Beyond Cryptogenic Stroke: PFO Closure for Migraine and More

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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.

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<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
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<tr>
<td>Study Investigator</td>
<td>WL Gore &amp; Associates (REDUCE)</td>
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<td>WL Gore &amp; Associates (ASSURED)</td>
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<td>WL Gore &amp; Associates (Migraine/PFO Trial)</td>
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<td>Abbott Medical (Amulet)</td>
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<td>Edwards Medical (COMPASSION S3)</td>
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<td>BSCI (PREVAIL, CAP2)</td>
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<td>Conformal Medical (Animal Work, First-in-Man Feasibility Trial)</td>
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<td>Physician Training</td>
<td>Abbott Medical (Amplatzer PFO)</td>
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<td>BSCI (Watchman)</td>
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4 Randomized PFO/Cryptogenic Stroke Trials

RESPECT NEJM 2017

Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke

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

CLOSE NEJM 2017

REDUCE NEJM 2017

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*

DEFENSE PFO JACC 2018

Cryptogenic Stroke and High-Risk Patent Foramen Ovale: The DEFENSE-PFO Trial

Running title: Device closure for high-risk PFO

Pil Hyung Lee, MD*, Jae-Kwan Song, MD, PhD*, Jong S. Kim, MD, PhD*, Ran Heo, MD*, Sahmin Lee, MD*, Dae-Hee Kim, MD, PhD*, Jong-Min Song, MD, PhD*, Duk-Hyun Kang, MD, PhD*, Sun U. Kwon, MD, PhD*, Dong-Wha Kang, MD, PhD*, Dongwhane Lee, MD*, Hyuk Sung Kwon, MD*, Sung-Ched Yoon, PhD*, Byung Joo Sun, MD, PhD*, Jae-Hyeong Park, MD, PhD*, Jae-Hwan Lee, MD, PhD*, Hye Seon Jeong, MD, PhD*, Hee-Jung Song, MD, PhD*, Jei Kim, MD, PhD*, and Seung-Jung Park, MD, PhD*
4 Randomized PFO/Cryptogenic Stroke Trials
4 Randomized PFO/Cryptogenic Stroke Trials

What’s next?
PFO – What’s Next?

- Systemic (non-cerebral) paradoxical embolization
- Hypoxemia
- Decompression Illness
- Obstructive Sleep Apnea
- High Altitude Pulmonary Edema
- Migraine Headache
Systemic (Non-cerebral) Paradoxical Thromboembolism

“The clot doesn’t have to go to the brain.”
Systemic Embolization

Hepatic Infarct

Renal Infarct
Systemic Embolization

Splenic Infarcts

Retinal Infarct
18 year old with acute myocardial infarct (thrombus in L main CA)
✓ Why the historical focus on Stroke?

- Largest portion of CO goes to the brain
- Other organs have functional redundancy that the brain does not
- The clinical impact of a smaller clot is more often clinically apparent

Cerebral Infarct
Systemic Embolization

Conclusion (without data)

- Systemic thromboembolism has the same differential diagnosis as cardioembolic stroke and is a “stroke equivalent”.
- In the absence of another source, the PFO in a patient with a systemic thrombotic event should also be closed.
PFO – Hypoxemia
PFO – Hypoxemia: Physiology

With LAp > RAp throughout the cardiac cycle in most patients, the PFO is closed or opens phasically.

- RA Hypertension, TR/TS
- RV Non-compliance, normal PAp
- Platypnea – Orthodeoxia: Streaming of IVC inflow
Closure of PFO for Hypoxemia: Literature

Transcatheter Device Closure of Interatrial Septal Defects in Patients with Hypoxia

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From the ¹Hospital of the University of Pennsylvania, Division of Cardiovascular Medicine, Department of Medicine, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania; ²Division of Cardiology, Weill Cornell Medical Center, New York, New York

Effectiveness of Percutaneous Closure of Patent Foramen Ovale for Hypoxemia

Brett E. Fenster, MDb,e, Bryant H. Nguyen, MD³, J. Kern Buckner, MD³, Andrew M. Freeman, MD³, and John D. Carroll, MDb

- N = 10
- Immediate resolution of hypoxemia

- N = 97
- Procedural success in 96/97
- Immediate resolution of low O₂ sats in 70%.
PFO Closure for Hypoxemia

