LA Appendage Occlusion Devices: Do they have a role?

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MY CONFLICTS OF INTEREST ARE:

Consultant: Boston Scientific, Zoll

Royalties: Zoll

Educational Grants: Boston Scientific, Medtronic, St Jude, Biosense Webster

Stroke Risk in Atrial Fibrillation

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc
(Note: maximum score is 9 since age may contribute 0, 1, or 2 points)

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	9

(c) Adjusted stroke rate according to CHA_2DS_2-VASc score

CHA_2DS_2-VASc score	Patients (n=7329)	Adjusted stroke rate (%/year)[b]
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

Bleeding Risk in Atrial Fibrillation

Table 10 Clinical characteristics comprising the HAS-BLED bleeding risk score

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

Risk Factors/ Score	N	Number of Bleeds	Bleeds per 100 Patient-Years
0	798	9	1.13
1	1286	13	1.02
2	744	14	1.88
3†	187	7	3.74
4	46	4	8.70
5	8	1	12.50
6	2	0	0.0
7	0	—	—
8	0	—	—
9	0	—	—
Any Score	3071	48	1.56
P-Value for Trend			.007

Conundrum of Concurrent CVA and Bleeding Risks

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc
(Note: maximum score is 9 since age may contribute 0, 1, or 2 points)

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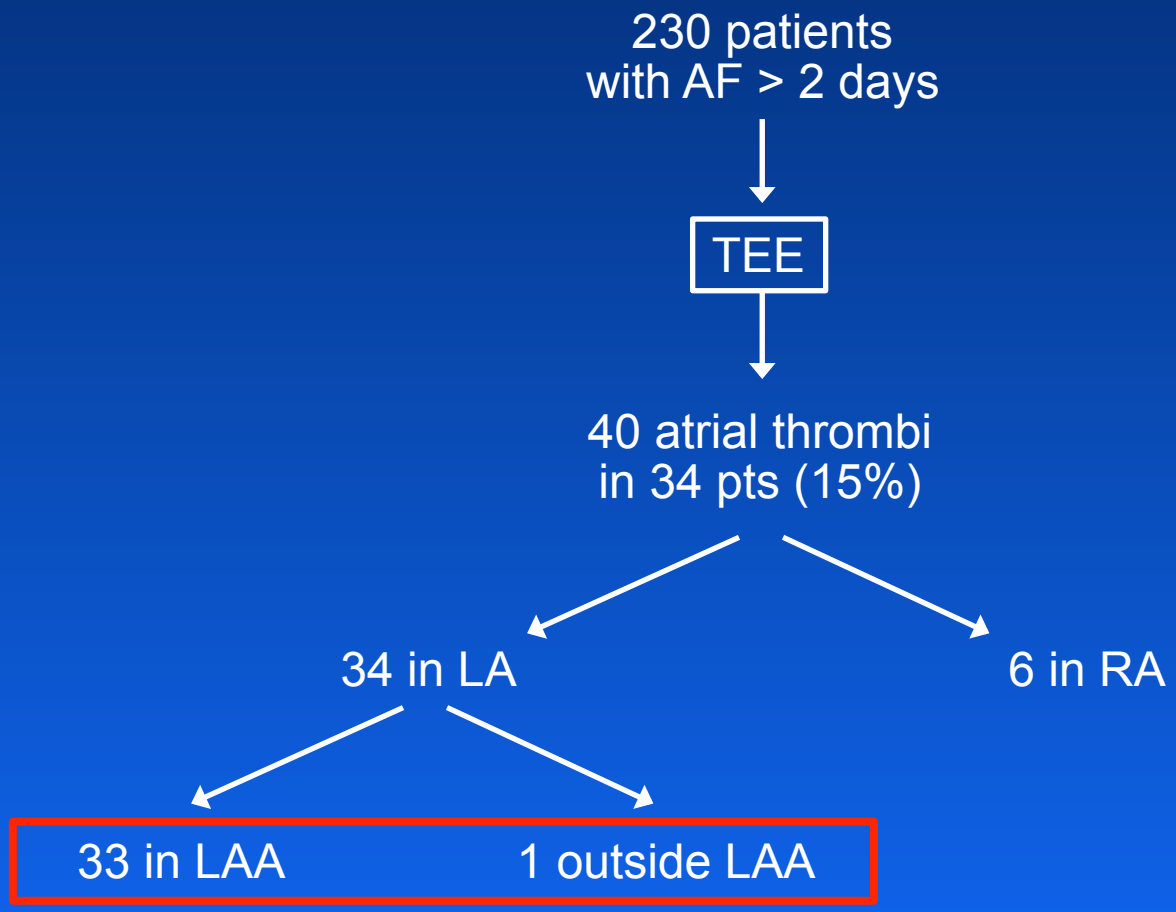
		Maximum 9 points

