

Device Options for Stroke Prevention in Atrial Fibrillation

David A. Sandler, MD, FACC, FHRS

Director, Heart Rhythm Service

Oklahoma Heart Institute



Disclaimers

- Janssen – speakers bureau
- Pfizer – speakers bureau
- Bristol-Myers Squibb – speaker bureau
- Boston Scientific – advisory board
- Abbott/St Jude - research grants



Agenda

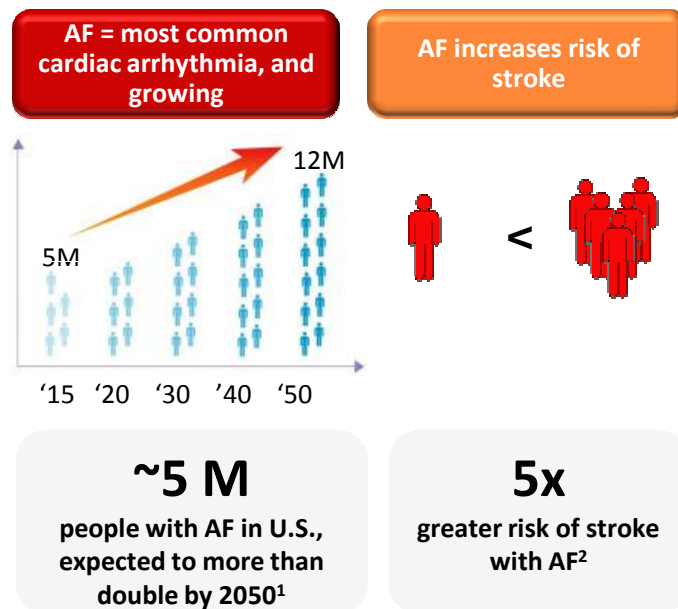
- Etiology of stroke in AF
- Pharmacologic therapy
- Device-based therapy

Agenda

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AF is a Growing Problem Associated with Greater Morbidity and Mortality



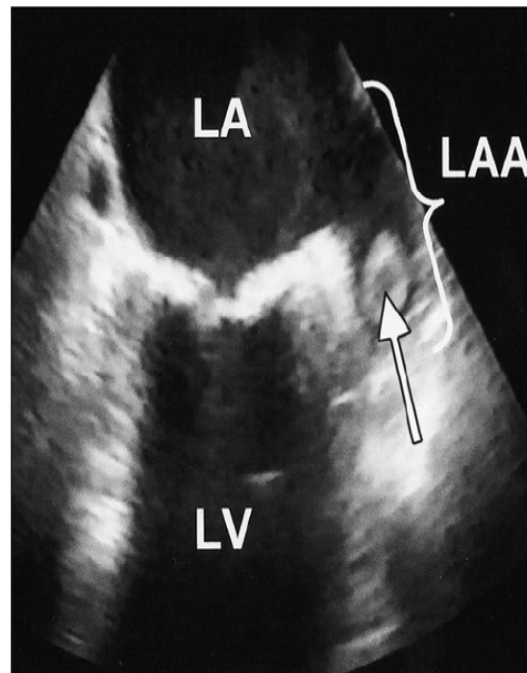
Higher stroke risk for older patients and those with prior stroke or TIA

15-20% of all strokes are AF-related

AF results in greater disability compared to non-AF-related stroke

High mortality and stroke recurrence rate

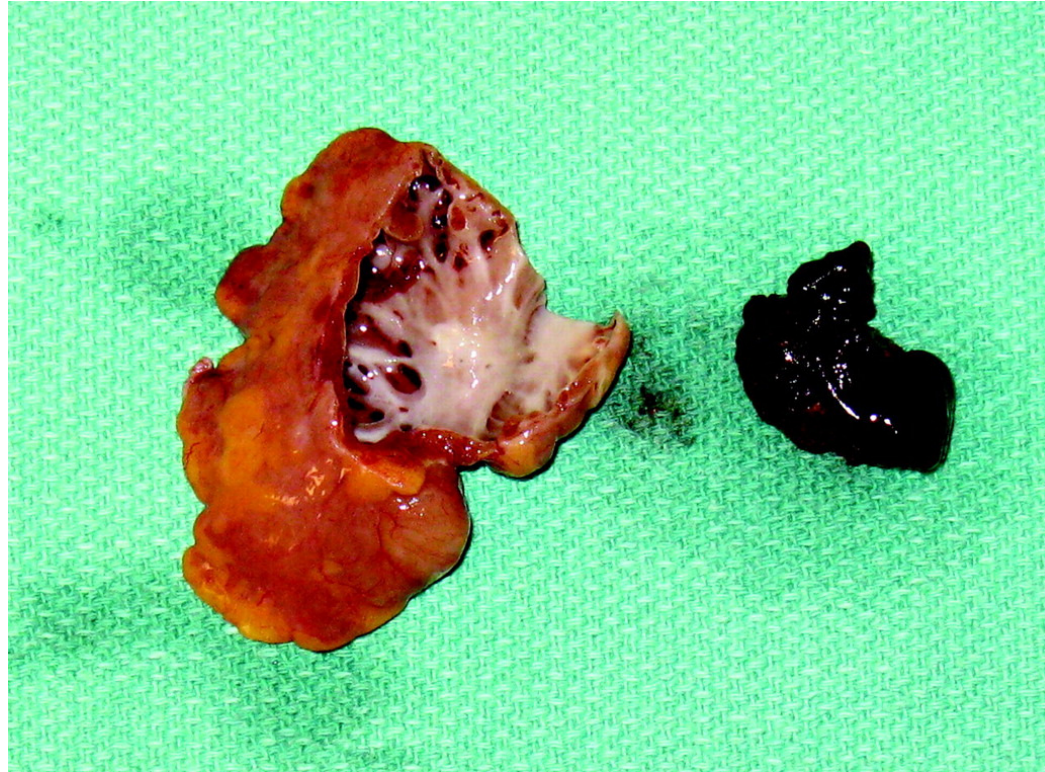
Left Atrial Appendage



Source of
thrombus in >90%
of NVAf patients

Blackshear JL and Odell JA. AnnThorac Surg 1996;61:755

Excised LAA with Extracted Thrombus



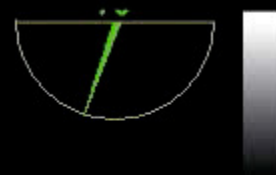
Richard P. Whitlock et al. *Circulation*. 2009;120:1927-1932

Lossy compression - not intended for diagnosis

Freq.: 5.0 MHz/5.0 MHz

Power: +3.0 dB

Depth: 10.0 cm



Agenda

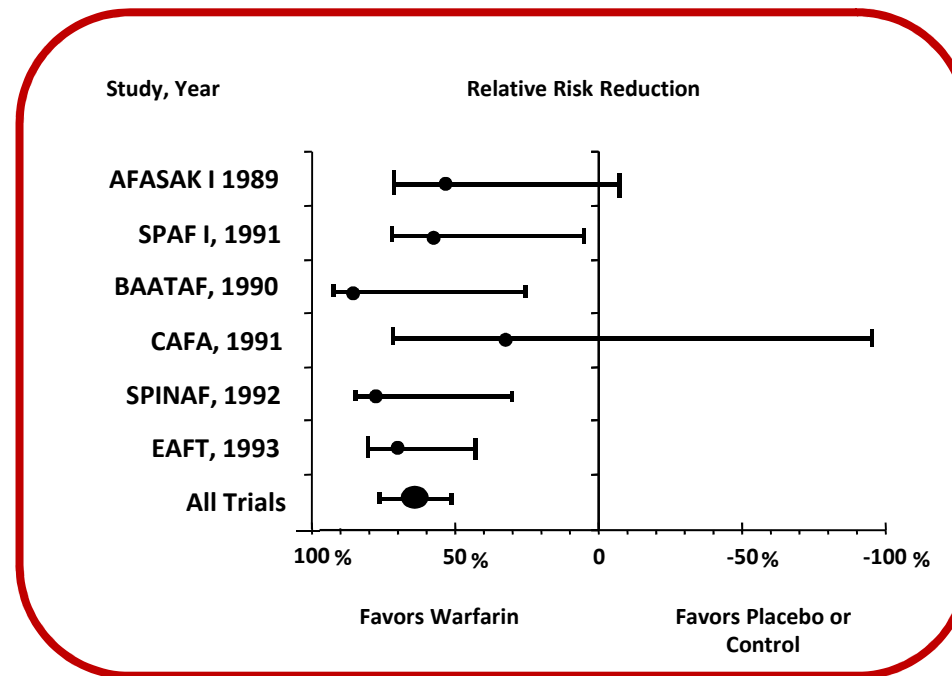
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Warfarin for AF

