PFO Closure in the Gore REDUCE Clinical Trial

Primary Results Update

Scott E. Kasner, Lars Søndergaard, John F. Rhodes, Lars Thomassen,

on behalf of REDUCE investigators

Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization listed below.

Affiliation/Financial Relationship	Company
Grant/Research Support	None
Consulting Fees/Honoraria	WL Gore & Associates
Major Stock Shareholder/Equity	None
Royalty Income	None
Ownership/Founder	None
Intellectual Property Rights	None
Other Financial Benefit	None

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ORIGINAL ARTICLE

Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke

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Gore REDUCE Clinical Trial

- **Aim** – Establish superiority of PFO closure in conjunction with antiplatelet therapy over antiplatelet therapy alone in reducing the risk of recurrent clinical ischemic stroke or new brain infarct
- **Design** – Randomized, controlled, open-label trial
- **664** subjects randomized in a 2:1 ratio to:
  - PFO Closure Arm: GORE® HELEX® or CARDIOFORM Septal Occluder + antiplatelet therapy
  - Medical therapy: antiplatelet therapy alone
- **Multinational** - 63 sites

Europe Sites & Principal Investigators

Study Site	Principal investigator
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Aarhus University Hospital	Jens Erik Nielsen-Kudsk, MD Grethe Andersen, MD
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North America Sites & Principal Investigators

Study Site	Principal investigator
The Methodist Hospital	John Volpi, MD
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Rush University Medical Center	Clifford Kavinsky, MD, PhD
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Study Site	Principal investigator
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Henry Ford Health System	Daniel J. Miller, MD
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University of Tennessee	Benjamin Waller III, MD
Aventura Hospital and Med Ctr,	Roberto Cubeddu, MD
Emory University	Michael McDaniel, MD
Morristown Memorial Hospital	Robert Kipperman, MD
Intermountain Medical Center	Brian Whisenant, MD
Beaumont Hospital	George Hanzel, MD
Neurology Associates	Wm. David Honeycutt, MD
Nationwide Children's Hospital	Darren Berman, MD
University of Wisconsin	Giorgio Gimelli, MD
Centennial Medical Center	John Riddick, MD
University of Utah	Rodney Badger, MD
Black Hills Cardiovascular	Joseph Tuma, MD
University of Colorado	John Carroll, MD

Gore REDUCE Clinical Trial

Medical Therapy

- **Antiplatelet standardized options:**
  - Aspirin alone (75-325 mg once daily)
  - Aspirin (50-100 mg) + dipyridamole (225-400 mg)
  - Clopidogrel (75 mg once daily)
  - Other combinations or OAC not permitted
- **All subjects – for duration of study**
- **All sites – same antiplatelet therapy**

Gore REDUCE Clinical Trial

Follow-up

- Up to 5 years
- Neurology assessments at 1, 6, 12, 18, 24, 36, 48, and 60 months
- Closure group – echo with “bubble” study at 1, 12, and 24 months
- MRI imaging – baseline & 24 months (if not performed for endpoint event)

Gore REDUCE Clinical Trial

- Steering committee
  - 2 neurologists: Scott Kasner, Lars Thomassen
  - 2 cardiologists: Lars Søndergaard, John Rhodes
  - 2 Sponsors: Jake Goble, Stuart Broyles (non-voting)
- Data Safety Monitoring Board
- Clinical Endpoint Committee (blinded)
- MRI core lab (blinded) and Echo core lab