- No randomized studies. But it works.
- With continuous R to L flow, balloon occlusion of PFO can assess change in RA pressure and prove that Ao sat will rise.
- Pulmonary hypertension as an underlying cause of R to L shunt is a contraindication to PFO closure.
PFO – Migraine Headache
PFO – Migraine

History

• 2000 – First reports of migraine amelioration with PFO closure for recurrent stroke prevention, followed by numerous retrospective series reporting similar migraine effect

• Four failed PFO-Migraine trials: MIST, ESCAPE, PREMIUM, PRIMA

• In part likely due to our inability to select the PFOs which were “causal” from those which were incidental to the migraines
In 2011:

- PFO/cryptogenic stroke patients with aspirin contraindication
- Treated with clopidogrel as an alternative agent
- Some noted dramatic reduction/elimination of pre-existing MHA

We postulated that some product of platelet aggregation or activation might be acting as a “trigger” substance, crossing the PFO to reach the brain in supra-physiologic levels.
PFO – Migraine
Columbia University Experience 2011-2017

✓ Over 6 years at our site:

• Began an exploratory off-label (open-label) use of clopidogrel therapy for refractory non-stroke / MHA / PFO population

• No patients excluded on basis of:
  - aura/non-aura
  - headache frequency
  - episodic/chronic or any other specific MHA characteristic
PFO – Migraine


461 MHA Referrals
All seen previously by Neurology
All met International MHA criteria
No alternate headache mechanism

176 Non-Stroke; + R to L Shunt; Frequent Severe MHA

P2Y12 Inhibition Rx:
40 Entered a formal Investigator-Initiated Ticagrelor Trial
136 Treated with clopidogrel

Excluded from further Rx:
35 found to have no R to L shunt
116 MHA too mild, too sporadic, other mechanism
134 Documented Stroke
PFO – Migraine

✓ Population:

• 86% Female
• 61% Migraine with aura
• Mean Age = 37.9 +/- 14.7 years (Range 14 – 71)
• Average Headache Burden: 14.7 +/- 9.3 days/month (Range 0.5 – 28)
✓ Patient Response prospectively defined as:

• Clopidogrel RESPONDER:
  - $\geq 50\%$ Reduction in Monthly MHA days
  - Migraine Elimination/Near Elimination: $\geq 90\%$ reduction in monthly MHA days

• Clopidogrel NON-RESPONDER:
  - $< 50\%$ Monthly Headache Reduction
PFO – Migraine


Response to clopidogrel
✓ No difference in response rate to clopidogrel:

- Aura vs. Non-aura (58% vs. 59%)
- Chronic vs. Episodic (61% vs. 57%)
- Large vs. small R to L shunt magnitude (73% vs. 59%)
PFO – Migraine

- 17 RESPONDERS, 45/56 NON-RESPONDERS were tested for adequacy of P2Y12 platelet inhibition (PRU testing)

PRU Testing – VerifyNow®, Accriva Diagnostics, San Diego CA
PFO – Migraine

Response to prasugrel in clopidogrel-resistant MHA NONRESPONDERS

- All patients had PRU < 100 on prasugrel
- Suggested that headache response was related to P2Y12 inhibition
- Implied that PFO Migraines are “platelet-mediated”

- Elimination or Near Elimination**: 5 (56%)
- > 50% Reduction: 4 (44%)

6 (33%) RESPONDER*
9 (67%) NON-RESPONDER

THE STRUCTURAL HEART DISEASE SUMMIT 2018
Transcatheter Valve Therapies (TVT) and LAA/PFO Closure
PFO – Migraine


Response to PFO Closure/Drug Withdrawal (N = 56):

- 1 pt with moderate persistent leak of the PFO device
- 1 patient with no MHA X 1 yr then onset of new/different headaches
- 1 patient with 3 years of complete relief, with mild MHA return when became pregnant

- 52 (93%)
- 3 (5%)
- 1 (2%)
PFO – Migraine


Response to Drug Withdrawal without PFO Closure (N = 8):

Typical MHA return time = 4-5 days (the effective elimination time of the thienopyridine)
PFO – Migraine


✓ Formal Ticagrelor feasibility trial (N = 40)
  • 48% Migraine RESPONDERS:
    - Less effective MHA relief
    - 9/9 had same or better response to PFO closure

✓ New National MHA/PFO Trial (End of 2018)
  • Thienopyridine responsiveness will be used as final screening step prior to randomized PFO closure or sham procedure