

PFO CLOSURE: WHAT'S NEW?



1. **Four new PFO/Stroke RCT prove PFO closure superiority**
2. **Five meta-analyses of PFO/Stroke RCT confirm PFO closure superiority**
3. **FDA approves WL Gore® Cardioform device for PFO closure**
4. **PREMIUM randomized PFO/Migraine trial published: endpoint confusion**
5. **Migraine-Stroke-PFO Relationship**

PFO CLOSURE IS SUPERIOR TO MEDICAL THERAPY

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

PFO CLOSURE RCT SIMILARITIES

REDUCE/RESPECT/CLOSE/DEFENSE-PFO

Significant reduction in recurrent stroke	ALL
Low device implant procedural complication rates	ALL
Increased peri-procedural atrial fibrillation in device arm	ALL
Early atrial fibrillation resolution in most patients	ALL
No device vs medical therapy differences for serious events over time	ALL
Holter monitor/ Long-term monitoring	DEFENSE-PFO
Low baseline DVT rates (<7%)	ALL
Increased benefit in “high shunt”/ IASA patients	ALL EXCEPT REDUCE
Used devices approved for ASD closure for PFO closure	CLOSE/REDUCE
Included small, subcortical infarcts (lacunar infarcts), if no HT or DM, <50	CLOSE/RESPECT

ALL PFO/STROKE RANDOMIZED CLINICAL TRIALS

RANDOMIZED CLINICAL TRIALS	% REDUCTION	P VALUE
POSITIVE TRIALS¹		
2017 REDUCE	77%	0.002
2017 RESPECT (ASCOD)	62%	0.007
2017 CLOSE	97%	0.001
2018 DEFENSE-PFO	100%	0.02
POSITIVE TREND (NS BY ITT)²		
2012 CLOSURE 1	23%	NS
2013 RESPECT ITT KM	51%	NS
PER PROTOCOL	63%	0.03
AS TREATED	72%	0.007
2013 PC TRIAL ITT COMPOSITE	37%	NS
STROKE	80%	NS

¹ IBID

² Furlan AJ et al, *Closure or medical therapy for cryptogenic stroke with PFO*. NEJM 2012; 366:991-9
 Carroll JD et al, *Closure of PFO vs medical therapy after cryptogenic stroke*. NEJM 2013; 368:1092-100
 Meier B et al, *Percutaneous closure of PFO in cryptogenic embolism*. NEJM 2013; 368:1083-91

META-ANALYSES CONFIRM SUPERIORITY OF DEVICE CLOSURE

(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: Cardivasc 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

FDA APPROVES GORE® CARDIOFORM FOR PFO CLOSURE

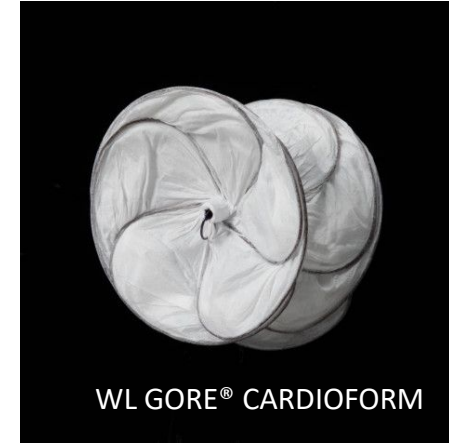
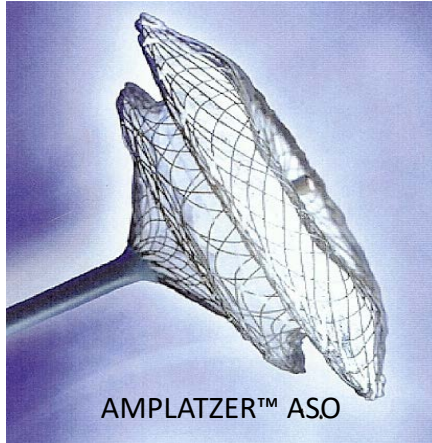


THE REDUCE TRIAL

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

FDA-APPROVED SECUNDUM ASD DEVICES

ALL THREE ASD DEVICES USED FOR PFO CLOSURE IN PFO/STROKE RANDOMIZED TRIALS



FDA-APPROVED PATENT FORAMEN OVALE DEVICES



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 ≥ 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

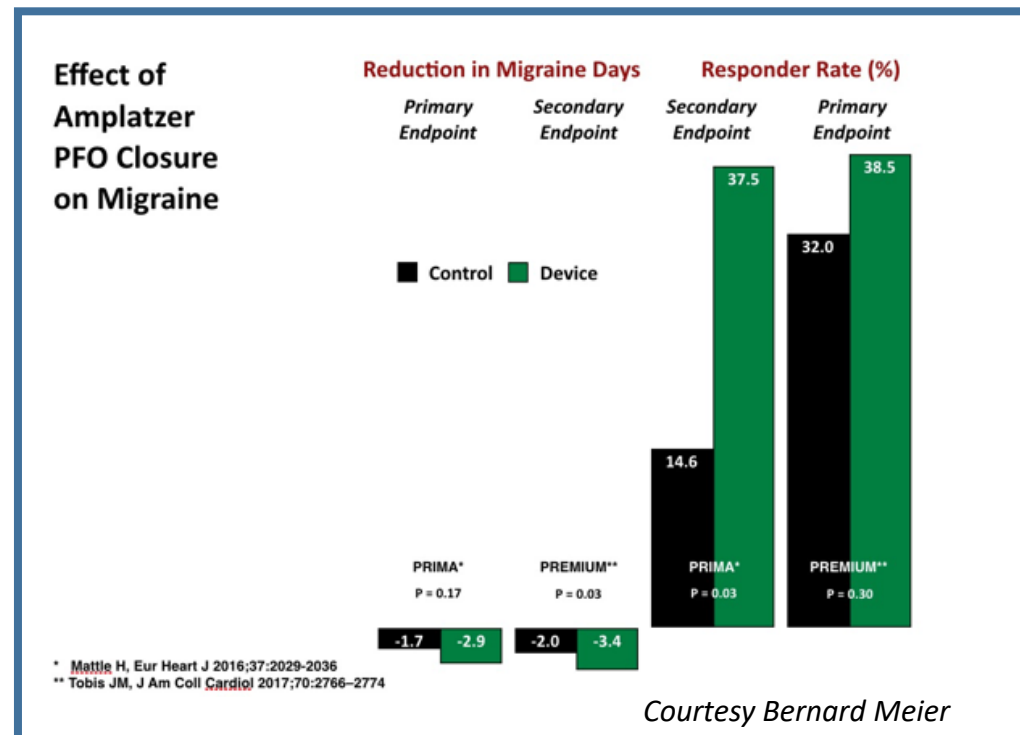
Investigator selected IHS defined primary end-point became regulatory secondary endpoint

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