Inclusion / Exclusion Criteria

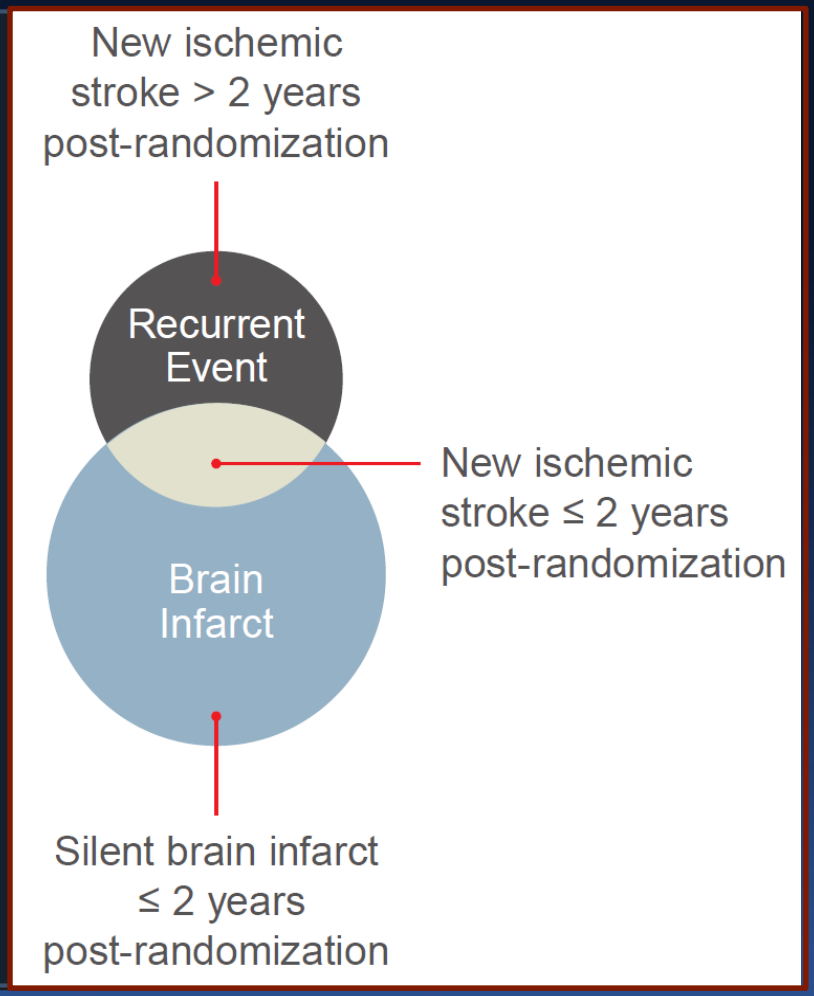
- Age 18 – 59 years
- Cryptogenic ischemic stroke within 180 days
  - Ischemic stroke
    - Clinical symptoms ≥24 hr or MRI evidence of infarction
  - Cryptogenic
    - No stenosis >50% or ulcerated plaque in relevant intra-or extracranial vessels
    - No atrial fibrillation or high risk source of cardioembolism
    - Non-lacunar (based on syndrome and/or size)
    - No evidence of hypercoagulable disorder
    - No other known cause of stroke

Inclusion / Exclusion Criteria

- Patent foramen ovale (PFO)
  - Confirmed by TEE with bubble study demonstrating right-to-left shunt at rest or during Valsalva maneuver
- No indication for anticoagulation
- No uncontrolled diabetes mellitus, hypertension, autoimmune disease, alcohol or drug abuse

Co-Primary Endpoints

- **Freedom from recurrent clinical ischemic stroke through at least 24 months**
- **Incidence of new brain infarct (defined as clinical ischemic stroke or silent brain infarct*) through 24 months**

