>
</tr>
<tr>
<td>2</td>
<td>0.98</td>
</tr>
<tr>
<td>3</td>
<td>0.97</td>
</tr>
<tr>
<td>4</td>
<td>0.96</td>
</tr>
<tr>
<td>5</td>
<td>0.95</td>
</tr>
<tr>
<td>6</td>
<td>0.94</td>
</tr>
<tr>
<td>7</td>
<td>0.93</td>
</tr>
</tbody>
</table>

HR: 0.273
Log-rank P-value: 0.0067
(95% Confidence interval = 0.100 - 0.747)

Device Group
n=5

Medical Group
n=16
# RESPECT Trial – Results

## Multivariate Risk Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Device Group</th>
<th>Medical Group</th>
<th>Hazard Ratio and 95% CI</th>
<th>P-value (Log Rank)</th>
<th>Interaction P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9/499 (1.8%)</td>
<td>16/481 (3.3%)</td>
<td>0.492 (0.217, 1.114)</td>
<td>0.0825</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 18-45</td>
<td>4/230 (1.7%)</td>
<td>5/210 (2.4%)</td>
<td>0.698 (0.187, 2.601)</td>
<td>0.5901</td>
<td></td>
</tr>
<tr>
<td>- 46-60</td>
<td>5/262 (1.9%)</td>
<td>11/266 (4.1%)</td>
<td>0.405 (0.140, 1.165)</td>
<td>0.0828</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Male</td>
<td>5/268 (1.9%)</td>
<td>10/268 (3.7%)</td>
<td>0.448 (0.153, 1.311)</td>
<td>0.1321</td>
<td></td>
</tr>
<tr>
<td>- Female</td>
<td>4/231 (1.7%)</td>
<td>6/213 (2.8%)</td>
<td>0.571 (0.161, 2.024)</td>
<td>0.3789</td>
<td></td>
</tr>
<tr>
<td><strong>Shunt Size</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- None, trace or moderate</td>
<td>7/247 (2.8%)</td>
<td>6/244 (2.5%)</td>
<td>1.034 (0.347, 3.081)</td>
<td>0.9527</td>
<td>0.0667</td>
</tr>
<tr>
<td>- Substantial</td>
<td>2/247 (0.8%)</td>
<td>10/231 (4.3%)</td>
<td>0.178 (0.039, 0.813)</td>
<td>0.0119</td>
<td></td>
</tr>
<tr>
<td><strong>Atrial septal aneurysm</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Present</td>
<td>2/180 (1.1%)</td>
<td>9/169 (5.3%)</td>
<td>0.187 (0.040, 0.867)</td>
<td>0.0163</td>
<td>0.1016</td>
</tr>
<tr>
<td>- Absent</td>
<td>7/319 (2.2%)</td>
<td>7/312 (2.2%)</td>
<td>0.889 (0.312, 2.535)</td>
<td>0.8259</td>
<td></td>
</tr>
<tr>
<td><strong>Index infarct topography</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Superficial</td>
<td>5/280 (1.8%)</td>
<td>12/269 (4.5%)</td>
<td>0.366 (0.129, 1.038)</td>
<td>0.0487</td>
<td>0.3916</td>
</tr>
<tr>
<td>- Small Deep</td>
<td>2/57 (3.5%)</td>
<td>1/70 (1.4%)</td>
<td>1.762 (0.156, 19.93)</td>
<td>0.6429</td>
<td></td>
</tr>
<tr>
<td>- Other</td>
<td>2/157 (1.3%)</td>
<td>3/139 (2.2%)</td>
<td>0.558 (0.093, 3.340)</td>
<td>0.5167</td>
<td></td>
</tr>
<tr>
<td><strong>Planned medical regimen</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Anticoagulant</td>
<td>4/132 (3.0%)</td>
<td>3/121 (2.5%)</td>
<td>1.141 (0.255, 5.098)</td>
<td>0.8628</td>
<td>0.1966</td>
</tr>
<tr>
<td>- Antiplatelet</td>
<td>5/367 (1.4%)</td>
<td>13/359 (3.6%)</td>
<td>0.336 (0.120, 0.944)</td>
<td>0.0299</td>
<td></td>
</tr>
</tbody>
</table>

Favors Device vs. Favors Medical
Is it safe?
## Transcatheter Closure of PFO

### Is it Safe?

<table>
<thead>
<tr>
<th>Event</th>
<th>Device Group N=499 n (%)</th>
<th>Medical Group N=481 n (%)</th>
<th>P-value 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombus on device</td>
<td>0 (0%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Device embolization</td>
<td>0 (0%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Atrial fibrillation¹</td>
<td>3 (0.6%)</td>
<td>3 (0.6%)</td>
<td>1</td>
</tr>
<tr>
<td>Transient ischemic attack (TIA)</td>
<td>3 (0.6%)</td>
<td>3 (0.6%)</td>
<td>1</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>8 (1.6%)</td>
<td>9 (1.9%)</td>
<td>0.810</td>
</tr>
<tr>
<td>Pericardial tamponade (procedure related)²</td>
<td>2 (0.4%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Major vascular complications</td>
<td>4 (0.8%)</td>
<td>0 (0%)</td>
<td>0.124</td>
</tr>
</tbody>
</table>

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


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

PFO – Stroke

Who should have interventional therapy?

✔ Consider for young healthy patients without traditional stroke risks


✔ Consider after recurrent event while on blood thinner therapy

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?

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.