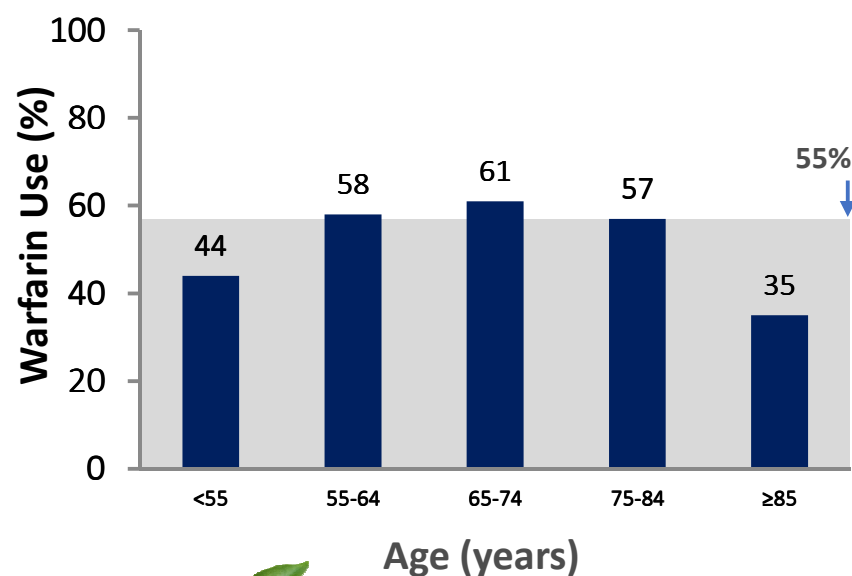
6 Trials
2,900 patients
Warfarin reduces
risk of stroke by
64%



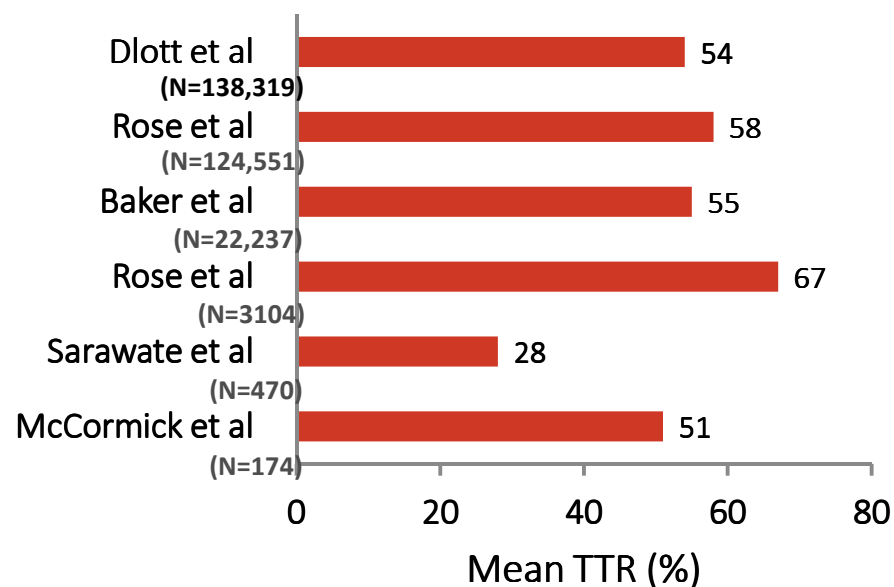
From: Hart RG, et al *Ann Intern Med.* 2007;146:857-867

Using Warfarin Remains Challenging

AF patients without contraindications

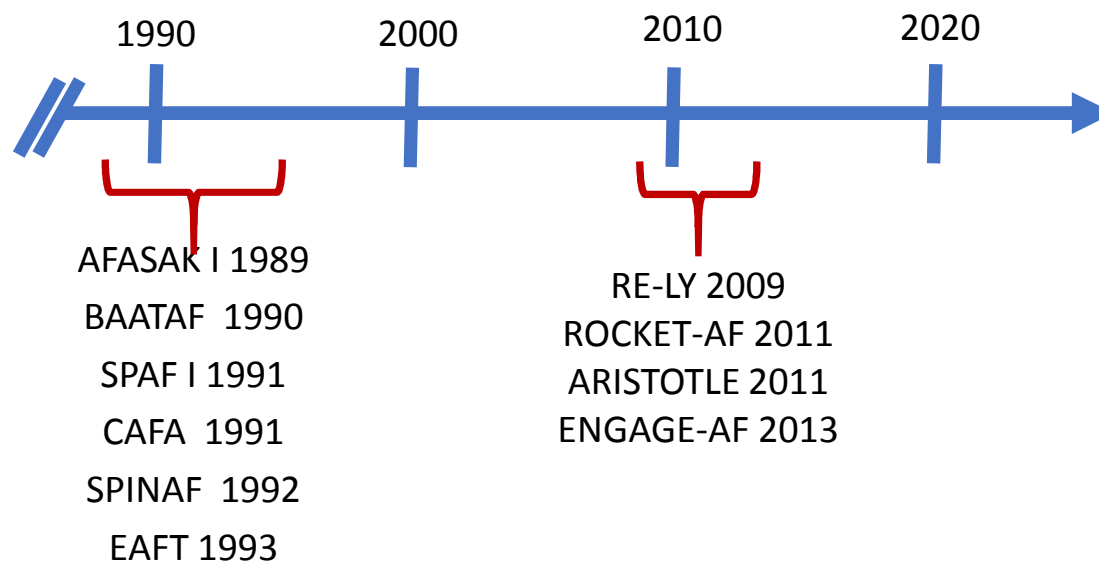


Mean Time in Therapeutic Range (TTR)



*Data from automated pharmacy, laboratory, and clinical administrative databases for 13,428 patients with nonvalvular AF were used to determine the prevalence of warfarin use in the 3 months before or after the identified diagnosis of AF (July 1996 – December 1997).

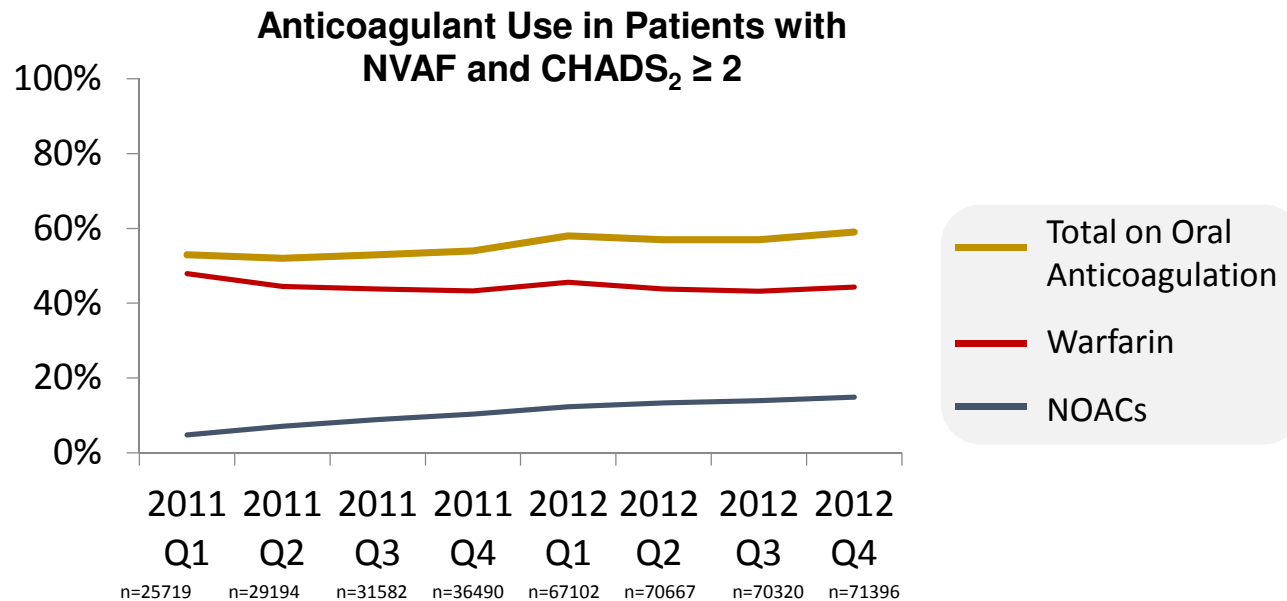
AF Timeline



The Novel Anticoagulants

	dabigatran (Pradaxa)	rivaroxaban (Xarelto)	apixaban (Eliquis)	edoxaban (Savaysa)
Mechanism	Direct Thrombin inhibitor	Factor Xa Inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Half-Life ($t_{1/2}$)	14 hours	5 – 13 hours	12 hours	6 – 11 hours
Dosing	150mg BID CrCl>30 75mg BID CrCl 15-30	20mg qd CrCl>50 15mg qd CrCl 30-49	5mg BID 2.5mg BID (age>80, Cr>1.5 or wt <60Kg)	60mg qd CrCl 50-95 30mg qd CrCl 15-50
Population in Study	Age 71.5 CHADS ₂ = 2.1 TTR 64%	Age 73 CHADS ₂ = 3.5 TTR 57.8%	Age 70 CHADS ₂ = 2.1 TTR = 62.2%	Age 72 CHADS ₂ = 2.8 TTR = 68.4%
Stroke Risk	Superior	Non-inferior	Superior	Similar
Bleeding Risk	Similar	Superior	Superior	Lower
Mortality Reduction	12% (p=0.051)	8% (p=0.15)	11% (p=0.047)	8% (p=0.08)