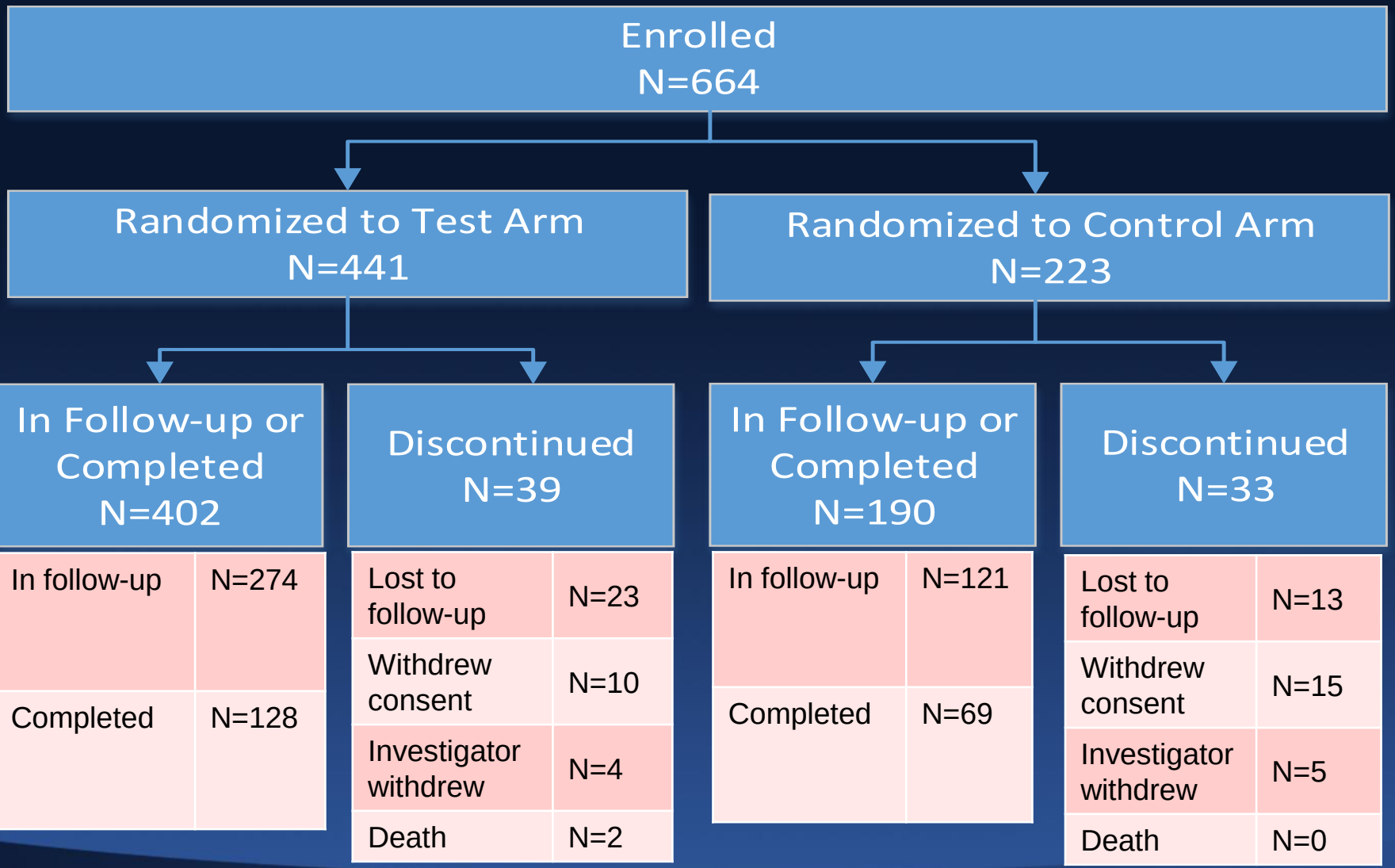


*New T2 hyperintense MRI lesion with diameter ≥3 mm; adjudicated by MRI Core Lab

Baseline Characteristics

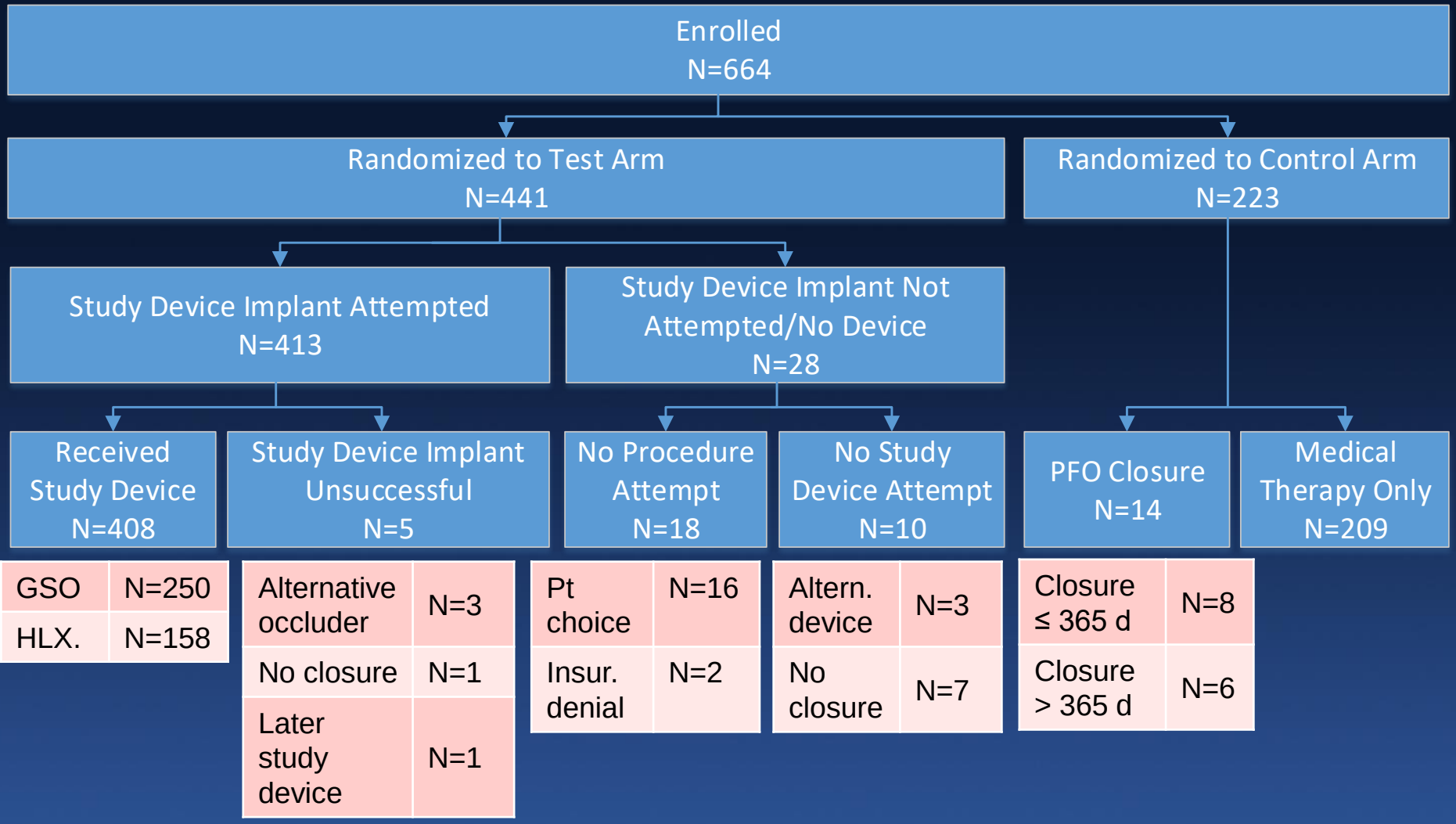
Demographic / Characteristic	Closure (N=441)	Medical (N=223)	p-value
Age, years	45.4 ± 9.3	44.8 ± 9.6	0.41
Days from qualifying event to randomization	100 ± 52	101 ± 53	0.90
Sex, male	59.2%	61.9%	0.56
Current Smoker	14.3%	11.2%	0.30
Diabetes mellitus	4.1%	4.5%	0.84
Hypertension	25.4%	26.0%	0.94
Previous Cerebrovascular Event	14.1%	10.3%	0.22
Maximal baseline shunt grade (bubbles)	N=425	N=216	0.32
Grade 0 Occluded (0)	0.0%	0.0%	-
Grade I Trivial/Small (1-5)	18.1%	19.9%	-
Grade II Moderate (6-25)	39.1%	43.5%	-
Grade III Large (>25)	42.8%	36.6%	-
Atrial septal aneurysm	20.4%	(did not collect)	-

Intention-to-Treat: Recurrent Event



**Completed includes primary endpoint events and finished 5 year follow-up*

As Treated / Peri-randomization Disposition



Duration of Follow-up

	Closure (n = 441)	Medical therapy (n = 223)	Total (n = 664)
Mean (SD), years	3.5 (1.4)	3.2 (1.5)	3.4 (1.4)
Median (IQR), years	3.3 (2.3 - 4.9)	3.0 (2.1 - 4.7)	3.2 (2.2 - 4.8)
Total exposure, pt. - years	1,529	703	2,232

