Updated Randomized Clinical Trial Data for PFO Closure in All-Comers and Subgroups with Cryptogenic Stroke: How Should the Guidelines be Updated

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Disclosure Statement of Financial Interest

- I DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

PFO Transcatheter Closure for Cryptogenic Ischemic Stroke

Randomized Clinical Trials

- CLOSURE I (2012)
- PC (2013)
- RESPECT (2013 and 2017)
- REDUCE (2017)
- CLOSE (2017)
- DEFENSE-PFO (2018)

Furlan, AJ, et al. N Engl J Med . 2012;366:991-9.
Meier B, et al. N Engl J Med . 2013;368:1083-91.
Carroll JD, et al. N Engl J Med . 2013;368:1092-100.
Saver JL, et al. N Engl J Med . 2017;377:1022-32.
Søndergaard L, et al. N Engl J Med. 2017;377:1033-42.
Mas JL, et al. N Engl J Med . 2017;377:1011-21.
Lee HP, et al. J Am Coll Cardiol. 2018;71:2335-42.

CLOSURE I

Randomized Clinical Trial (2012)

- *STARFlex Septal Closure System* vs. medical therapy (aspirin and/or warfarin).
- 909 subjects followed for 2 years.
- Included patients with cryptogenic ischemic stroke or TIA (did not require verification by imaging possibly leading to diagnostic inaccuracy).
- No significant difference in composite of stroke, TIA, death from any cause, or death from neurologic causes with PFO closure (5.5%) vs. medical therapy alone (6.8%; p= 0.37).
  - No significant difference in recurrent stroke or TIA
- Device associated with lower rates of effective PFO closure.
- Highest incidence of device thrombosis (3.6%).

Taaffe M, et al. Am J Cardiol. 2008;101:1353–8.
Furlan, AJ, et al. N Engl J Med . 2012;366:991-9.

PC

Randomized Clinical Trial (2013)

- *Amplatzer PFO Occluder* vs. medical therapy (anti-platelet or anti-coagulation).
- 414 subjects followed for a mean of 4 years.
- Included patients with cryptogenic ischemic stroke or TIA verified by imaging, or peripheral thromboembolic event.
- No significant difference in composite of death, nonfatal stroke, TIA, or peripheral embolism with PFO closure (3.4%) vs. medical therapy alone (5.2%; p= 0.34).
  - No significant difference in recurrent stroke or TIA
- Trial statistically underpowered; also, included patients with peripheral thromboembolism (non-cerebral).

Meier B, et al. N Engl J Med . 2013;368:1083-91.

RESPECT

Randomized Clinical Trial (2013 & 2017)

- *Amplatzer PFO Occluder* vs. medical therapy (aspirin, clopidogrel, aspirin plus dipyridamole, or warfarin).
- 980 subject (largest) followed for a mean of 5.9 years (longest follow-up).
- Included patients with cryptogenic ischemic stroke symptoms > 24 hours or if < 24 hours confirmation by imaging.
- Significant decrease in recurrent stroke with PFO closure (3.6%) vs. medical therapy alone (5.8%; p=0.046).
- Number needed to treat to prevent 1 stroke in 5 years was 42 patients.

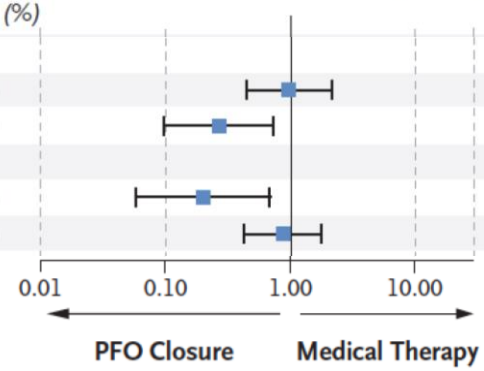
Saver JL, et al. N Engl J Med . 2017;377:1022-32.
Carroll JD, et al. N Engl J Med . 2013;368:1092-100.

Shunt Size and Atrial Septal Aneurysm

RESPECT Trial

Rate of Recurrent Ischemic Stroke According to Subgroup

Subgroup	PFO Closure Group	Medical-Therapy Group	Hazard Ratio (95% CI)	P Value by Log-Rank Test	P Value for Interaction
	no. of patients with event/total no. (%)				
Shunt size					0.04
None, trace or moderate	13/247 (5.3)	12/244 (4.9)	0.96 (0.44–2.11)	0.93	
Substantial	5/247 (2.0)	16/231 (6.9)	0.26 (0.10–0.71)	0.005	
Atrial septal aneurysm					0.04
Present	3/179 (1.7)	13/170 (7.6)	0.20 (0.06–0.70)	0.005	
Absent	15/320 (4.7)	15/311 (4.8)	0.86 (0.42–1.76)	0.68	



Modified from Saver JL, et al. N Engl J Med . 2017;377:1022-32.