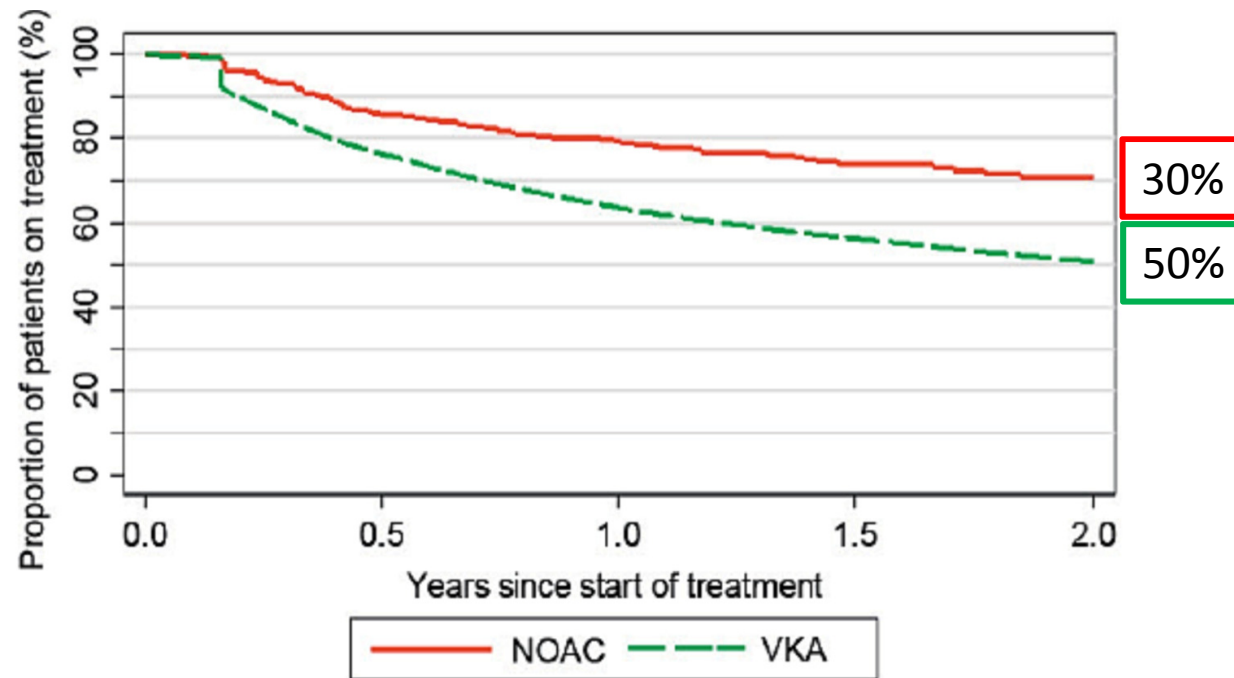
Rate of Anticoagulation in High-Risk NVAF Patients Has Not Improved



Results from the NCDR PINNACLE Registry¹

1. Jani, et al. Uptake of Novel Oral Anticoagulants in Patients with Non-Valvular and Valvular Atrial Fibrillation: Results from the NCDR-Pinnacle Registry. ACC

Estimate of Persistence of OAC Therapy



Martinez et al. Thromb Haemost 2015; 115:31

Discontinuation Rates of Anticoagulation

Treatment	Study Drug Discontinuation Rate	Major Bleeding (rate/year)
Rivaroxaban ¹	24%	3.6%
Apixiban ²	25%	3.1%
(60 mg / 30 mg)	25.7% / 24.7%	2.87% / 2.87%
Warfarin ¹⁻⁴	17 – 28%	3.1 – 3.6%

There is an unmet need of stroke risk reduction for patients with AF who are seeking an alternative to long-term OACs

The Dilemma

HAS-BLED

CHA₂DS₂VASc

Clinical Characteristic	Score	Clinical Characteristic	Score
Hypertension (>160mmHg)	1	Congestive Heart Failure	1
Abnormal renal/liver function	1 or 2	Hypertension	1
Stroke	1	Age > 75	2
Bleeding	1	Diabetes	1
Labile INR	1	Stroke/TIA	2
Elderly age	1	Vascular Disease	1
Drugs or alcohol (1 each)	1 or 2	Age > 65	1
		Sex (female gender)	1

Bleeding Risk Increases Over Lifetime

HAS-BLED Score	Annual % Bleed Risk	10-Year Bleeding Risk (%)
0	0.9	8.6
1	3.1	29.2
2	4.1	34.2
3	5.8	45.0
4	8.9	60.6
5	9.1	61.5

