

## PFO CLOSURE: WHAT'S NEW?



1. AHA rescinds major sections of 2018 AHA/ASA Stroke Guidelines
2. PFO closure is cost effective
3. Now 12 meta-analyses of PFO/Stroke RCT confirm PFO closure superiority
4. FDA approves WL Gore® Cardioform device for PFO closure
5. PREMIUM randomized PFO/Migraine trial published: endpoint confusion
6. Migraine/ Aura-Stroke-PFO Relationship

# AHA RESCINDS 2018 AHA/ASA STROKE GUIDELINES

MEDSCAPE July 10, 2018:

*“..the American Heart Association (AHA)/ American Stroke Association (ASA) has rescinded its recently released stroke guidelines, publishing a “correction” in which large parts of the document have been deleted.*

*The sections that have been deleted are the following:*

- *Section 1.3: EMS Systems Recommendation 4*
- *Section 1.4: Hospital Stroke Capabilities Recommendation 1*
- *Section 1.6: Telemedicine Recommendation 3*
- *Section 2.2: Brain Imaging Recommendation 1*
- *Section 3.2: Blood Pressure Recommendation 3*
- *Section 4.3: Blood Pressure Recommendation 2*
- *Section 6.0: All subsections*

*The rescinding of the Guidelines was done without the agreement of the Guideline writing committee.”*

Correction to: 2018 Guidelines for the Early Management of Patients with  
Acute Ischemic Stroke. Stroke April 18, 2018



# AHA RESCINDS 2018 AHA/ASA STROKE GUIDELINES

Reasons for rescinding:

1. Guidelines based upon “a very narrow perspective”.
2. Guidelines “focused totally on stroke outcomes rather than on the patient”.
3. Guidelines “question many of the things that we do in our routine treatment of stroke patients. It is not possible to do randomized trials of everything we do.”
4. “who could possibly argue that doing an MRI scan to confirm the diagnosis and pattern of stroke is not important? That is nonsensical—it defies common sense.”
5. “..just because it doesn’t have randomized data doesn’t mean it’s not the right thing to do; lack of evidence is not necessarily equivalent to lack of efficacy.”
6. The AHA leadership received a large number of complaints questioning the 2018 stroke guidelines which lead to the deletions.

Hughes S, Medscape July 14, 2018

Previously, ACEP and AAN joint Stroke Guidelines were rescinded by the ACEP in 2013 and revised and published in 2015 by the ACEP without ASA or AAN.

Calls to revise/ rescind the AHA/ASA 2013 PFO closure guidelines have been ignored despite practitioner, national meeting public, and published criticism have been ignored



# PFO CLOSURE IS COST EFFECTIVE

Leppert MH et al, Cost-Effectiveness of Patent Foramen Ovale Closure Versus Medical Therapy for Secondary Stroke Prevention. Stroke 2018;49:1443-1450

15 year cost and outcomes associated with PFO closure using Markov Model

Employing meta-analyses of the 5 PFO/Stroke Randomized trials:

PFO closure cost effectiveness was \$458,558 per addition QALY  
(QALY = Quality-Adjusted Life Years)

“CONCLUSIONS: PFO closure for cryptogenic stroke in the right setting is cost-effective, Producing benefit in QALYs and potential cost savings.....”



# PFO CLOSURE IS SUPERIOR TO MEDICAL THERAPY

| PFO CLOSURE VS MEDICAL THERAPY RCT | % REDUCTION | p VALUE |
|------------------------------------|-------------|---------|
| <b>REDUCE (N=664)</b>              |             |         |
| STROKE REDUCTION                   | <b>77%</b>  | 0.002   |
| NEW BRAIN INFARCTION REDUCTION     | <b>49%</b>  | 0.04    |
| <b>RESPECT (N=980)</b>             |             |         |
| ALL STROKE REDUCTION               | <b>45%</b>  | 0.046   |
| ASCOD ADJUDICATED STROKE REDUCTION | <b>62%</b>  | 0.007   |
| TOAST ADJUDICATED STROKE REDUCTION | <b>92%</b>  | 0.01    |
| <b>CLOSE (N=663)</b>               |             |         |
| STROKE REDUCTION                   | <b>97%</b>  | 0.001   |
| STROKE/TIA/ SYSTEMBIC EMBOLIZATION | <b>61%</b>  | 0.01    |
| <b>DEFENSE-PFO (n=120)</b>         |             |         |
| STROKE REDUCTION                   | <b>100%</b> | 0.02    |