REDUCE

Randomized Clinical Trial (2017)

- *Gore Helex or Cardioform Septal Occluder* vs. medical therapy (aspirin, aspirin plus dipyridamole, or clopidogrel).
- 664 subjects followed for a median of 3.2 years.
- Included patients with cryptogenic ischemic stroke symptoms > 24 hours or if < 24 hours confirmation by imaging.
- Significant decrease in recurrent clinical ischemic stroke in PFO closure (1.4%) vs. medical therapy (5.4%; p=0.002).
- Significant decrease in new brain infarct (clinical ischemic stroke or silent brain infarct by MRI) in PFO closure (5.7%) vs. medical therapy (11.3%; p=0.04).
- Number needed to treat to prevent 1 stroke in 2 years was ~ 28 patients.

Søndergaard L, et al. N Engl J Med. 2017;377:1033-42.

CLOSE

Randomized Clinical Trial (2017)

- *Any CE Marked PFO Device* vs. medical therapy (aspirin, aspirin plus dipyridamole, clopidogrel, vitamin K antagonists or DOAC).
- 663 subjects followed for a mean of 5.3 years.
- Included patients with cryptogenic ischemic stroke seen on imaging plus high-risk PFO features (atrial septal aneurysm or large interatrial shunt).
- Significant decrease in recurrent nonfatal/fatal ischemic stroke in PFO closure (0%) vs. anti-platelet therapy alone (5.9%; $p<0.001$).
- Number needed to treat to prevent 1 stroke in 5 years was 20 patients.
- In the medically treated group, no significant difference in recurrent stroke between anti-platelet vs. anti-coagulation therapy.

Mas JL, et al. N Engl J Med . 2017;377:1011-21.

DEFENSE-PFO

Randomized Clinical Trial (2018)

- *Amplatzer PFO Occluder* vs. medical therapy (aspirin, aspirin plus clopidogrel, aspirin plus cilostazol, or warfarin).
- 120 subjects followed for a median of 2.8 years.
- Included patients with cryptogenic ischemic stroke plus high-risk PFO features (atrial septal aneurysm, hypermobile septum, or increase PFO size).
- Significant decrease in recurrent ischemic stroke in PFO closure (0%) vs. medical therapy (10.5%; p=0.023).
- Number needed to treat to prevent 1 stroke in 2 years was 10 patients.

Lee HP, et al. J Am Coll Cardiol. 2018;71:2335-42.

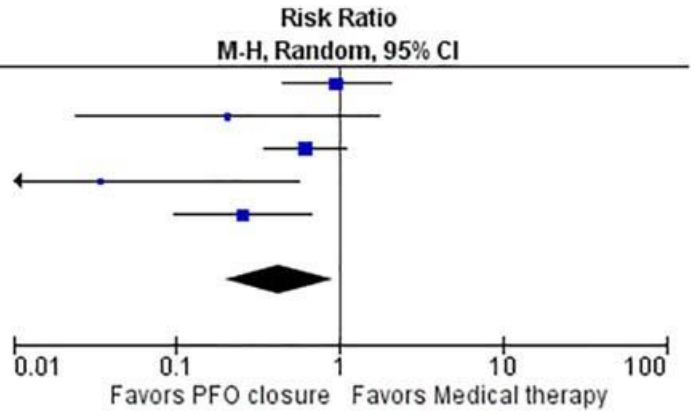
PFO Closure vs. Medical Therapy Alone in the Incidence of Recurrent Stroke

Meta-Analysis of Cryptogenic Ischemic Stroke Randomized Trials

Study or Subgroup	PFO Closure Events	PFO Closure Total	Medical Therapy Events	Medical Therapy Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
CLOSURE 1	12	447	13	462	28.0%	0.95 [0.44, 2.07]	2012
PC trial	1	204	5	210	9.5%	0.21 [0.02, 1.75]	2013
RESPECT Trial	18	499	28	481	32.2%	0.62 [0.35, 1.11]	2013
CLOSE	0	238	14	235	6.1%	0.03 [0.00, 0.57]	2017
REDUCE	6	441	12	223	24.1%	0.25 [0.10, 0.66]	2017
Total (95% CI)		**1829**		**1611**	**100.0%**	**0.42 [0.20, 0.91]**	
Total events	37		72				

Heterogeneity: $Tau^2 = 0.38$; $Chi^2 = 9.72$, $df = 4$ ($P = 0.05$); $I^2 = 59\%$

Test for overall effect: $Z = 2.22$ ($P = 0.03$)



Favors PFO closure (2.0%) over medical therapy alone (4.2%) in decreasing recurrent stroke (p=0.03).

Hakeem A, Cilingiroglu M, Katramados A, Boudoulas KD, et al. Catheter Cardiovasc Interv. 2018.