*Lip JACC 2011

** Assumes constant risk despite increasing age and bleeding risk is independent from bleeding risk in previous years

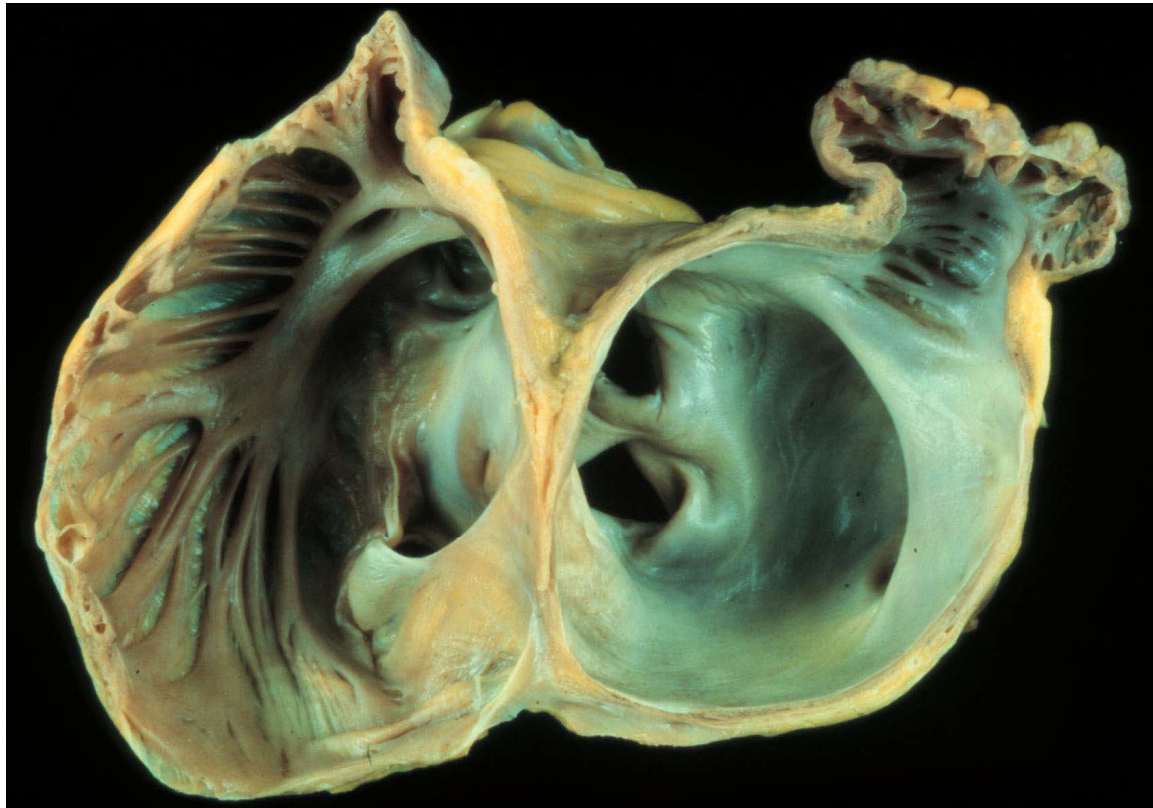
Agenda

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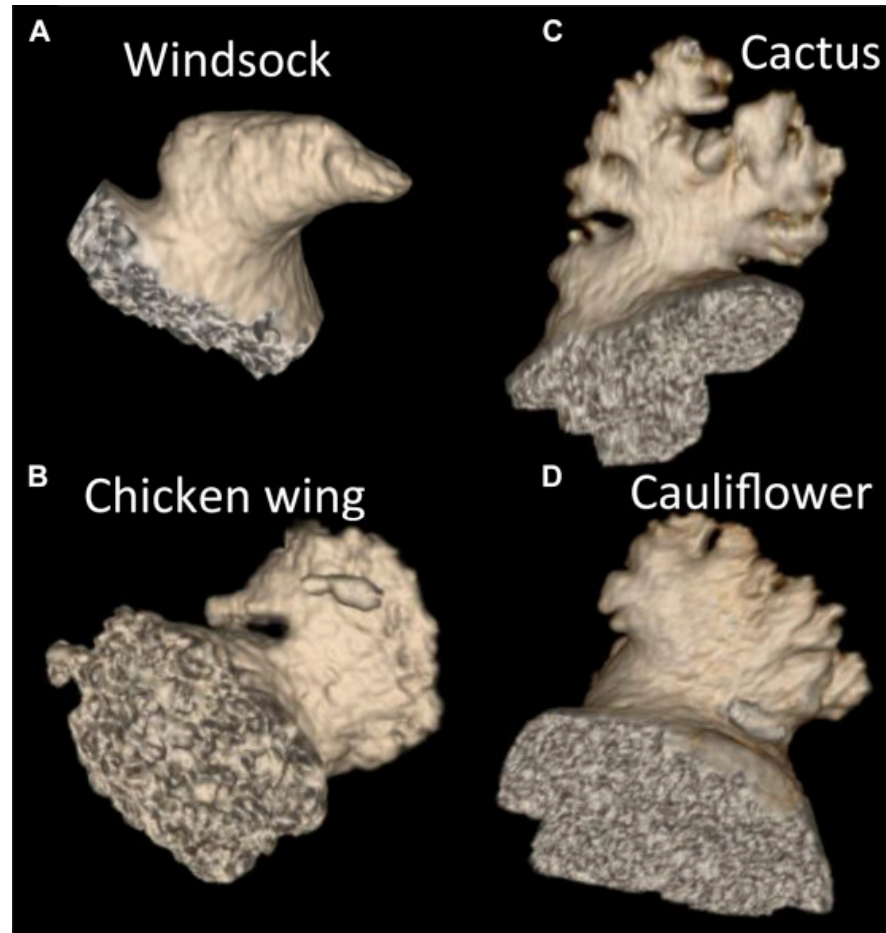


Right Atrium

Left Atrium







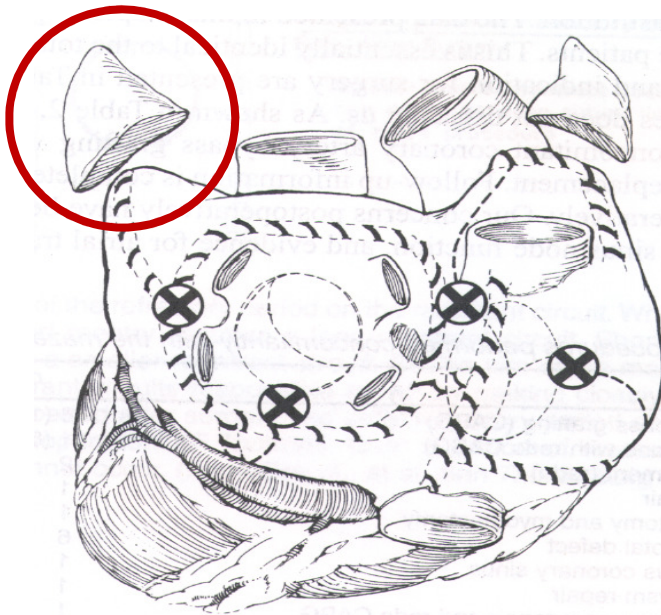
Hypothesis

Eliminating blood flow in the LAA will reduce the risk of stroke without the inherent risks of anticoagulation

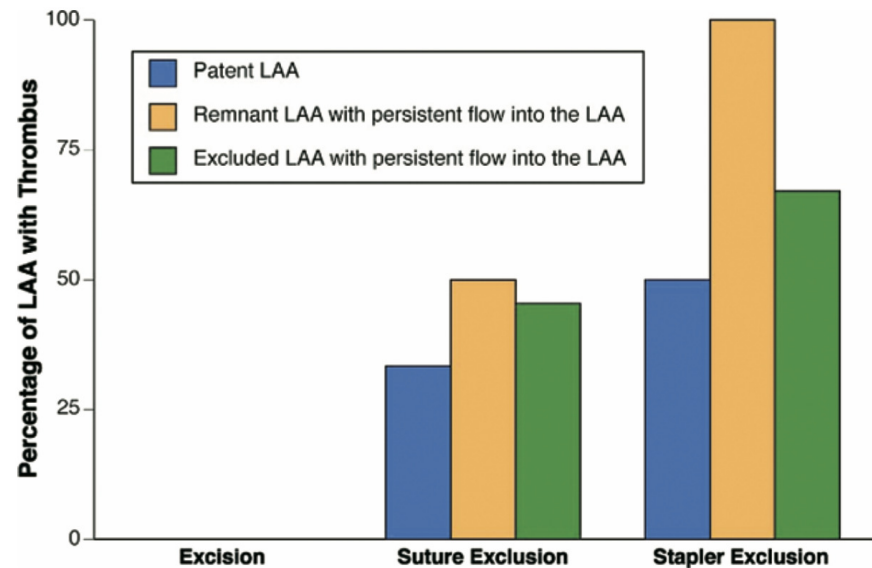


Surgical Experience

LAA Exclusion



Paucity of data
Variable closure rates



AtriClip



EXCLUDE Trial

Subject has any one of the following risk factors and is thought to benefit from LAA exclusion:

- CHADS score > 2
- Age > 75 years
- Hypertension and age > 65 years
- History of AF (any classification)
- Previous Stroke

- 70/70 clips placed successfully
- 69/70 complete exclusion confirmed by intra-op TEE
- 60/61 exclusion confirmed by 3 month CT Scan
- No device or clip procedure-related adverse events reported in the study

Ailawadi G *J Thorac Cardiovasc Surg.* 2011;142(5):1002-9,



... “occlusion of the LAA, under direct visualization, in conjunction with other open-heart cardiac procedures” which we hope and pray leads to...

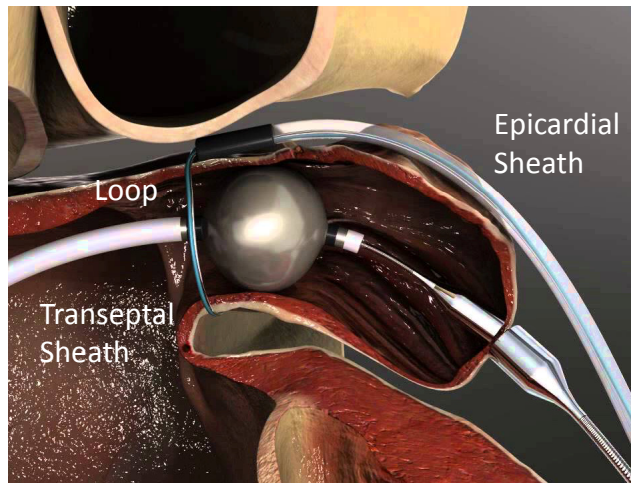
FDA Approves the AtriClip for Stroke Prevention in Atrial Fibrillation Patients **Λ**