Sondegard L et al, *Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. NEJM 2017; 377:1033-42*

Saver JL et al, *Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. NEJM 2017; 377:1022-32*

Mas J-L et al, *Patent foramen ovale closure or anticoagulation vs antiplatelets after stroke. NEJM 2017;377:1011-21*

Lee PH et al, *Cryptogenic stroke and high-risk Patent Foramen Ovale. JACC 2018;DOI 10.10161/JACC 2018.02.046*



# META-ANALYSES CONFIRM SUPERIORITY OF DEVICE CLOSURE ( NOW 27!)

(prompting further calls to revise PFO Guidelines)

| PFO/STROKE META-ANALYSIS | % STROKE REDUCTION |
|--------------------------|--------------------|
| Ando T et al             | 58%*               |
| De Rosa S et al          | 71%                |
| Shah R et al             | 68%                |
| Mojadidi MK et al        | 58%*               |
| Schulze V et al          | 59%*               |

REDUCE + RESPECT + CLOSE + PC-TRIAL; \* Includes CLOSURE 1 ; (DEFENSE-PFO not included)

1. Ando T et al, *Meta-analysis comparing PFO closure vs medical therapy to prevent recurrent stroke*. Amer J Cardiol 2018; 121:649-655
2. De Rosa S et al, *Percutaneous closure vs medical therapy in stroke patients with PFO. A systematic review and meta-analysis*. Ann Int Med 2018; epub
3. Shah R et al, *Device closure vs medical therapy alone for PFO in patients with cryptogenic stroke. A systematic review and meta-analysis* Ann Int Med 2018; epub
4. Mojadidi MK et al, *Trans-catheter PFO closure after cryptogenic stroke. An updated meta-analysis of randomized clinical trials*. JACC: Cardiovasc Interv 2017; 10:2228-30
5. Schulze V et al, *PFO closure or medical therapy for cryptogenic ischemic stroke. An updated meta-analysis of randomized clinical trials*. Clin Res Cardiol 2018; epub

6. Anantha-Narayanan, 7. Elbadawi A, 8. Turc G, 9. Reinthaler M, 10. Pasceri V, 11. Mazzucco S, 12. Saber H, 13. Tsigoulis G, 14. Garg L, 15. Xu HB, 16. Smer A, 17. Lattanzi S, 18. Alushi B, 19. Wang TKM, 20. Akobeng AK, 21. Darmoch F, Ahmad Y, 22. Palaiodimos L, 23. Kheiri B, 24. Zhang XL, 25. Abo-Salem, 26. Piccolo R, 27. Ntaios G



# FDA APPROVES GORE® CARDIOFORM FOR PFO CLOSURE



## ***THE REDUCE TRIAL***

**77 %** REDUCTION IN RECURRENT CLINICAL STROKE  
**49 %** REDUCTION IN NEW BRAIN INFARCTION  
ANNULIZED EVENT RATE ( per 100 patient years)

**DEVICE:** 0.39 events per year

**MEDICAL:** 1.71 events per year

# PREMIUM: PFO CLOSURE FOR MIGRAINE RCT PUBLISHED

Tobis JM et al, *Percutaneous Closure of Patent Foramen Ovale in Patients with Migraine: the PREMIUM TRIAL*. JACC 2017; 70:2766-2074

A randomized, sham-controlled, double-blind study of PFO closure using the Amplatzer™ PFO Occluder to treat refractory migraine in patients with  $\geq 4$  Spencer Grade TCD shunt PFO.

| PREMIUM N = 230                        | DEVICE | MEDICAL | P VALUE |
|--|--------|---------|---------|
| Primary Endpoint                       |        |         |         |
| Investigator selected: Migraine Days * | 3.4    | 2.0     | 0.025   |
| FDA-defined: 50% Responder Rate**      | 38%    | 32%     | NS      |
| Subset Analysis                        |        |         |         |
| Migraine with Aura Improvement         | 49%    | 23%     | 0.015   |
| Complete Migraine Resolution           | 8.6%   | 0.9%    | 0.01    |

\* International Headache Society Guidelines for controlled trials of preventative RX of migraine  
Cephalgia 1998; 11: 1-12 Cephalgia 2001; 20: 765-786 Cephalgia 2008; 28: 484-495

