



**A Prospective, Multicenter, Randomized Controlled Trial to
Evaluate the Safety and Efficacy of the STARFlex® Septal Closure
System Versus Best Medical Therapy in Patients with a Stroke or
Transient Ischemic Attack due to Presumed Paradoxical
Embolism through a Patent Foramen Ovale**

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For the CLOSURE I Investigators

Trial Sponsor: NMT Medical Boston

DISCLOSURES

Anthony J Furlan MD

- Consultant NMT Medical Boston
- Principal Investigator CLOSURE I

Study Design

- **Prospective, multi-center, randomized, open-label, two-arm superiority trial** designed to test whether PFO closure using STARFlex® plus medical therapy is superior to medical therapy alone for preventing recurrent stroke or TIA in patients with cryptogenic stroke or TIA and a PFO
 - IRB approved at each site and all patients signed informed consent
- **Study population:** Patients 60 years old or younger with a cryptogenic stroke or TIA and a PFO documented by TEE, with or without atrial septal aneurysm, within 6 months of randomization
 - DVT, hypercoagulopathy excluded
- **Primary endpoint** : 2-year incidence of stroke or TIA, all cause mortality for the first 30 days, and neurological mortality 31 days to 2 years
- **Followup** at 1 month, 6 months, 12 months and 24 months by a board certified neurologist
 - repeat TEE at 6 months all patients and 12/24 months if residual leak

Statistical Design

- **Sample size:**
 - expected primary endpoint 6% for medical therapy and 2% for STARFlex
 - 900 patients (450 per treatment group) provides 80% power and a two-sided significance level (alpha) of 0.05
- **Primary analysis** intent-to-treat
- **Safety analyses** performed on the Safety Analysis population, defined as all randomized patients who received the randomized treatment

Data Management and Core Labs

- ***Data Management:*** Harvard Clinical Research Institute (HCRI)
- ***Core Laboratories :***
 - Echocardiography (University of Pennsylvania),
 - Chest X-ray (Valerie Mandell, MD/Taylor Chung, MD)
 - MR (Perceptive Informatics).
 - Data from cores transmitted to HCRI and used by the independent CEC in event *adjudication*
- ***Clinical Events Committee (CEC)*** fully independent from the study and sponsor blindly adjudicated all neurological and study endpoints (D Cutlip, M Fisher)
- ***Data Safety Monitoring Board (DSMB)*** fully independent from the study and sponsor periodically reviewed and evaluated the incidence of adverse events with the ability to stop the study at any time for a safety concern. (JP Mohr, Chairman)

Cardiac Definitions

- ***Shunting and residual leaking:*** Core Echo Lab classified based on bubbles appearing in the left atrium either spontaneously or after provocative maneuver within five cardiac cycles after opacification of the right atrium. (***none, trace, moderate, substantial***)
- ***Procedural success:*** successful delivery of one or more STARFlex devices to the site during the index procedure without a procedural complication, deployment of the device at the intended site, and removal of the delivery system without a major procedural complication by discharge
- ***Effective closure:*** device success with grade 0 (none) or 1 (trace) residual leaking by TEE.
- ***Atrial septal aneurysm (ASA):*** hypermobile septum primum with total septal mobility of 10mm or greater