The Left Atrial Appendage is the Culprit



Manning et al, JACC 1995; 25:1354-61

Surgical Closure of Left Atrial Appendage

Table 2 Success of Different Techniques of LAA Closure

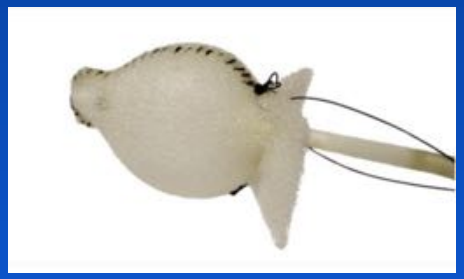
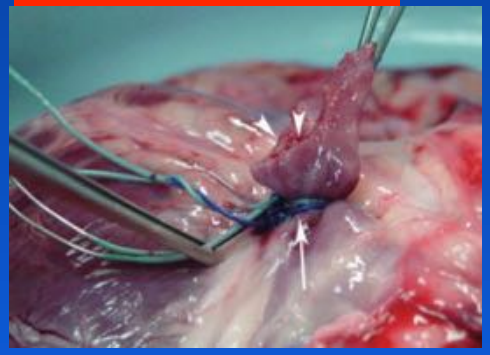
Type of Closure	n	Patent LAA	Remnant LAA	Excluded LAA With Persistent Flow	Successful LAA Closure
Excision	52	0	14 (27%)	0	38 (73%)*
Suture exclusion, n (%)	73	6 (8)	6 (8)	44 (61)	17 (23)*
Stapler exclusion, n (%)	12	2 (17)	7 (58)	3 (25)	0 (%)†
Total, n (%)	137	8 (6)	27 (20)	47 (34)	55 (40)