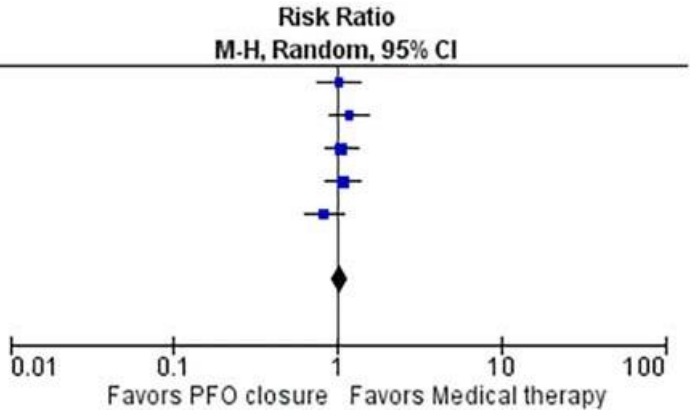
PFO Closure vs. Medical Therapy Alone in the Incidence of Adverse Outcomes

Meta-Analysis of Cryptogenic Ischemic Stroke Randomized Trials

Study or Subgroup	PFO Closure Events	PFO Closure Total	Medical Therapy Events	Medical Therapy Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
CLOSURE 1	68	402	76	458	15.6%	1.02 [0.76, 1.37]	2012
PC trial	71	204	62	210	17.6%	1.18 [0.89, 1.56]	2013
RESPECT Trial	114	499	104	480	25.4%	1.05 [0.83, 1.33]	2013
CLOSE	85	238	78	235	22.5%	1.08 [0.84, 1.38]	2017
REDUCE	102	441	62	223	18.9%	0.83 [0.63, 1.09]	2017
Total (95% CI)		**1784**		**1606**	**100.0%**	**1.03 [0.91, 1.16]**	
Total events	440		382				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.43$, $df = 4$ ($P = 0.49$); $I^2 = 0\%$

Test for overall effect: $Z = 0.45$ ($P = 0.65$)



No significant difference in adverse events between PFO closure and medical therapy alone groups.

Hakeem A, Cilingiroglu M, Katramados A, Boudoulas KD, et al. Catheter Cardiovasc Interv. 2018.

PFO Closure and Incidence of Atrial Fibrillation Across Randomized Trials for Cryptogenic Ischemic Stroke

- Meta-analysis showing incidence of atrial fibrillation greater in PFO closure (4.0%) compared to medical therapy alone (0.6%; p=0.0002).

- Risk of atrial fibrillation device/trial dependent:
  - non-significant in PC, RESPECT and DEFENSE-PFO (*Amplatzer*)
  - significant in CLOSURE I (*STARFlex*), REDUCE (*Gore*) and CLOSE (*any CE Marked PFO Device*)

- ~ 80-90% of atrial fibrillation occurred ≤ 45 days after PFO closure and at least partially related to time of procedure; low or no recurrence of atrial fibrillation on long-term follow-up, however, limited data.