Neurological Definitions

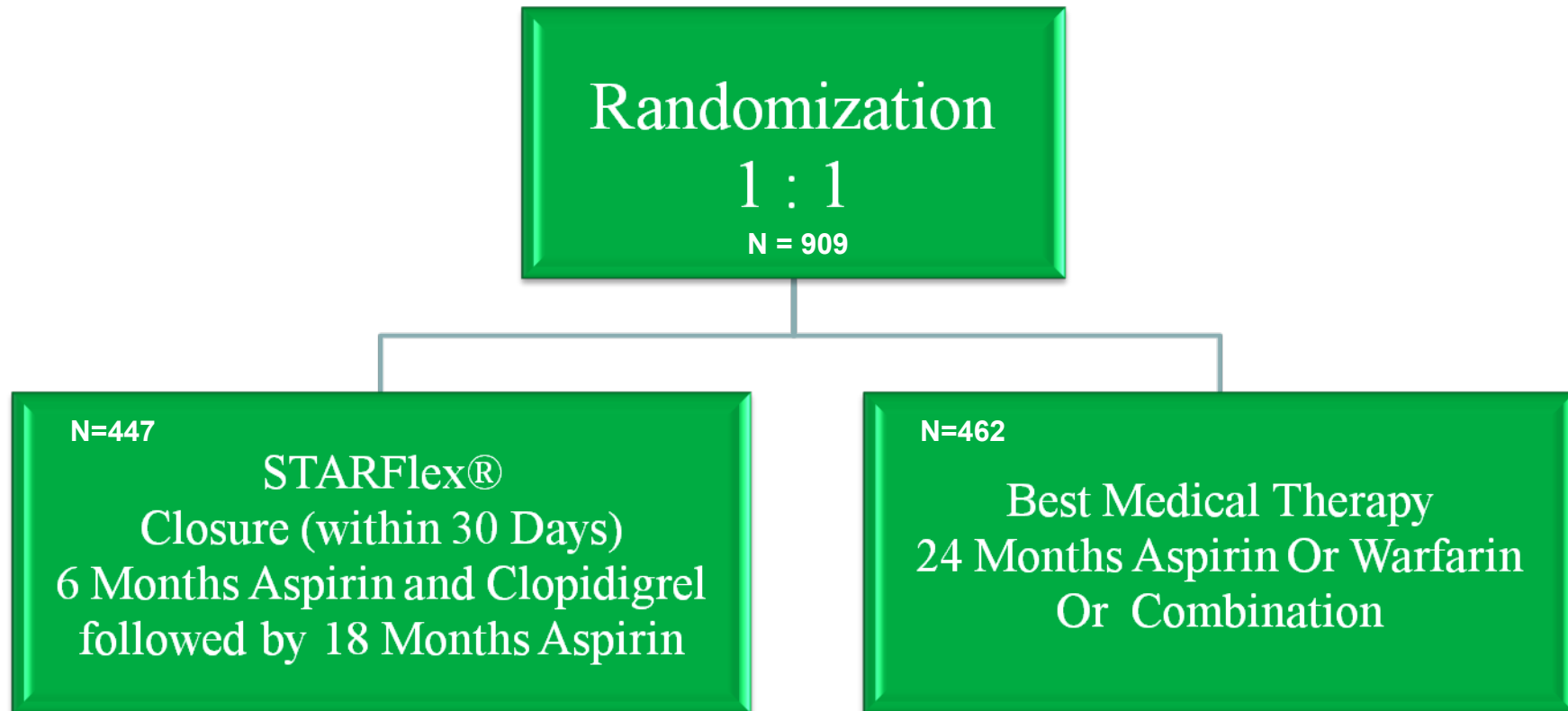
- **Definite TIA** : sudden focal neurological event lasting at least 10 minutes without evidence of acute ischemic brain injury on DWMR and consisting of hemiplegia/paresis, monoplegia/paresis, quadriplegia/paresis, language disturbance other than isolated slurred speech, blindness in one or both eyes, or significant difficulty walking
- **Ischemic stroke**: acute focal neurological event that shows evidence of corresponding tissue injury on brain imaging (DWMR)
- Events possibly due to migraine were excluded
- The diagnosis of either definite TIA or stroke was made by a board-certified study neurologist at each site and required blinded adjudication by the Clinical Events Committee (CEC) completely independent of the trial and Sponsor

STARFlex®



- Double umbrella comprised of MP35N framework with attached polyester fabric
- 23mm, 28mm, 33mm

Randomization



Between June 23, 2003 and October 24, 2008, 909 patients were randomized at 87 sites in the United States and Canada. Block randomization with stratification by study site and by the presence or absence of an ASA viewed by TEE.

Baseline Characteristics ITT

	STARFlex	Medical	P value
N randomized	447	462	
Mean Age	46.3 (18-61)	45.7(18-61)	
Male	52.1%	51.5%	
White	89%	90%	
Index cryptogenic stroke	73%	71%	
Mod/substantial shunt*	58% (231/400)	51% (228/451)	0.04
ASA \geq 10 mm*	38% (151/400)	35% (160/451)	0.49