Kanderian et al, JACC 2008; 52:924-9

Left Atrial Appendage Closure

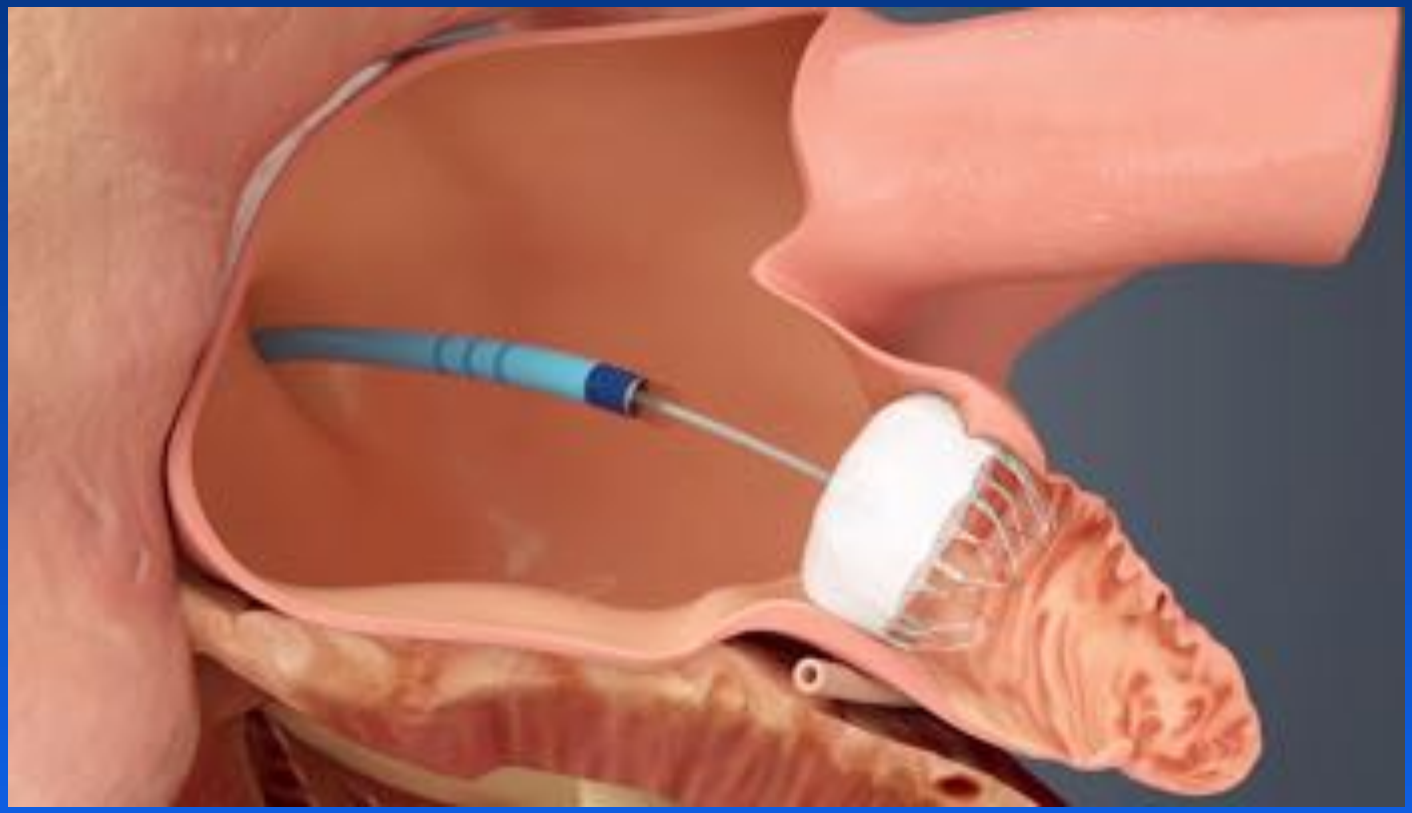







Left Atrial Appendage Closure – Watchman

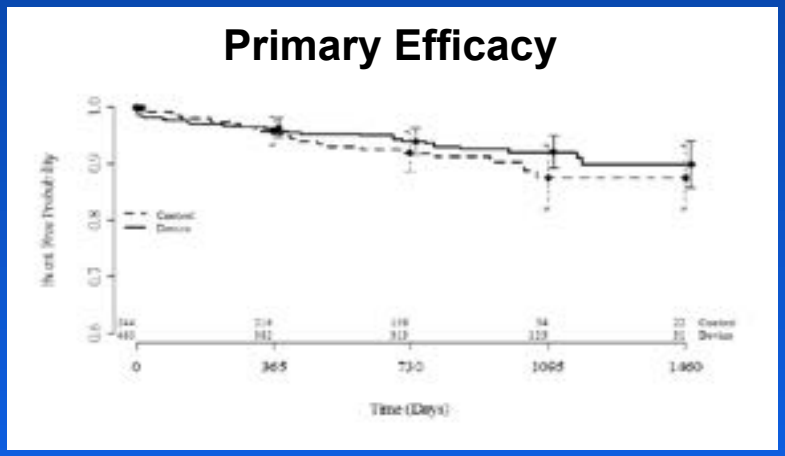


Left Atrial Appendage Closure – Watchman

PROTECT AF Study

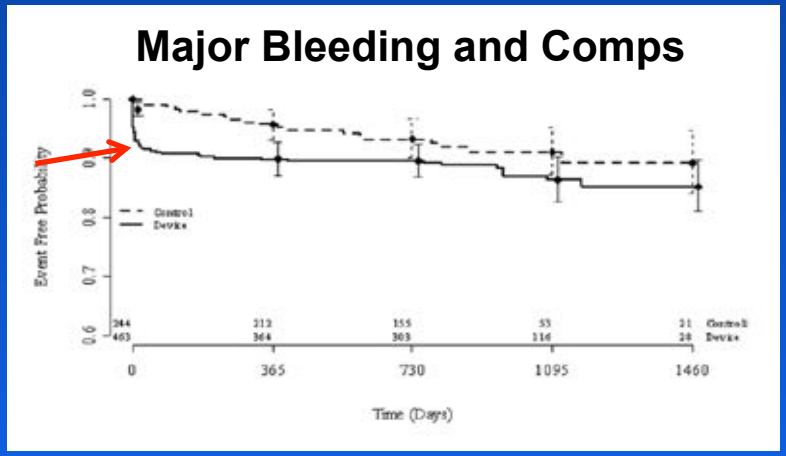
- 707 patients with non-valvular AF and CHADS score ≥ 1
- 59 sites in US and Europe
- Randomized 2:1 Watchman vs warfarin
- 1° endpoint: stroke, systemic embolism, CV death

Primary Efficacy



Noninferiority criteria met.

Major Bleeding and Comps



Excess complications in device arm.
FDA required additional study.

Reddy et al, Circ. 2013; 127:720-9

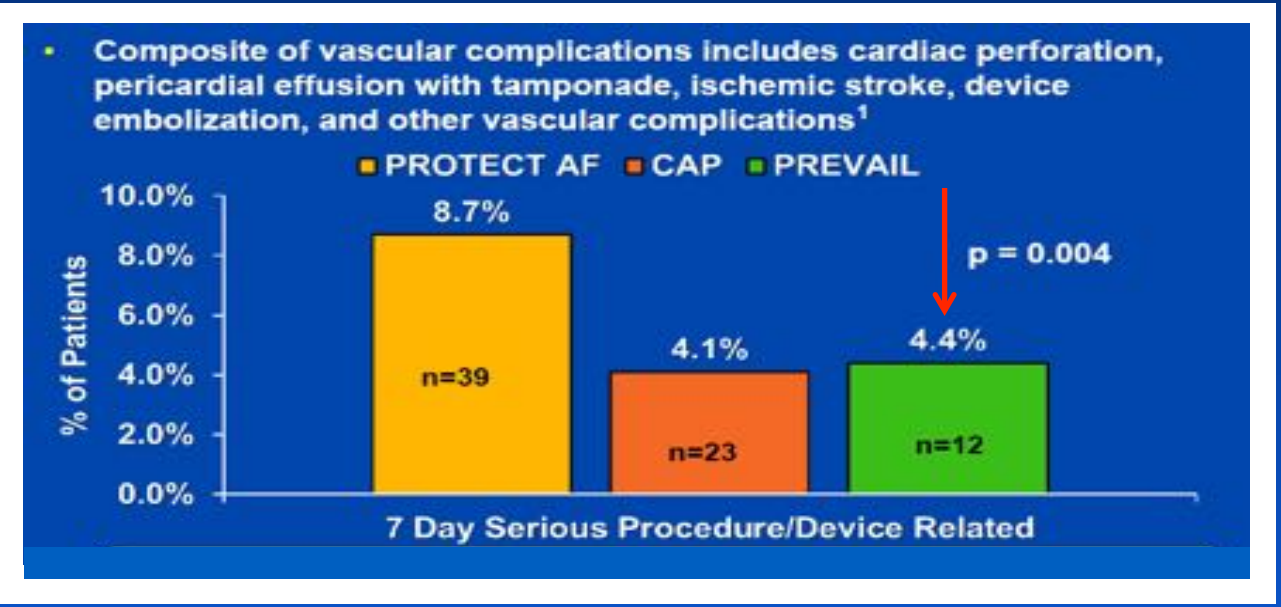
Left Atrial Appendage Closure – Watchman