Furlan, AJ, et al. N Engl J Med . 2012;366:991-9.
Meier B, et al. N Engl J Med . 2013;368:1083-91.
Carroll JD, et al. N Engl J Med . 2013;368:1092-100.
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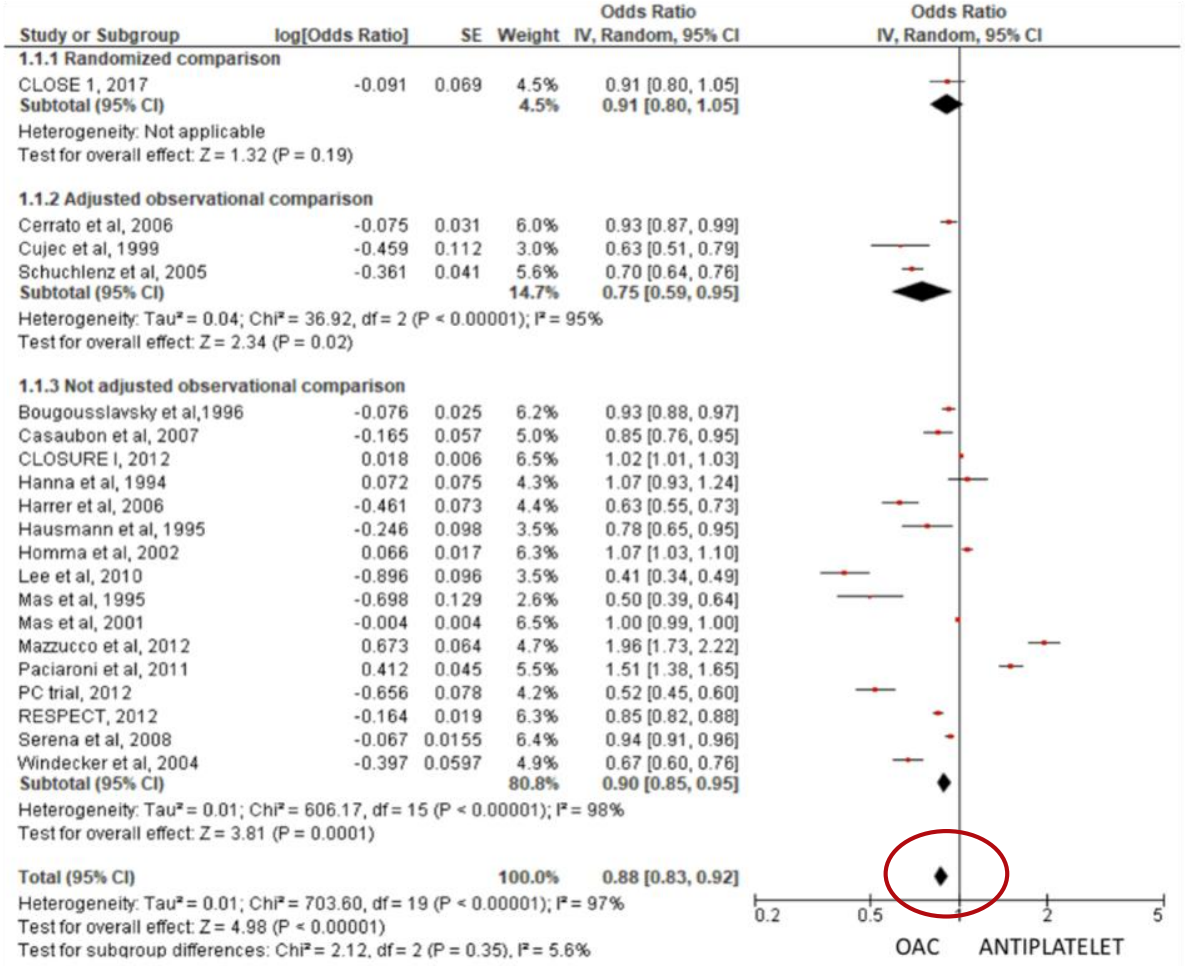
Mas JL, et al. N Engl J Med . 2017;377:1011-21.
Lee HP, et al. J Am Coll Cardiol. 2018. In press.
Hakeem A, et al. Catheter Cardiovasc Interv. 2018.

Anticoagulant vs. Antiplatelet Therapy for Stroke Prevention after Cryptogenic Ischemic Stroke with PFO

Meta-Analysis



Pristipino C, et al. EuroIntervention. 2018.

PFO Occluder Devices

United States FDA Approval

- *Amplatzer PFO Occluder* (October 28, 2016).

- *Gore Cardioform Septal Occluder* (March 30, 2018).

- Device indicated for percutaneous transcatheter closure of a 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.

PFO Closure for Secondary Prevention of Cryptogenic Stroke: Operator and Institutional Requirements

An Expert Consensus Statement of the
Society of Cardiovascular Angiography and Interventions (SCAI)
and the American Academy of Neurology (AAN)

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Time to Update the Guidelines

- In selected patients with a PFO and cryptogenic stroke, transcatheter PFO closure is the most effective treatment to reduce the risk of recurrent stroke in accordance with evidence based randomized data.
- This information should be incorporated in the guidelines.
- The guidelines, however, should be written in such a way that can easily be applied to the individual patient.

Updated RCT Data for PFO Closure

Summary

- In selected patients with a PFO and cryptogenic stroke, transcatheter PFO closure is the most effective treatment to reduce the risk of recurrent stroke in accordance with evidence based randomized data.
- Large sized-PFO associated with a significant shunt and/or an atrial septal aneurysm may increase likelihood that an ischemic stroke was PFO-related.
- FDA recently has approved 2 PFO occluder devices.
- No significant difference in overall adverse events between PFO closure and medical therapy alone; however, atrial fibrillation was seen more with PFO closure (majority likely transient peri-procedure).
- In those with a PFO and cryptogenic stroke who decline closure or closure is contraindicated, anticoagulants may be slightly superior to antiplatelet therapy.

PFO Closure in PFO-Mediated (Cryptogenic) Ischemic Stroke

Concluding Remarks

- PFO closure in selected patients appears to be effective in preventing stroke, which should be reflected in the guidelines.
- Close collaboration between a cardiologist and a neurologist is required to define those patients.
- PFO closure is an effective therapy compared to alternative options (i.e., life-long anticoagulation therapy).
- Further research is needed to define the long-term incidence of atrial fibrillation and possible superiority of anticoagulants compared to antiplatelets in those who decline PFO closure or when PFO closure is contraindicated.
- National and international registries will assist in advancing our knowledge in the field and help to better manage this group of patients.

Thank you

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