\*\*Responder rate recommended as secondary endpoint only by above

Investigator selected IHS defined primary end-point became regulatory secondary endpoint



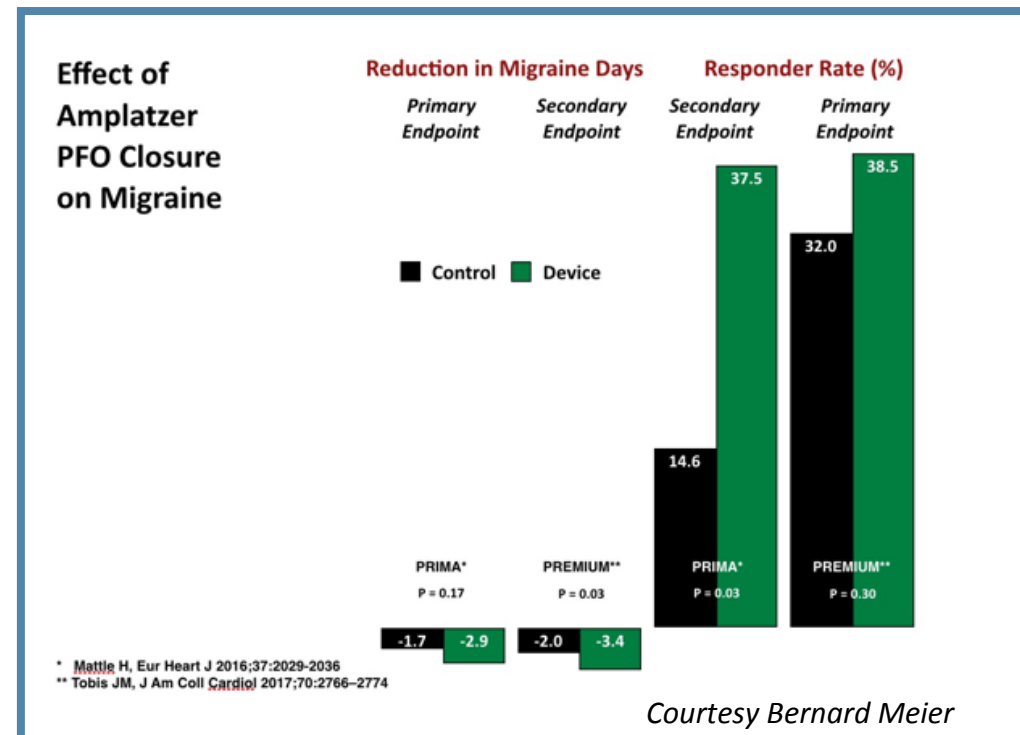


# PREMIUM ENDPOINT CONFUSION

Option A: The investigator-selected primary endpoint (IHS Guideline 1998, 2001, 2008) is valid and PFO closure therefore reduces migraine headache

Option B: The regulatory defined primary endpoint (FDA IHS over-ride) is valid and therefore PFO closure is not a treatment option for refractory migraine

Are these endpoint designations arbitrary and semantic? PRIMA/PREMIUM comparison:



# MIGRAINE-STROKE RELATIONSHIP

West BH et al, *Frequency of patent foramen ovale and migraine in patients with cryptogenic stroke*. Stroke 2018 April; DOI 10.1161/STROKEAHA.117.026160

712 stroke patients 127 (18%) cryptogenic stroke PFO diagnosis TCD,TTE, or TEE

| CRYPTOGENIC STROKE                        | % w/ PFO* |
|---|-----------|
| Cryptogenic Stroke but No Migraine        | 59%       |
| Cryptogenic Stroke and Migraine           | 79%       |
| Cryptogenic Stroke and Migraine with Aura | 93%       |

“Conclusions: In Patients with cryptogenic stroke who have migraine, there is a high prevalence (79%) of PFO with right-to-left shunt. The timing of stroke in migraineurs is usually not related to a migraine attack. These observations are consistent with the hypothesis that the mechanism of stroke in migraineurs is most likely because of paradoxical embolus. Future cryptogenic stroke classification schemes should consider including PFO as a separate etiologic category.”

- Compares with Wilmshurst P et al Am J Cardiol 2006; 98:831-833  
Stroke/No Migraine (56%); Stroke/+Migraine (75%); Stroke/ Migraine +Aura (84%)

