Cryptogenic Stroke/PFO with Thrombophilia and VTE:

Do We Know What To Do?

Robert J. Sommer, MD
Columbia University Medical Center
New York, NY
Disclosure Statement of Financial Interest

Within the past 12 months, I, Robert Sommer, 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>
</thead>
<tbody>
<tr>
<td>Grant/Research Support</td>
<td>W.L. Gore</td>
</tr>
<tr>
<td>Consulting Fees</td>
<td>W.L. Gore</td>
</tr>
<tr>
<td>National PI – ASSURED Trial</td>
<td>W.L. Gore</td>
</tr>
</tbody>
</table>
“The Amplatzer PFO Occluder 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 – 60 years, who have 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.”
Cryptogenic Stroke Work-up

- Acute onset neurologic symptoms with corresponding ischemic Infarct by cerebral imaging without other identifiable stroke source:
  - Cerebral vascular anomalies
  - Atrial Fibrillation
  - Carotid artery disease
  - Aortic atheroma
  - LAA thrombus
  - LV mural thrombus
  - L sided AV valve anomalies
Hypercoagulable Work-up

• Inherited Thrombophilias:
  – Prothrombin Gene Mutation (G20210A)
  – Factor V Leiden Mutation (G1691A)
  – Protein S, Protein C, Anti-thrombin III deficiencies
  – MTHFR Mutations with elevated homocysteine levels
  – Others

• Acquired Thrombophilias
  – Anti-phospholipid Syndrome
  – Generally require OAC
Do we know what to do when thrombophilia (TP) is identified in a patient with CS/PFO without other known sources?

• No. There is no RCT data to guide us.

• What we do know...
Blood thinners reduce PFO/stroke risk

• In all PFO RCT’s, OACs and antiplatelet therapy both reduce recurrent stroke risk, compared with historical controls

  - RESPECT Trial. Carrol et al. 5 Year data presented at TCT 2015.

• By reducing the clot burden returning to the RA, lessening chance of paradoxical embolization
Inherited Thrombophilia

- Inherited thrombophilias are associated with venous thrombus formation (not intra-arterial) and are known to increase the risk of VTE events


- Increased RA clot burden will increase the risk of paradoxical embolization across a PFO
RESPECT 5 Year Follow-up Data

• Recurrent cryptogenic stroke with PFO is more strongly associated with:
  - Atrial septal aneurysm
  - Large R to L flow by bubble contrast

• Consistent with the accepted mechanism of paradoxical embolization through the PFO

• In this high risk population, closure of the PFO was 75% better than on-going blood thinners

Carroll et al. Presented at TCT, October 2015
Do common prothrombotic mutations influence the risk of cerebral ischaemia in patients with patent foramen ovale? Systematic review and meta-analysis.


- Meta-analysis:
  - 6 studies, 856 pts with CS/PFO, 1001 controls
  - In CS/PFO group, the PT (G20210A) more prevalent {OR = 3.85 (CL 2.22 – 6.66)}
  - FV (G1691A) less strong (OR = 1.28 (CL 1.03 – 2.57))
  - Carrying either PT or FV mutation increased CS risk - OR 1.98 (CL 1.23 -2.83), OR 1.62 (CL 1.03 – 2.57)
Recurrent CVA +/- Thrombophilia
Before PFO Closure

Thresholds should be lower for closing CS/PFO in patients with TP than in the general CS/PFO population, especially in those with higher risk PFO anatomy.
What were they thinking???

AHA/ASA Guideline

Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack
A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons
AHA/ASA Recommendations?

PFO Recommendations

1. There are insufficient data to establish whether anticoagulation is equivalent or superior to aspirin for secondary stroke prevention in patients with PFO (Class IIb; Level of Evidence B).

2. For patients with an ischemic stroke or TIA and a PFO who are not undergoing anticoagulation therapy, antiplatelet therapy is recommended (Class I; Level of Evidence B). (Revised recommendation)

3. For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics (Class I; Level of Evidence A). When anticoagulation is contraindicated, an inferior vena cava filter is reasonable (Class IIa; Level of Evidence C). (New recommendation)

4. For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for DVT, available data do not support a benefit for PFO closure (Class III; Level of Evidence A). (Revised recommendation)

5. In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT (Class IIb; Level of Evidence C). (New recommendation)
Oral Anticoagulation has never been shown to be superior to antiplatelet therapy in the CS/PFO population in preventing recurrent CS.

- WARSS Trial ($p = \text{NS}$)
- PICSS Trial ($p = \text{NS}$)
- CLOSURE I Trial ($p = \text{NS}$)
- PC Trial ($p = \text{NS}$)
- RESPECT Trial ($p = \text{NS}$)
IVC Filter

Multiple catheters passed through an IVC filter
Is it safe to implant a PFO device with a known thrombophilia?
Is PFO Closure Safe with TP?

• Does TP increase the risk of device thrombosis?
  – Personal experience:
    • Over 4000 devices implanted over 20 yrs
    • All have had TP work-up, positive in ~ 15 - 20%
    • Five clinical cases of device thrombosis, none with documented TP
Is PFO Closure Safe with TP?

Comparison of Results of Percutaneous Closure of Patent Foramen Ovale for Paradoxical Embolism in Patients With Versus Without Thrombophilia

Alessandro Giardini, MD, Andrea Donati, MD, Roberto Formigari, MD, Gabriele Bronzetti, MD, Daniela Prandstraller, MD, Marco Bonvicini, MD, Gualtiero Palareti, MD, Donata Guidetti, MD, Oscar Gaddi, MD, and Fernando Maria Picchio, MD

• 72 consecutive patients with PFO and Stroke/TIA
• 28% documented thrombophilia
• No outcomes difference post closure at (20 +/- 11 mos)
Is PFO Closure Safe with TP?

Safety and long-term results of patent foramen ovale transcatheter closure in patients with thrombophilia.

Rigatelli G\textsuperscript{1}, Dell’Avvocata F, Giordan M, Camerotto A, Panin S, Ronco F, Cardaioli P.

- 98 Consecutive Patients with PFO and Stroke/TIA
- 31% had documented thrombophilia
- No difference in device thrombosis or recurrent CVA events

Recommendation

• With standard post-implant anti-platelet therapy, there is no clear additional risk of device thrombosis in patients with TP
Conclusions (Editorial):

• Cryptogenic stroke/PFO with:
  – Documented TP: should have a lower threshold for PFO closure than the non-TP CS/PFO population
  – Venous source: OAC X 6 months only, then long-term anti-platelet therapy, or closure with antiplatelet therapy, depending on presence/absence of high-risk PFO features.
  – No venous source: long-term antiplatelet Rx or closure with antiplatelet therapy depending on presence/absence of high-risk PFO features.