Device Performance

Performance Outcome	%
Technical success	†98.8%
Complete closure @ 12 months	74.9%
Effective closure @ 12 months	*94.1%

† ***No significant differences in safety, performance, or efficacy between the two test devices***

* ***12 month freedom from large shunt*** ***(>25 particles)*** ***adjudicated by echo core lab***

Device Safety

All Enrolled Subjects (N = 664)	Closure (n = 441)	Medical (n = 223)	p-value
Any serious adverse event (SAE)	102 (23.1%)	62 (27.8%)	0.22
Device-related SAE	6 (1.4%)	-	-
Procedure-related SAE	11 (2.5%)	-	-
Death	2 (0.5%)	0 (0%)	0.55

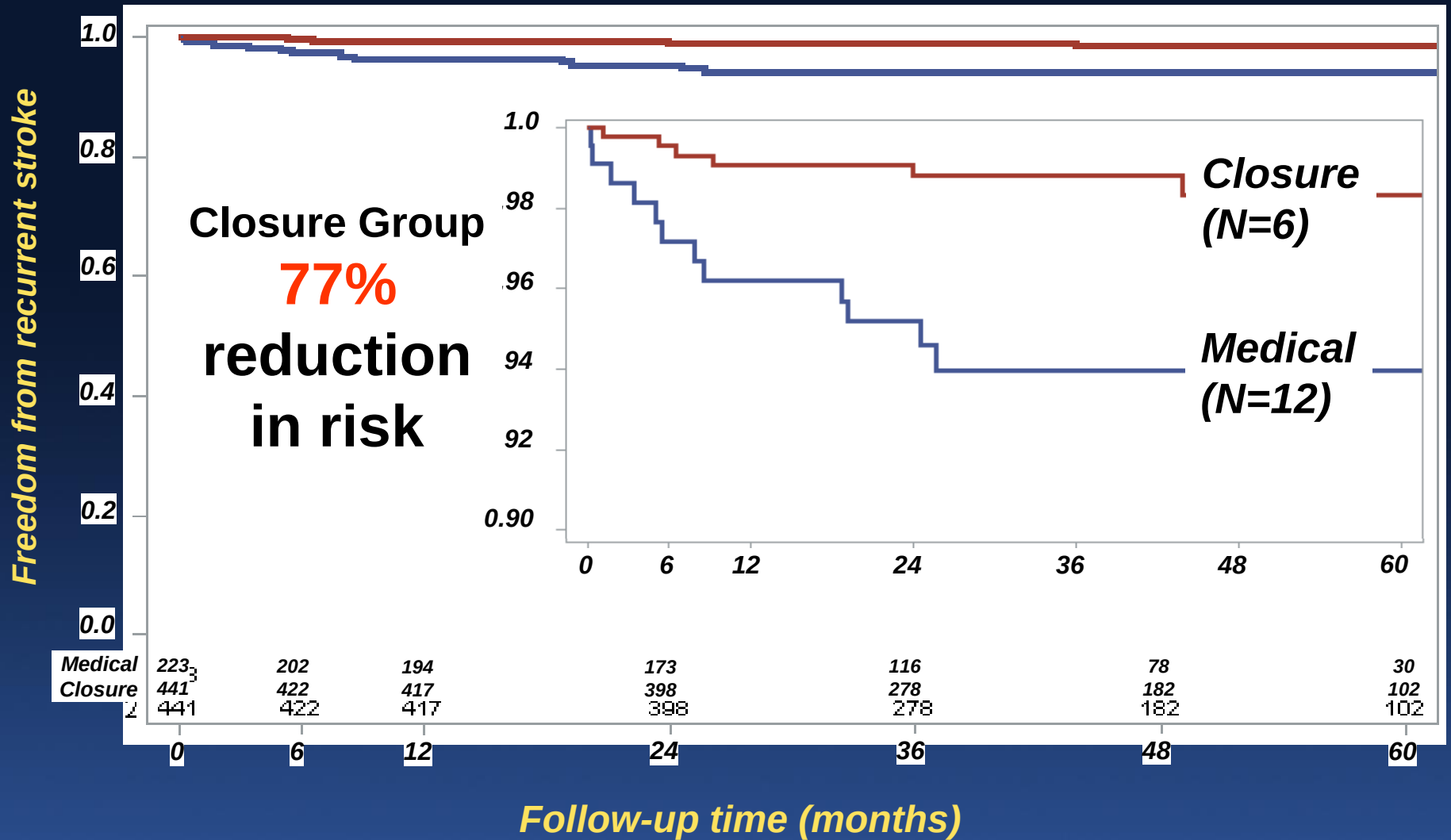
- No difference in overall serious adverse events (SAE)
- Low risk of device- or procedure-related SAE – 3.6%
- Deaths were uncommon and unrelated to study
  - Depression leading to suicide
  - Prior CV disease leading to an acute CV event