PREVAIL Study

- 407 patients with non-valvular AF and CHADS-VASC score ≥2
- 41 U.S. sites with 25% enrollment by new operators
- Randomized 2:1 Watchman vs warfarin
- 1° endpoints:
  - 7-day death, stroke, systemic embolism, major complication
  - 18-month stroke, systemic embolism, CV death
  - 18-month stroke, systemic embolism

Holmes et al, ACC 2013

Left Atrial Appendage Closure – Watchman



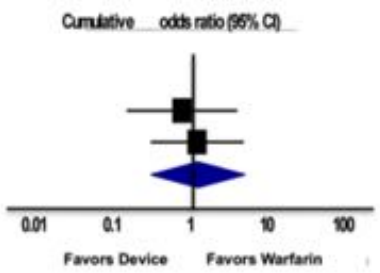
- 2nd FDA panel in Dec 2013 voted 13-1 in favor, but FDA asked for further f/u data.
- 3rd FDA panel in Oct 2014 voted 7-6 in favor of approval.
- FDA approval in March 2015

Holmes et al, ACC 2013

Left Atrial Appendage Closure – Watchman

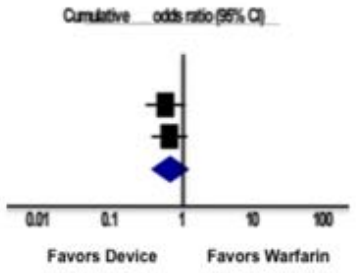
Stroke or Systemic Embolism

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value	Device	Coumadin
PROTECT-AF	0.78	0.15	4.13	-0.29	0.77	18 / 463	12 / 244
PREVAIL	1.23	0.30	4.98	0.29	0.77	25 / 732	13 / 382
	1.23	0.30	4.98	0.29	0.77		



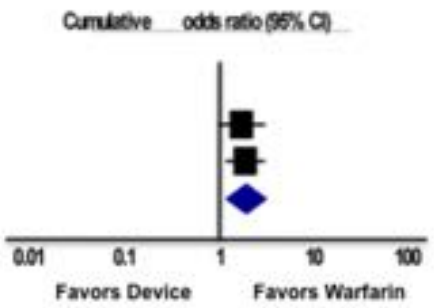
All-Cause Mortality

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value	Device	Coumadin
PROTECT-AF	0.60	0.31	1.14	-1.56	0.12	21 / 463	18 / 244
PREVAIL	0.68	0.38	1.22	-1.29	0.20	28 / 732	21 / 382
	0.68	0.38	1.22	-1.29	0.20		



Major Bleeding or Procedure Related Complications

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value	Device	Coumadin
PROTECT-AF	1.687	0.938	3.034	1.745	0.081	49 / 463	16 / 244
PREVAIL	1.853	1.143	3.006	2.501	0.012	78 / 732	23 / 382
	1.853	1.143	3.006	2.501	0.012		



Briceno et al, Circ. A&E 2015

Left Atrial Appendage Closure – Watchman

FDA Approval:

- Indicated for patients with non-valvular Afib with increased risk of stroke
- Suitable for warfarin, but have an appropriate rationale to seek a non-pharmacologic alternative to warfarin

Recommended Mgt:

- Warfarin (INR 2-3) for 45 days post-procedure
- TEE at 45 days
- Then clopidogrel 75 mg qd for 6 months, and ASA indefinitely

Left Atrial Appendage Closure – Watchman

ASAP Study

- 150 patients with non-valvular AF and CHADS-VASC score ≥1
- Contraindication to even short-term anticoagulation
- Received 6 months of treatment with clopidogrel or ticlopidine and lifelong ASA