June 18, 2010 12:05 AM CT

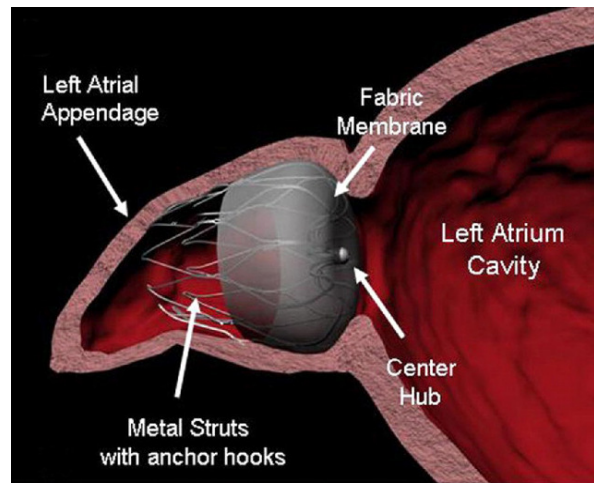


Types of Percutaneous Appendage Closure

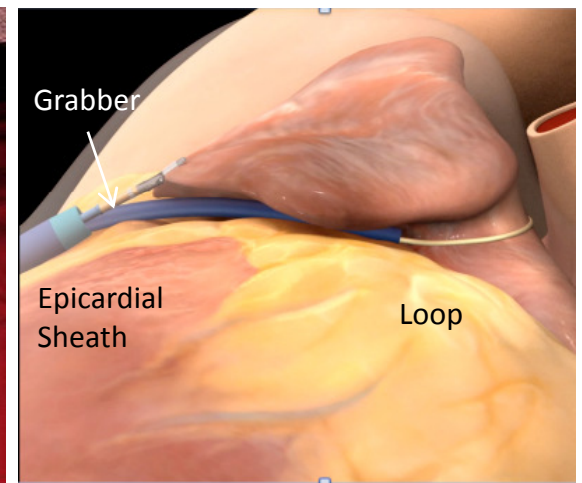
Hybrid
Endo/Epi Loop



Endocardial
Plug



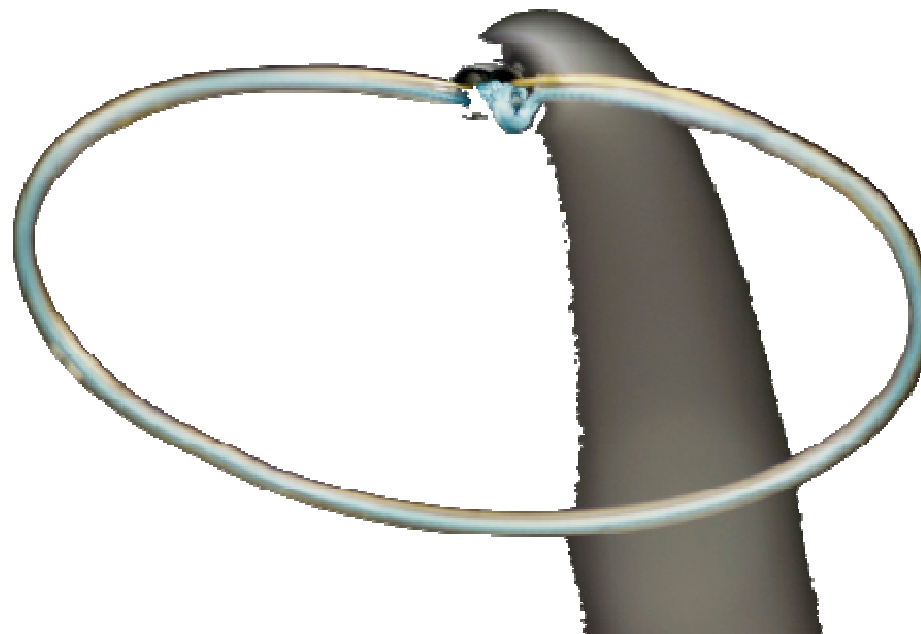
Epicardial
Loop

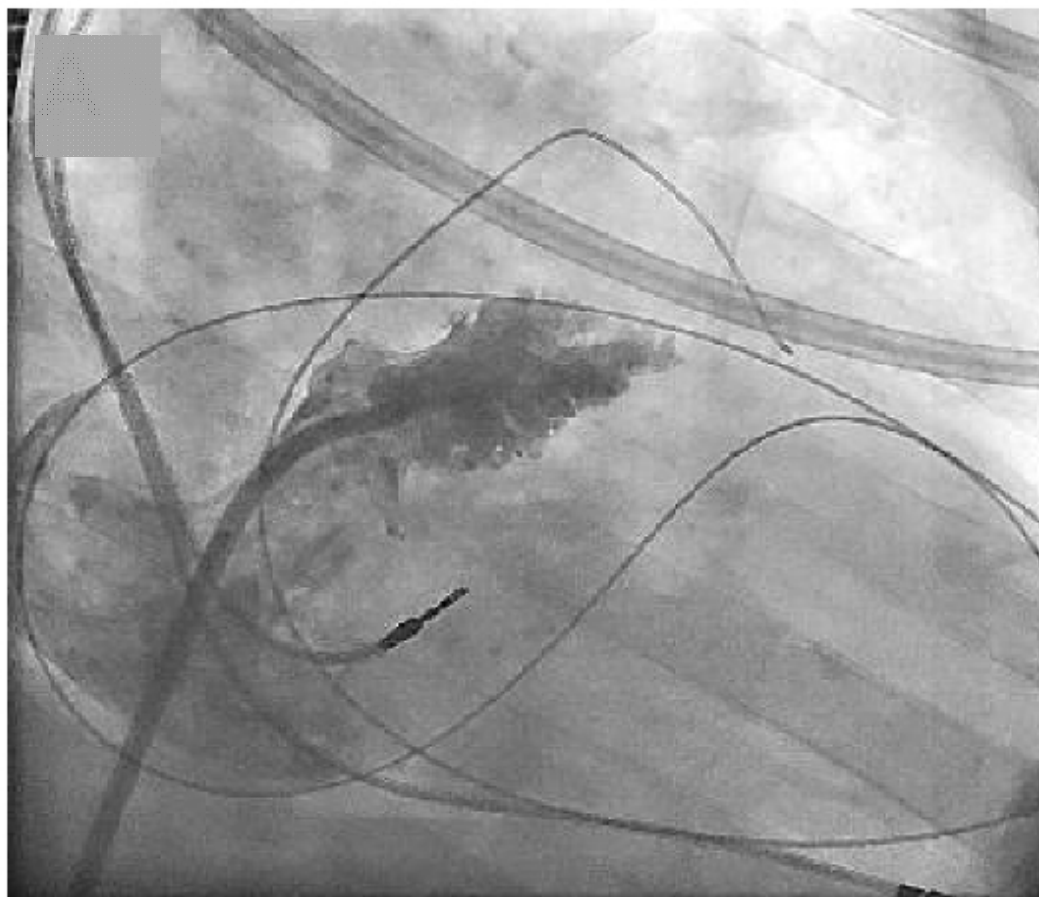


LARIATTM

SUTURE DELIVERY DEVICE

FDA Approval in 2009 for “soft tissue approximation”