Device Safety

- **Bleeding similar**
- **Atrial fib/flutter rate higher in the closure group**
  - **non-serious (63%)**
  - **onset in 1st month (79%)**
  - **resolved w/in 2 wks. (59%)**
  - **1/29 w/ AF post closure had stroke**
- **Device event rate low & generally peri-implant**
  - **1/2 with device thrombosis had a recurrent stroke**
- **DVT & PE similar**

All Enrolled Subjects (N = 664)	Closure (n=441)	Medical (n=223)	p-value
Serious bleeding adverse events	**8 (1.8%)**	**6 (2.7%)**	**0.57**
Procedure-related	4 (0.9%)	-	0.31
Other	4 (0.9%)	6 (2.7%)	0.09
Any AF/ flutter adverse events	**29 (6.6%)**	**1 (0.4%)**	**<0.001**
Serious AF / flutter	10 (2.3%)	1 (0.4%)	<0.001
Serious device adverse events	**6 (1.4%)**	**-**	**-**
Device dislocation	3 (0.7%)	-	-
Device thrombosis	2 (0.5%)	-	-
Aortic dissection	1 (0.2%)	-	-
Any DVT or PE adverse events	**3 (0.7%)**	**2 (0.9%)**	**1.0**

1st Co-Primary EP: Clinical Stroke, Intention-To-Treat

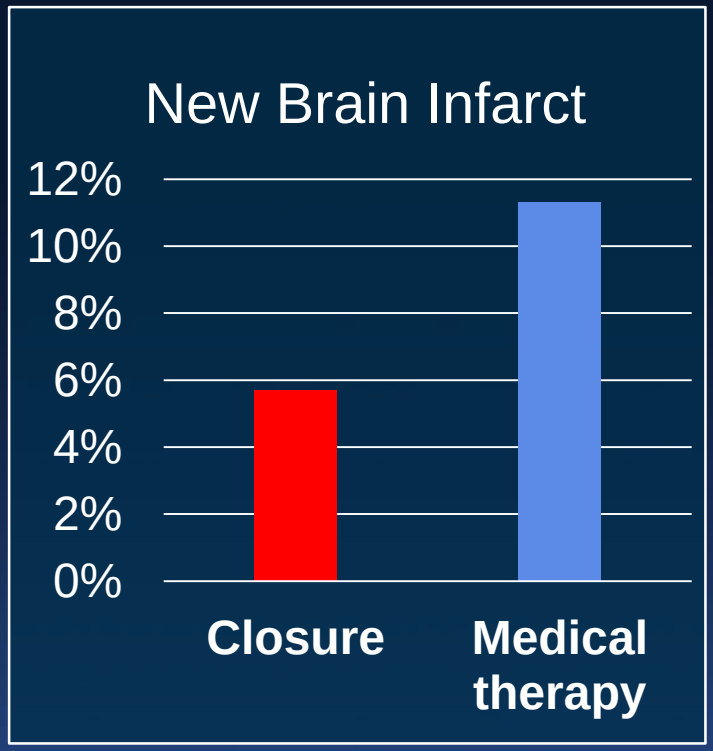


Hazard ratio, 0.23 with 95% CI, 0.09-0.62
Log-rank p=0.001 (Adjusted for multiple testing)