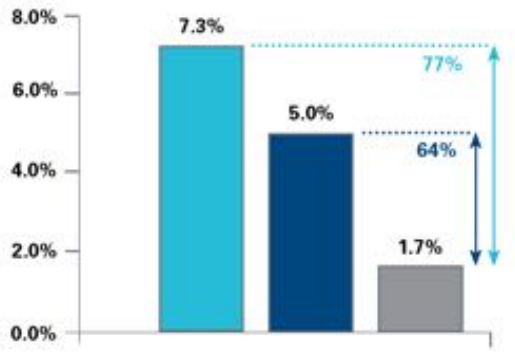
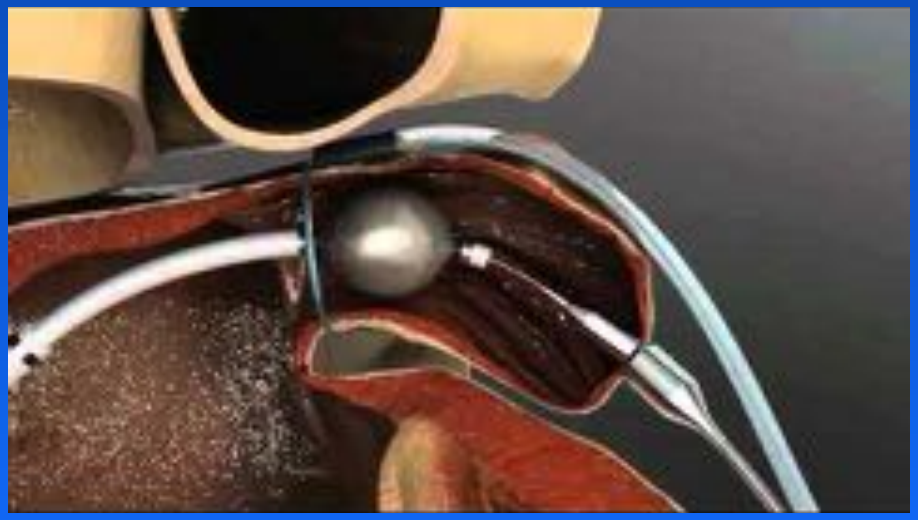


Table 3 Procedure and Device-Related Serious Adverse Events (N = 150)

Device embolization	2 (1.3%)
Pericardial effusion with tamponade (percutaneous drainage)	2 (1.3%)
Pericardial effusion, no tamponade (no intervention required)	3 (2.0%)
Device thrombus with ischemic stroke*	1 (0.7%)
Femoral pseudoaneurysm (surgically repaired)	1 (0.7%)
Femoral hematoma/bleeding	2 (1.3%)
Other†	3 (2.0%)
Total patients with procedure- and device-related SAEs	13 (8.7%)

Reddy et al, JACC 2013; 61:2551–6

Left Atrial Appendage Closure – Lariat



Left Atrial Appendage Closure – Lariat

May, 2009: FDA granted 510K approval:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The

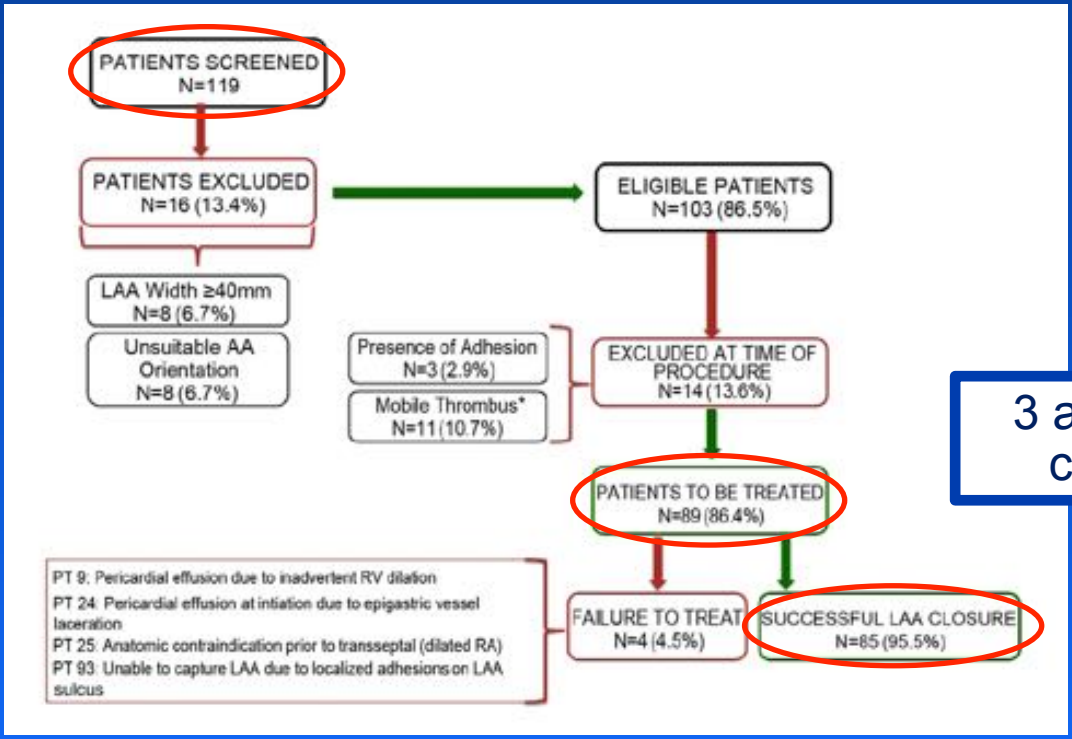
Intended Use:

The LARIAT II Suture Delivery Device facilitates suture placement and knot tying for use in surgical applications where soft tissue are being approximated and/or ligated with a pre-tied polyester suture.

Left Atrial Appendage Closure – Lariat

Permanent **L**igation **A**pproximation **C**losure **E**xclusion (PLACE) Study

- Sponsor: SentreHeart
- Single center (Krakow, Poland) single-arm study
- 119 pts with non-valvular AF and CHADS score ≥1
- Poor candidate or ineligible for warfarin therapy



3 access related complications

Bartus et al, JACC 2013; 62:108-18

Left Atrial Appendage Closure – Lariat

Permanent **L**igation **A**pproximation **C**losure **E**xclusion (PLACE) Study

Table 3 LAA Ligation Results (N = 89)

Successful ligation	85 (96%)
Complications	3 (3.3%)
Device related	0 (0%)
Access related	3 (3.3%)
Pericardial access	2 (2.2%)
Transseptal access	1 (1.1%)
Inability to complete ligation	
Pericardial adhesions in LAA sulcus	1 (1.1%)
End-of-procedure closure (n = 85)	
Complete or <1-mm leak	82 (96%)
<2-mm leak	2 (3%)
<3-mm leak	1 (1%)
1 day post-procedure closure by TEE (n = 85)	
Complete or <1-mm leak	81 (95%)
<2-mm leak	3 (4%)
<3-mm leak	1 (1%)
30 days post-procedure closure by TEE (n = 85)	
Complete or <1-mm leak	81 (95%)
<2-mm leak	3 (4%)
<3-mm leak	1 (1%)

Bartus et al, JACC 2013; 62:108-18

Left Atrial Appendage Closure – Lariat

8-Center Retrospective Analysis – 154 Patients

TABLE 1 Baseline Demographic and Clinical Characteristics of the Study Population (n = 154)

Age (yrs)	72.1 ± 9.4
Age >75 yrs	70 (45)
Male	96 (62)
Hypertension	125 (81)
Diabetes mellitus	56 (36)
History of heart failure	53 (34)
Peripheral arterial disease	21 (
Prior CVA/TIA	58 (
Prior hemorrhagic CVA	21 (
Prior major bleed or propensity for bleeding	96 (
Labile INR measurements	31 (
Concomitant chronic NSAID use	22 (
Liver disease	9 (
Renal disease	14 (
Significant alcohol consumption	16 (
$CHADS_2$ score	3 (
CHA_2DS_2VASC score	4 (
HAS-BLED score	3 (
$CHADS_2$ score	2.8 ±
CHA_2DS_2VASC score	4.1 ±
HAS-BLED score	3.2 ±

Successful LAA closure with residual leak <5 mm: 94%

TABLE 2 Major Bleeding Events During Hospitalization in the Study Population (n = 154)*

Major bleed	14 (9.1)
Any transfusion with overt bleeding	7 (4.5)

TABLE 4 Medical Therapy at Discharge After Transcatheter Left Atrial Appendage Ligation (n = 154)

Aspirin monotherapy	47 (31)
Dual antiplatelet therapy	37 (24)
Oral anticoagulation	36 (23)
Warfarin	24 (16)
Rivaroxaban	7 (5)
Dabigatran	5 (3)
No antiplatelet or oral anticoagulation	29 (19)
Clopidogrel monotherapy	11 (7)
Aggrenox	1 (0.6)

Price et al, JACC 2014; 64:565-72

Lariat vs Watchman

Observational study – Lariat at 6 centers, Watchman at 2 centers

Table 1 Comparison of baseline characteristics between the Watchman and the Lariat group

Clinical variable	Watchman group (N = 219)	Lariat group (N = 259)	*P*
Age (y)		68 ± 11	<.0001
Sex: male		58	.017
White		96	.900
Body mass index (kg/m		30 ± 8	.1
$CHADS_2$ score		2.6 ± 1.3	.0006