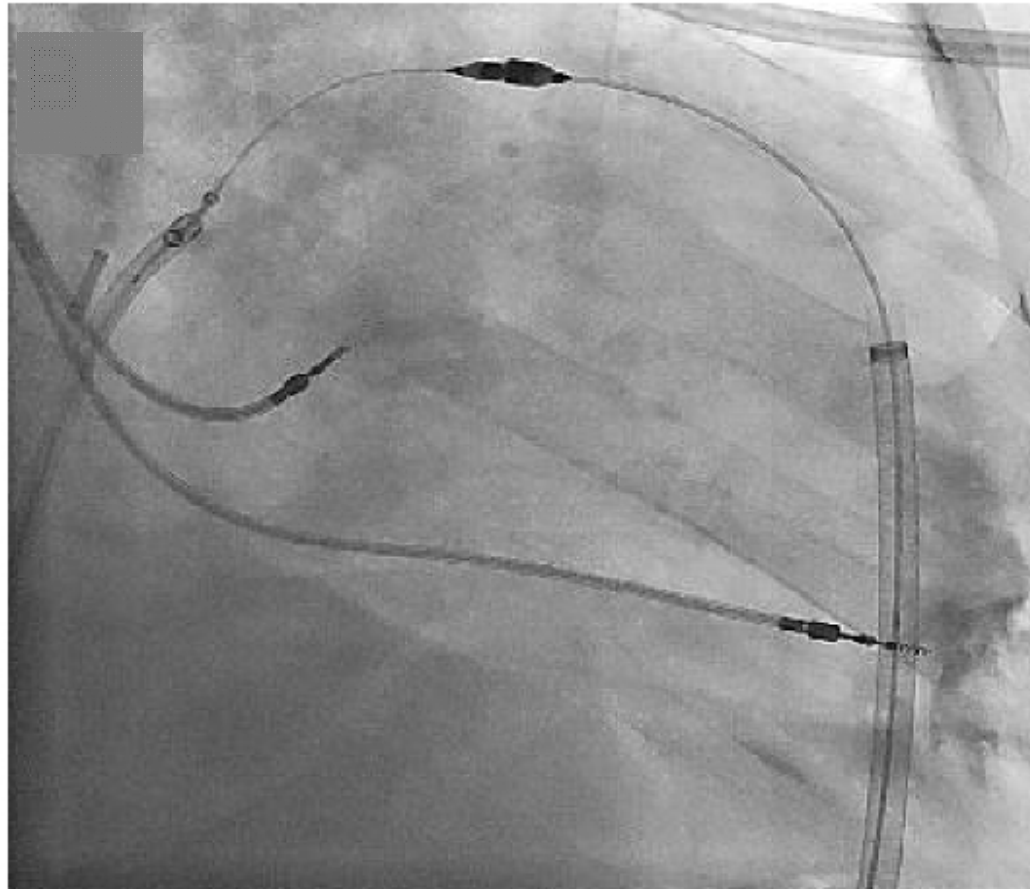




**Changing
Lives**
@ HILLCREST



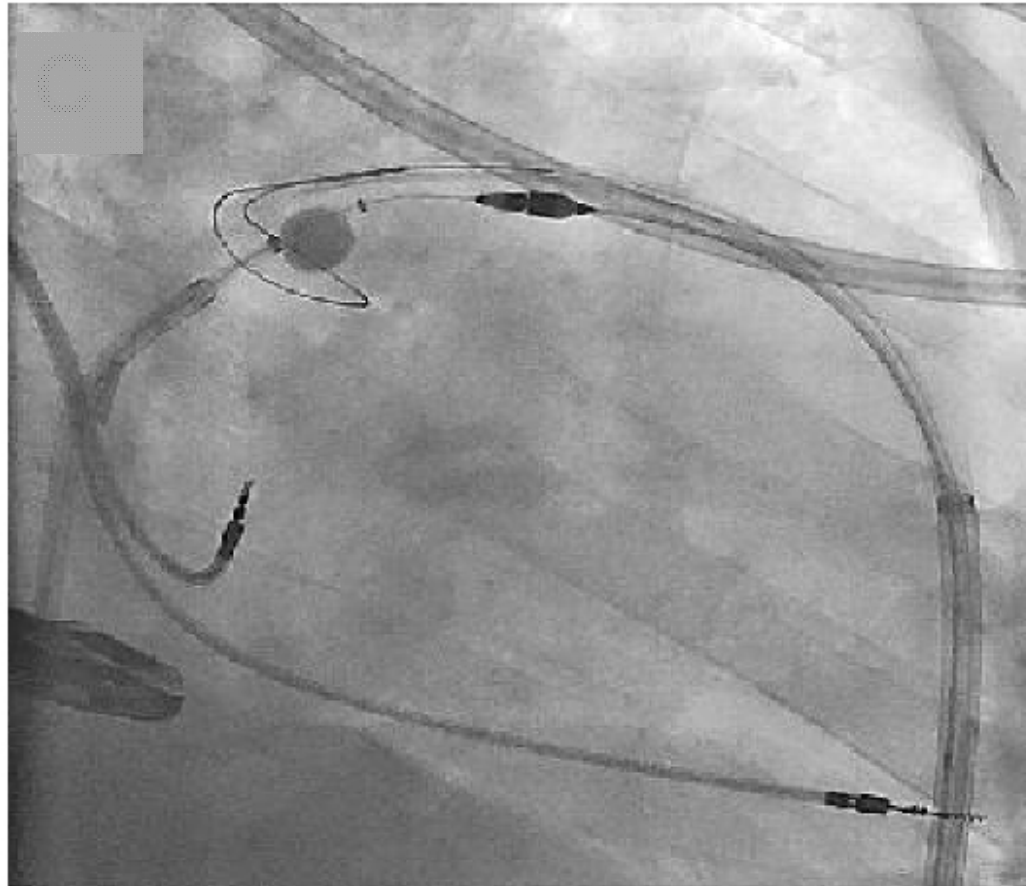
Oklahoma Heart Institute
all new. all heart.



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Lives**
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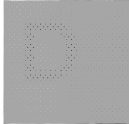
Oklahoma Heart Institute
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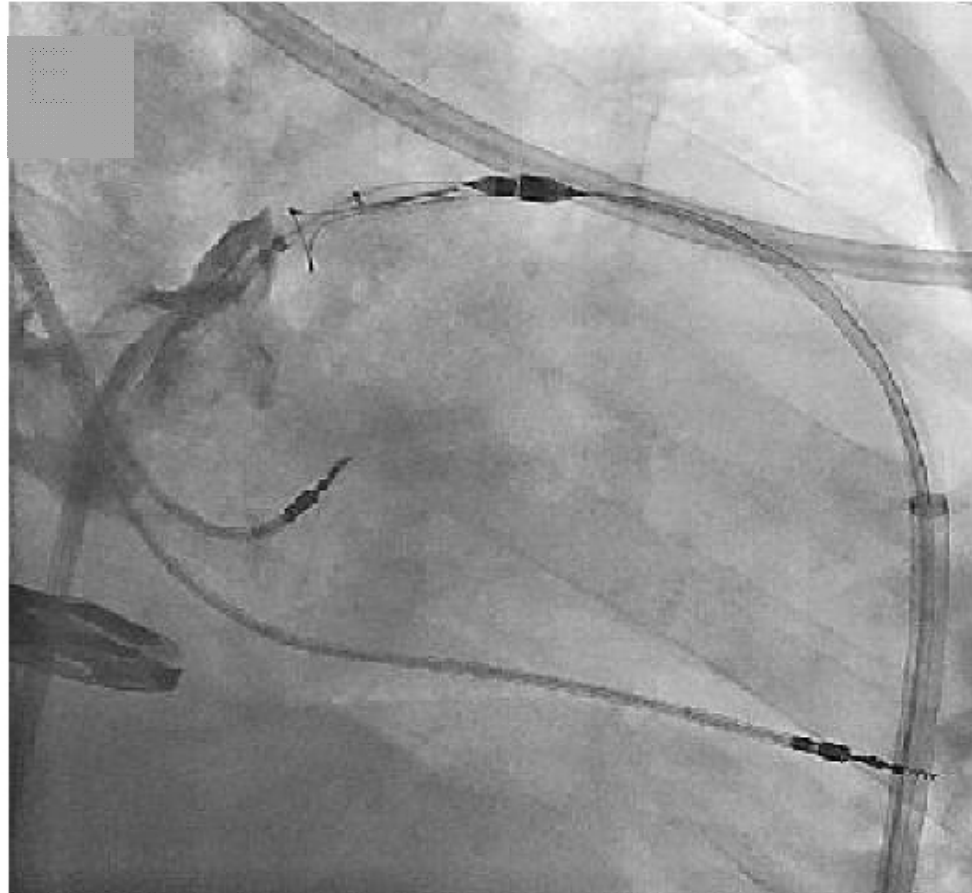


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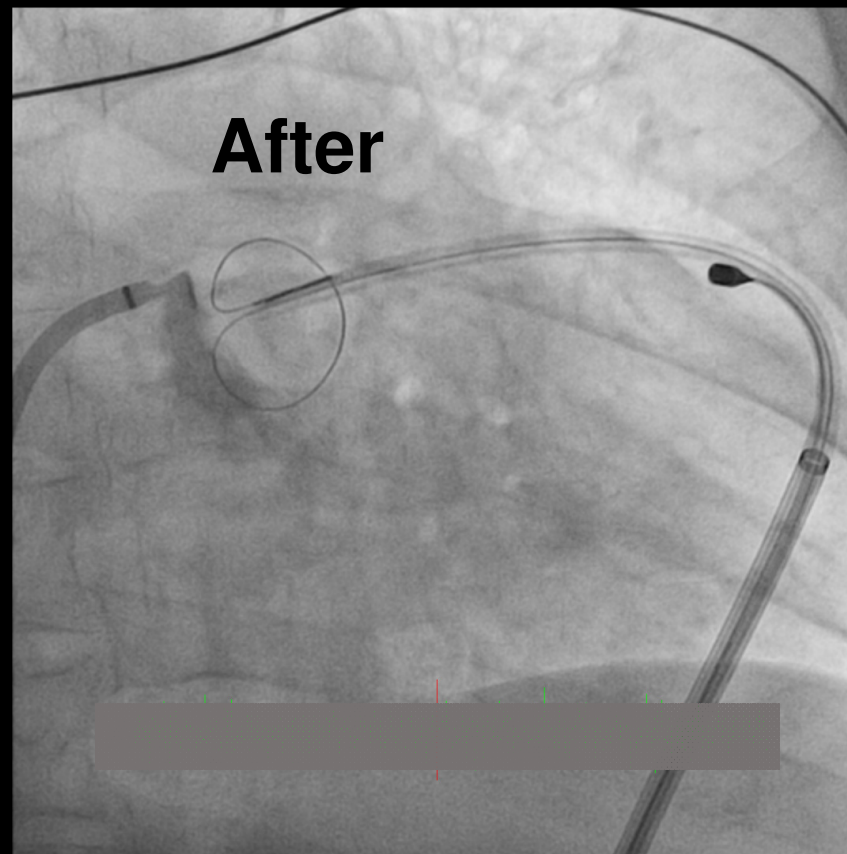
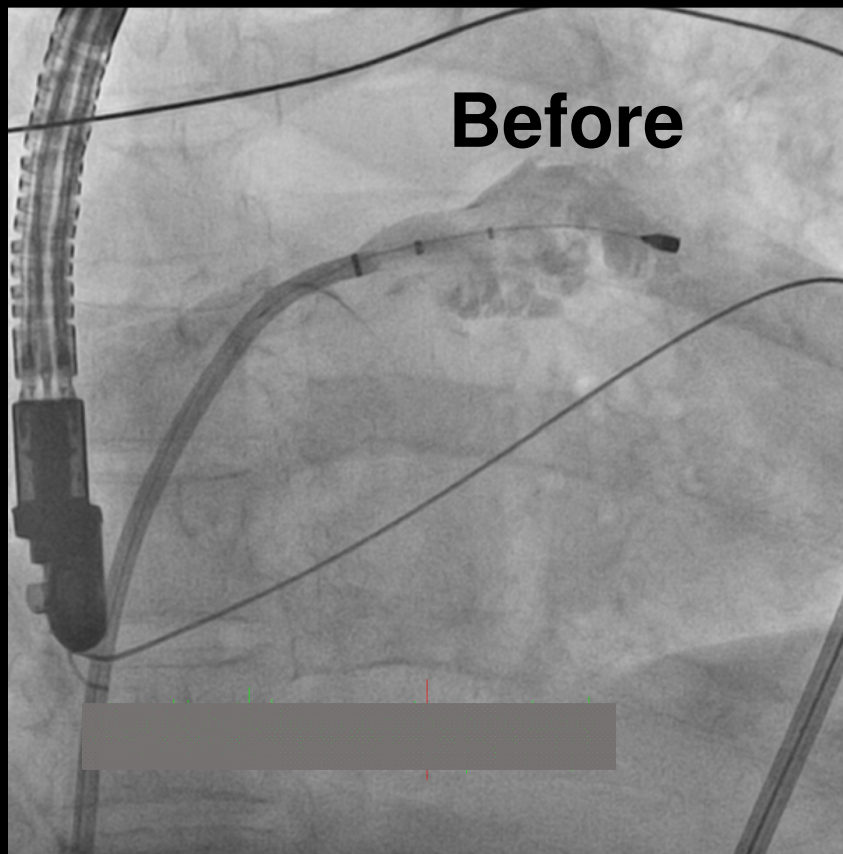