Annualized event rates
Closure: 0.39 per 100 person-years
Medical: 1.70 per 100 person-years

2nd Co-Primary Endpoint: New Brain Infarct, Intent-to-Treat

	Closure (N=441)	Medical (N=223)
Subjects without Evaluation	58	46
Brain Infarct Evaluable	383	177
Brain Infarct Present	**22 (5.7%)**	**20 (11.3%)**
Recurrent Stroke Only	3	6
Both	2	6
Silent Brain Infarct Only	17	8
Brain Infarct Absent	361 (94.3%)	157 (88.7%)



- **Difference in incidence of new brain infarct of 5.6%**
- **Relative risk 0.51; 95% CI: 0.29 to 0.91**
- **p=0.024 after adjustment for multiple testing**
- **Silent infarcts about twice as common as clinical stroke**

Efficacy – Secondary Analysis Sets

End point	Analysis cohort	HR or RR	95% CI	Unadjusted one-sided p-value
Recurrent stroke	Intention-to-treat	0.23	0.09 to 0.62	0.0008
Recurrent stroke	Per protocol	0.25	0.09 to 0.65	0.0011
Recurrent stroke	As-treated	0.25	0.09 to 0.66	0.0013
New brain infarct	Intention-to-treat	0.51	0.29 to 0.91	0.018
New brain infarct	Per protocol	0.56	0.31 to 1.01	0.037
New brain infarct	As-treated	0.58	0.32 to 1.03	0.044

- **Consistent with primary intention-to-treat analysis**
- **No recurrent clinical strokes among as-treated crossovers or per protocol exclusions**
- **One silent brain infarct in medical arm subject was excluded from per protocol and crossed over to as-treated closure**

Subpopulation Analysis

Subgroup	Closure n/N (%)	Medical n/N (%)	Hazard Ratio (95% CI)	P-Value*	Interaction P-Value
Overall	6/441 (1.4%)	12/223 (5.4%)	0.23 (0.09, 0.62)	0.002	
Age					0.85
18-45	3/204 (1.5%)	6/114 (5.3%)	0.26 (0.07, 1.04)	0.041	
46-59	3/237 (1.3%)	6/109 (5.5%)	0.21 (0.05, 0.84)	0.015	
Sex					0.62
Male	3/261 (1.1%)	8/138 (5.8%)	0.19 (0.05, 0.71)	0.006	
Female	3/180 (1.7%)	4/85 (4.7%)	0.31 (0.07, 1.40)	0.109	
Region					1.00
Europe & CA	3/225 (1.3%)	6/108 (5.6%)	0.23 (0.06, 0.93)	0.025	
US	3/215 (1.4%)	6/115 (5.2%)	0.24 (0.06, 0.94)	0.026	
Shunt Size					0.77
Trivial	1/77 (1.3%)	2/43 (4.7%)	0.27 (0.03, 3.03)	0.258	
Moderate-Large	4/348 (1.1%)	10/173 (5.8%)	0.18 (0.06, 0.58)	0.001	

*Two-sided log-rank

Gore REDUCE Clinical Trial

Strengths

- Standardized approach to medical therapy
- Selection criteria for cryptogenic stroke similar to recent ESUS definition
- Multinational trial enhances generalizability
- MRI at baseline and 2 yrs adds objective confirmation to unblinded trial

Limitations

- Total number of events was small, limiting subgroup and other exploratory analysis
- Potential for bias due to differential drop-out and small number of events relative to drop-out rate
- Limited generalizability due to concurrent closure outside of trial
- Duration of study

Conclusions

- **Cryptogenic stroke** pts that take antiplatelet therapy + undergoing PFO closure with the Gore Septal Occluder will significantly reduced (**77%**) the risk of recurrent stroke and brain infarct compared to antiplatelet therapy alone
- **Gore Septal Occluder** PFO closure is **low** risk for device- or procedure-related events
- These results are likely to change clinical practice & **REDUCE** stroke risk for these pts