* modified ITT

Baseline Characteristics

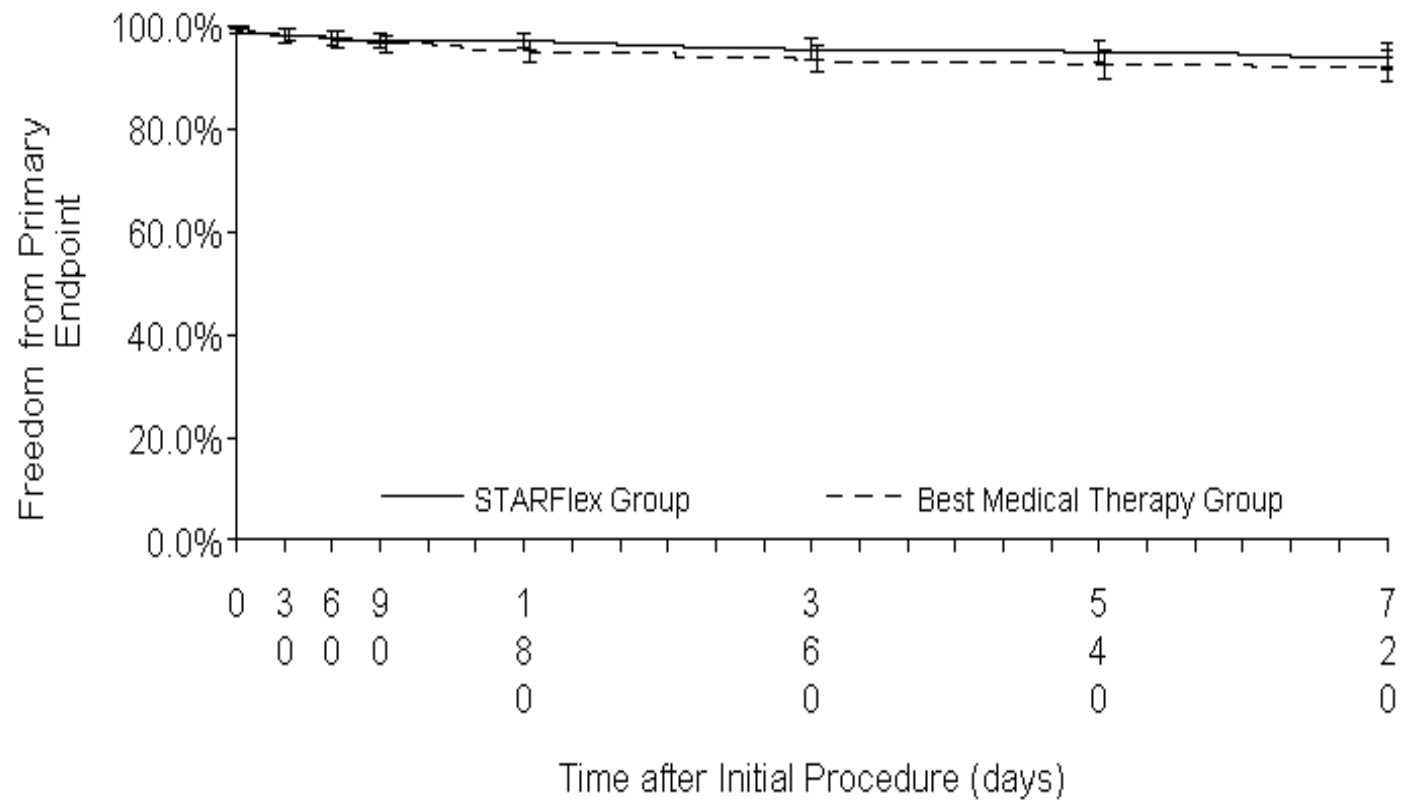
- No statistical differences between STARFlex versus medical therapy
 - medical history
 - prior events
 - stroke risk factors
- CLOSURE I patient population is representative of patients \leq age 60 with cryptogenic stroke/TIA and a PFO

2 Year Primary Endpoint ITT

	STARFlex n = 447	Medical n = 462	Adjusted P value*
Composite	5.9% (n=25)	7.7% (n=30)	0.30
Stroke	3.1% (n=12)	3.4% (n=13)	0.77
TIA	3.3% (n=13)	4.6% (n=17)	0.39

*Adjusting performed using Cox Proportional Hazard Regression and adjusting for related patient characteristics including: age, atrial septal aneurysm, prior TIA/CVA, smoking, hypertension, hypercholesterolemia

Kaplan-Meier for Primary Endpoint ITT



Composite Primary Endpoint

Baseline Shunt and Atrial Septal Aneurysm (TEE)

	STARFlex N=400	Medical N=451	P value
Trace shunt	7.0% (n=8/114)	8.0% (n=10/126)	0.75
Moderate shunt	5.3% (n=7/132)	8.4% (n=12/143)	0.31
Substantial shunt	3.6% (n=3/84)	5.3% (n=3/57)	0.62
No atrial septal aneurysm	6.4% (n=15/236)	8.5% (n=20/236)	0.38
Atrial septal aneurysm	4.9% (n=7/142)	6.5% (n=9/139)	0.58