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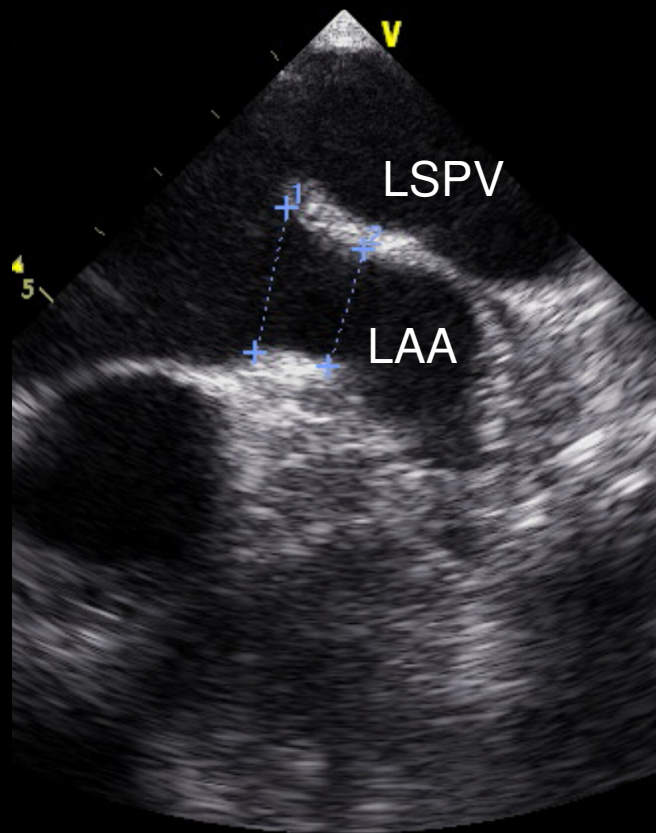


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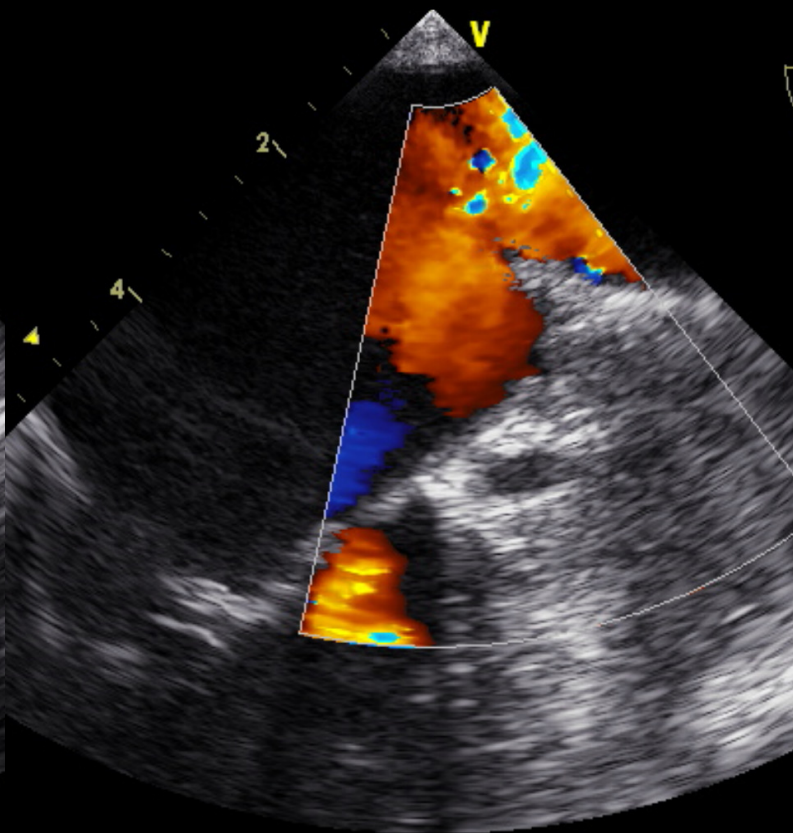
Fluoroscopy



TEE



Before



After

Lariat Registry of 154 Patients

TABLE 3 Reasons for Procedural Failure of Left Atrial Appendage Ligation With the Lariat Device (N = 22)

Lariat unable to be deployed	9 (48)
Pericardial adhesions	5
LAA anatomy	2
Aborted procedure after RV perforation	2
Residual Leak \geq 5 mm	1 (6)
Major complication before discharge	15 (71)

9.7%

Values are n or n (%). In 2 patients with procedural failure, there was both a major complication and the lariat was not deployed. In 1 patient, there was both a residual leak \geq 5 mm and a major complication.

LAA = left atrial appendage; RV = right ventricular.

Price MJ et al *J Am Coll Cardiol* 2014;64:565–72



U.S. FOOD & DRUG
ADMINISTRATION

We identified 45 adverse events through June 30, 2015 that occurred in patients undergoing LAA closure procedures with the LARIAT Suture Delivery Device and/or its associated devices. These reports describe 6 patient deaths and other serious medical complications including laceration and/or perforation of the heart, complete LAA detachment from the heart, bleeding (hemorrhage), low blood pressure (hypotension), fluid collection around the heart (pericardial effusion), fluid collection around the heart that causes low blood pressure and decreased heart function leading to shock (cardiac tamponade), and fluid collection around the lung (pleural effusion). Of the 45 adverse events reported to the FDA, 34 (approximately 75%) resulted in the need to perform emergency heart surgery.

Be aware that the safety and effectiveness of the LARIAT Suture Delivery Device to close the LAA and prevent stroke in patients with atrial fibrillation has not been established.

July 13, 2015



Oklahoma Heart Institute
all new. all heart.