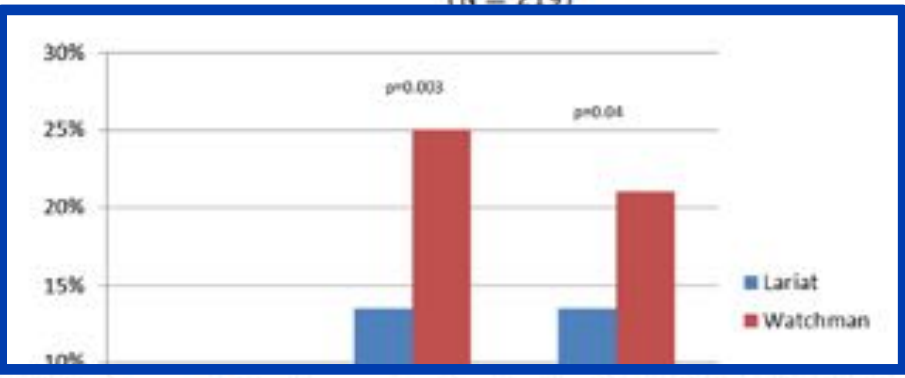


Table 4 Differences in the incidence of thrombus or transient ischemic attack (TIA)/stroke in patients with and without leaks in the Watchman and Lariat groups

	Watchman group (N = 219)		Lariat group (N = 259)	
Leaks	Leak (n = 46)	No leak (n = 173)	Leak (n = 33)	No leak (n = 222)
Thrombus (n)	2	6	2	2
TIA/stroke (n)	1 (thrombus)	2	1 (no thrombus)	2
Noncerebral embolism (n)	0	0	0	0

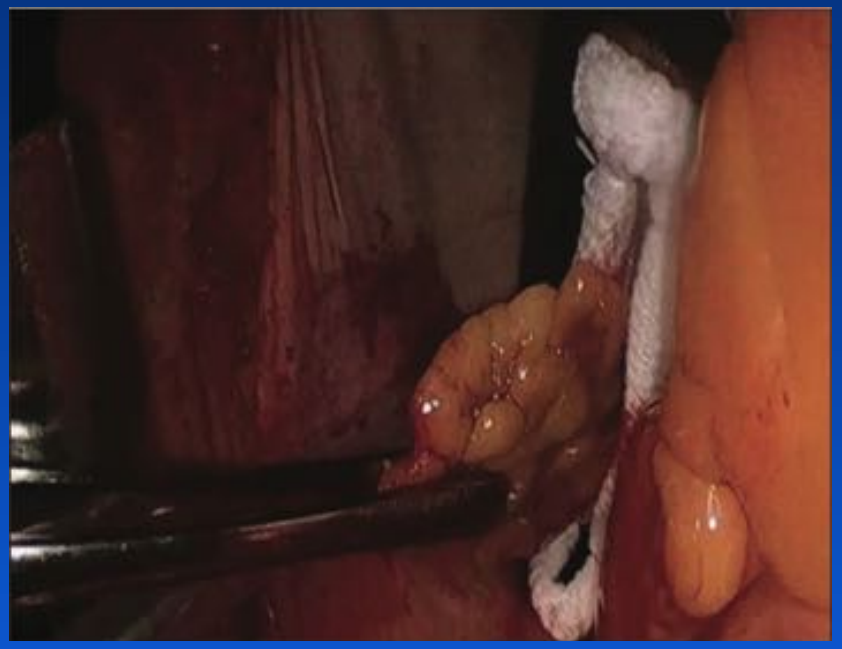
Pillarisetti et al, Heart Rhythm 2015;12:1501-7

Left Atrial Appendage Closure

	PROS	CONS
Transcatheter LAA ligation (Lariat)	• No device left behind • One size fits all	• Anatomic exclusions • Requires pericardial access • Peri-procedural complications, including PE, ventricular perforation, pericarditis • Possible late central leak • Possible late stump thrombus • Optimal post-procedural medication unknown, short-term OAC appears reasonable • Lack of long-term safety and efficacy data
Transcatheter device occlusion (Watchman)	• Trans-septal access only • Long-term safety and efficacy data from RCTs • Post-procedural medication (short-term OAC) well-evaluated in RCTs	• Anatomic exclusions • Peri-procedural complications, including PE, air embolism, and device embolization • Possible late edge leak • Possible late device thrombus

Price et al, JACC 2014; 64:565-72

LAA Closure – Gillinov-Cosgrove Clip



June, 2010: FDA granted 510K approval:

Intended Use

The AtriClip LAA Exclusion System is indicated for the occlusion of the left atrial appendage, under direct visualization, in conjunction with other open cardiac surgical procedures.