Adverse Events

	STARFlex N=402	Medical N=458	P value
Major vascular complications*	3.2% (n =13)	0.0%	<0.001
Atrial fibrillation	5.7% (n= 14/23 periprocedural)	0.7% (n=3)	<0.001
Major bleeding	2.6% (n=10)	1.1% (n=4)	0.11
Deaths (all non endpoint)	0.5% (n=2)	0.7% (n=3)	ns
Nervous system disorders	3.2% (n=12)	5.3% (n=20)	0.15
Any SAE	16.9% (n=68)	16.6% (n=76)	ns

*Perforation LA (1); hematoma >5cm at access site (4); vascular surgical repair (1); peripheral nerve injury (1); procedural related transfusion (3);retroperitoneal bleed (3)

STARFlex Technical Success

	STARFlex n=402	95% CI
Procedural success	90.0%	(86.7%,92.8%)
Thrombus by TEE	1.0% (n=4; stroke in 2 at days 4, 52)	
Effective closure	No recurrent stroke or TIA in patients with residual leaks	
TEE 6 mos	86.1% closed	(82.1%,89.4%)
TEE 12 mos	86.4% closed	(82.5%,89.8%)
TEE 24 mos	86.7% closed	(82.8%,90.0%)

Procedural success was defined as successful delivery of one or more STARFlex devices to the site during the index procedure, deployment of the device at the intended site, and removal of the delivery system without a major procedural complication prior to discharge. **Effective closure** was defined as procedural success with either grade 0 (none) or 1 (trace) residual shunt by TEE.

Aspirin versus Warfarin

	Aspirin alone (n=243)	Warfarin alone (n=139)	P value
Composite	6.7% (n=14)	8.1% (n=9)	0.63
Stroke	3.9% (n=8)	2.7% (n=3)	0.67
TIA	2.9% (n=6)	6.3% (n=7)	0.09

Recurrent Stroke Multiple Etiologies

STARFlex strokes (n =12)

- **3 periprocedural (within 30 days)**
 - 1 a fib
 - 1 clot in LA
 - 1 retinal embolism day 1 presumed procedural embolism
- **3 cryptogenic**
- **3 ASO/lacunar**
- **2 a fib (with LA clot day 52; one day 238)**
- **1 cardiac cath complication day 232 (for CAD)**

Medical therapy strokes (n=13)

- **0 within 30 days of randomization**
- **6 multiple (complex migraine, risk factors, psychogenic)**
- **3 lacunar infarcts**
- **1 arch atheroma**
- **1 afib with off label device**
- **1 cryptogenic**
- **1 vasculitis**

CONCLUSIONS

- **CLOSURE I is the first completed, prospective, randomized, independently adjudicated PFO device closure study**
- **Superiority of PFO closure with STARFlex® plus medical therapy over medical therapy alone was not demonstrated**
 - no significant benefit related to degree of initial shunt
 - no significant benefit with atrial septal aneurysm
 - insignificant trend (1.8%) favoring device driven by TIA
 - 2 year stroke rate essentially identical in both arms (3%)
- **Major vascular (procedural) complications in 3% of device arm**
- **Significantly higher rate of atrial fibrillation in device arm (5.7%)**
 - 60% periprocedural

CONCLUSIONS

- **Alternative explanation unrelated to paradoxical embolism present in 80% of patients with recurrent stroke or TIA**
 - cryptogenic stroke and TIA include multiple etiologies
 - in many patients with cryptogenic stroke or TIA a PFO may be coincidental
 - diagnostic criteria for paradoxical embolism are imprecise
 - potential efficacy of PFO device closure in better defined patient subgroups requires further study
- **Percutaneous closure with STARFlex® plus medical therapy does not offer any significant benefit over medical therapy alone for the prevention of recurrent stroke or TIA in patients \leq age 60 presenting with cryptogenic stroke or TIA and a PFO**

Acknowledgement

CLOSURE I *Executive Committee*

- **Anthony Furlan** (Principal Investigator), University Hospitals Case Medical Center, Cleveland, OH
- **Mark Reisman** (Co-Principal Investigator), Swedish Medical Center, Seattle, WA
- **NEUROLOGY**
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