LAA Closure – Gillinov-Cosgrove Clip

EXCLUDE Trial

TABLE 2. Concomitant cardiac operations performed in the EXCLUDE study

Surgical procedure	
CABG	
Mitral valve	
Repair	
Replacement	
Tricuspid valve	
Repair	
Aortic valve	
Replacement	
ASD/PFO closure	
Surgical (ablation or cut-and sew) Maze procedure	35.2% (25)

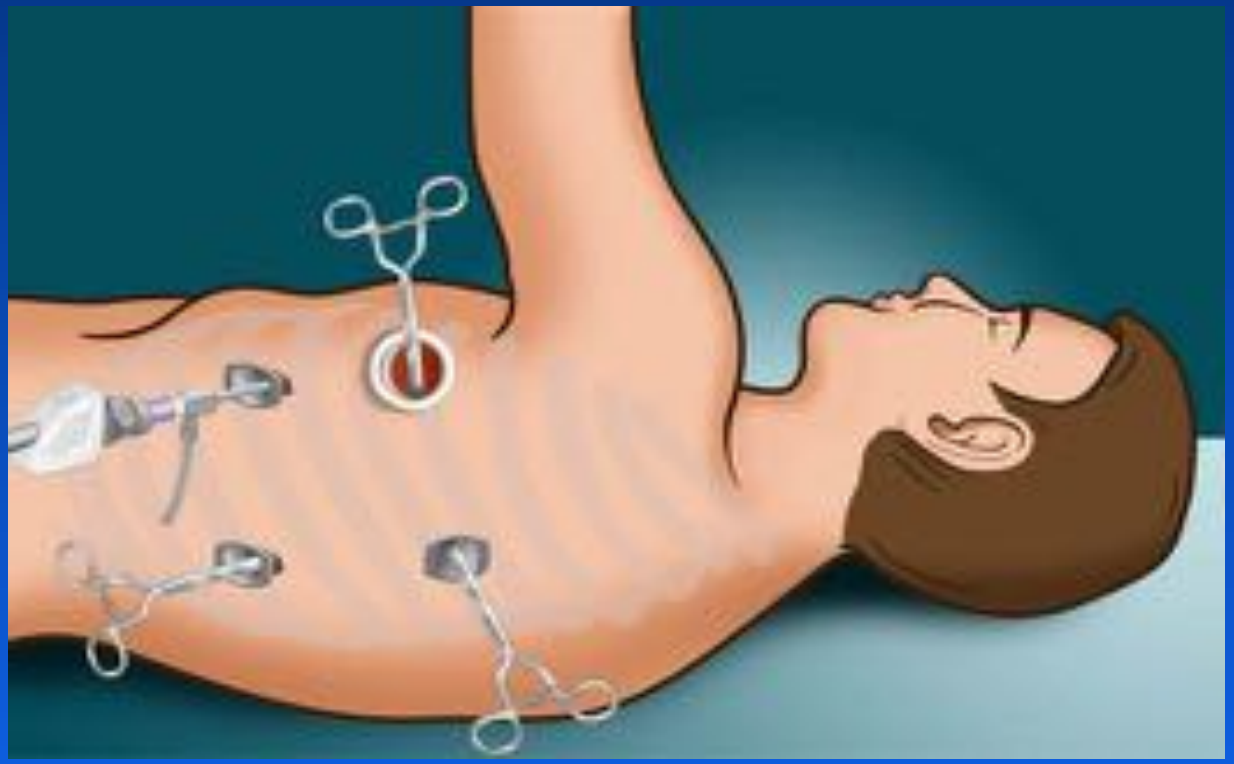
Efficacy end points	% (n/N)
Procedural success	95.7 (67/70)
by visual assessment	97.1 (68/70)
	95.7 (67/70)
	98.4 (60/61)
CT evaluation by core laboratory	98.2 (55/56)
TEE evaluation by site	100 (5/5)
Composite end point success (primary end point)	95.1 (58/61)

At 12 month follow-up:

- **2 strokes (not thromboembolic)**
- **30% on warfarin**

Ailawadi et al, J Thorac Cardiovasc Surg 2011;142:1002-9

Video-Assisted Thoracoscopic Surgery (VATS)



Left Atrial Appendage Closure

ESC:

Recommendations for LAA closure/occlusion/excision

Recommendations	Class[a]	Level[b]	Ref[c]
Interventional, percutaneous LAA closure may be considered in patients with a high stroke risk and contraindications for long-term oral anticoagulation.	IIb	B	115, 118
Surgical excision of the LAA may be considered in patients undergoing open heart surgery.	IIb	C	

Eur Heart J 2012; 33:2719–47

AHA/ACC/HRS:

CLASS IIb

1. Surgical excision of the LAA may be considered in patients undergoing cardiac surgery. *(Level of Evidence: C)*

JACC 2014; 64:e1-e76

Conclusions

- LAA closure emerging as alternative to OAC.
- Watchman shown equivalent to OAC (warfarin) in RCTs, but trades off implant bleeding/compllications for long-term stroke prevention.
- Watchman FDA approved for OAC eligible patients, and short-term OAC recommended post-implant.
- Lariat FDA approved (510K) as tissue closure device. No hardware left behind. Presumably can be used when even short-term OAC is contraindicated, but RCTs are lacking.
- Gillinov-Cosgrove AtriClip attractive option with concomitant cardiac surgery, or standalone with VATS. Post-procedure OAC regimen remains unclear.