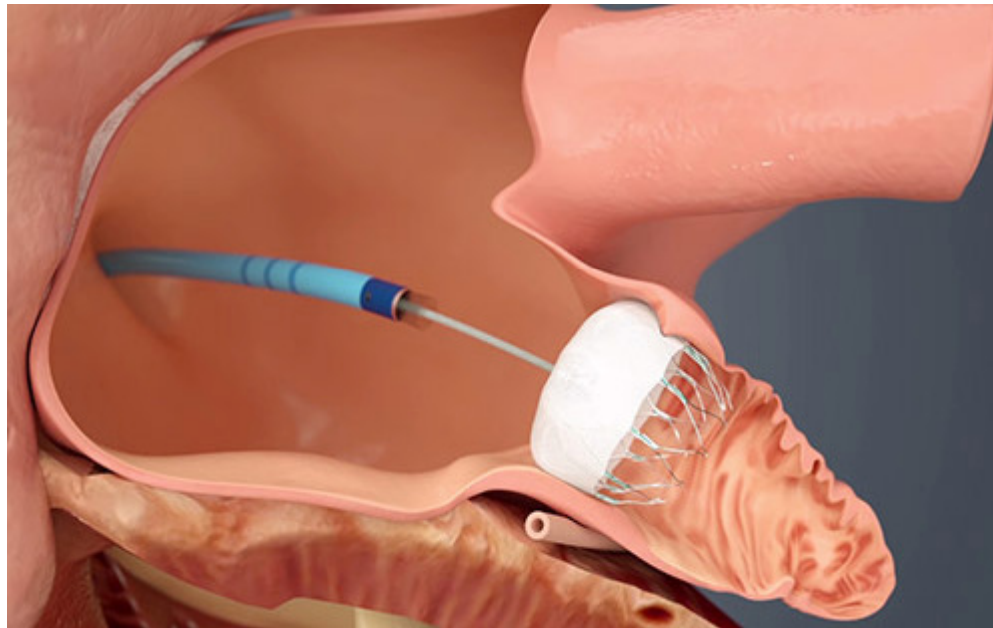


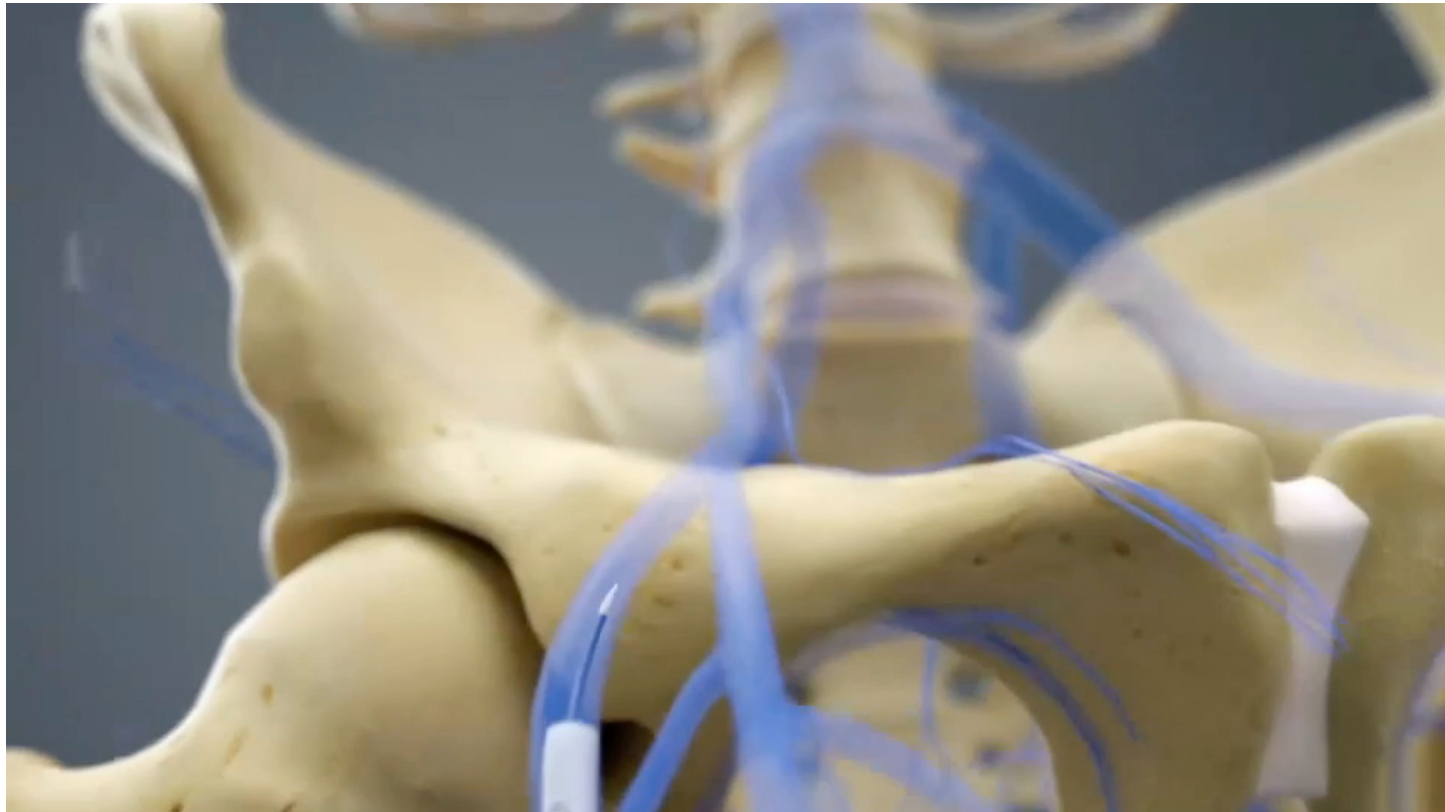
**Changing
Lives**
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Oklahoma Heart Institute
all new. all heart.

Endocardial Plug Concept: Exclude the LAA from central circulation





PROTECT AF Study Overview

Study Design & Objective	Prospective, randomized (2:1), non-inferiority trial of LAA closure vs. warfarin in non-valvular AF patients for prevention of stroke
Primary Endpoint	<u>Efficacy</u> : Composite end point of stroke, cardiovascular death or systemic embolization <u>Safety</u> : Major bleeding, device embolization or pericardial effusion
Statistical Plan	All analyses by intention-to-treat Bayesian (stratified for CHADS ₂ score) : Primary Efficacy and Safety endpoints Cox Proportional: All Secondary Analyses
Patient Population	n = 707 Mean CHADS ₂ = 2.2, CHA ₂ DS ₂ -VASc = 3.5
Key Inclusion Criteria	Paroxysmal / Persistent / Permanent AF CHADS ₂ ≥ 1 (93% had a CHA ₂ DS ₂ -VASc Score ≥ 2) Eligible for long-term warfarin therapy
Mean Follow-Up	2,717 patient-years , 48 months
Number of Sites	59 in the United States and Europe Enrollment Feb 2005 – June 2008

PROTECT AF 4-Year Results

	Device group rate	Control group rate	Hazard ratio WATCHMAN/ warfarin (95% CI)	P
Primary efficacy	2.3	3.8	0.61 (0.38, 0.97)	0.0348
CV death	1.0	2.4	0.40 (0.21, 0.75)	0.0045
All stroke	1.5	2.2	0.70 (0.39, 1.26)	0.2244
Hemorrhagic stroke	0.2	1.1	0.16 (0.04, 0.51)	0.0049
Ischemic stroke	1.4	1.1	1.30 (0.64, 2.84)	0.4921
Disabling stroke	0.5	1.2	0.37 (0.15, 1.00)	
All-cause mortality	3.2	4.8	0.66 (0.45, 0.98)	0.0379
Primary safety	3.6	3.1	1.21 (0.78, 1.94)	0.4051

- **Device superior to Control: primary efficacy, CV death, hemorrhagic stroke and all-cause mortality**

Reddy, VY et al. JAMA. 2014;312(19):1988-1998.

PROTECT AF 4-Year Results

	Device group rate	Control group rate	Hazard ratio WATCHMAN/ warfarin (95% CI)		P
Primary efficacy	2.3	3.8			
CV death	1.0	2.4			
All stroke	1.5	2.2			
Hemorrhagic stroke	0.2	1.1	0.24	0.47	P=<.001
Ischemic stroke	1.4	1.1	0.97	1.05	P=.42
Disabling stroke	0.5	1.2			
All-cause mortality	3.2	4.8			

Apixaban

Warfarin

0.24

0.47

P=<.001

0.97

1.05

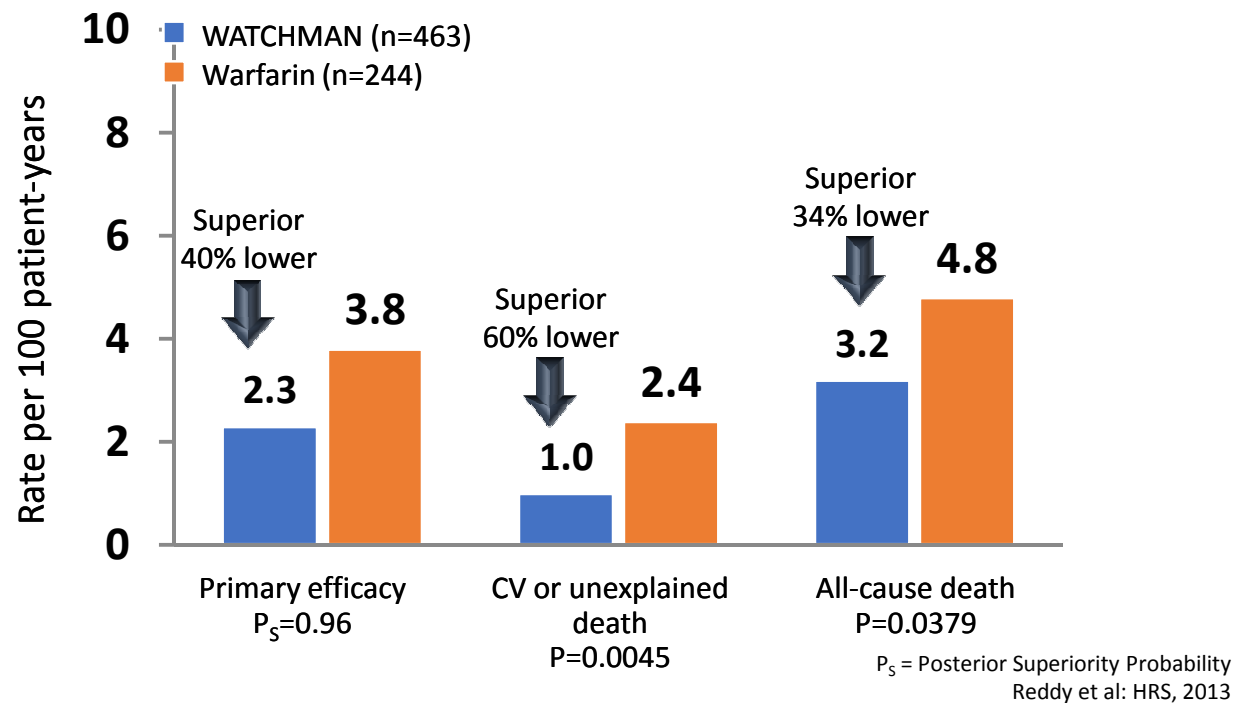
P=.42

Aristotle, NEJM 2011

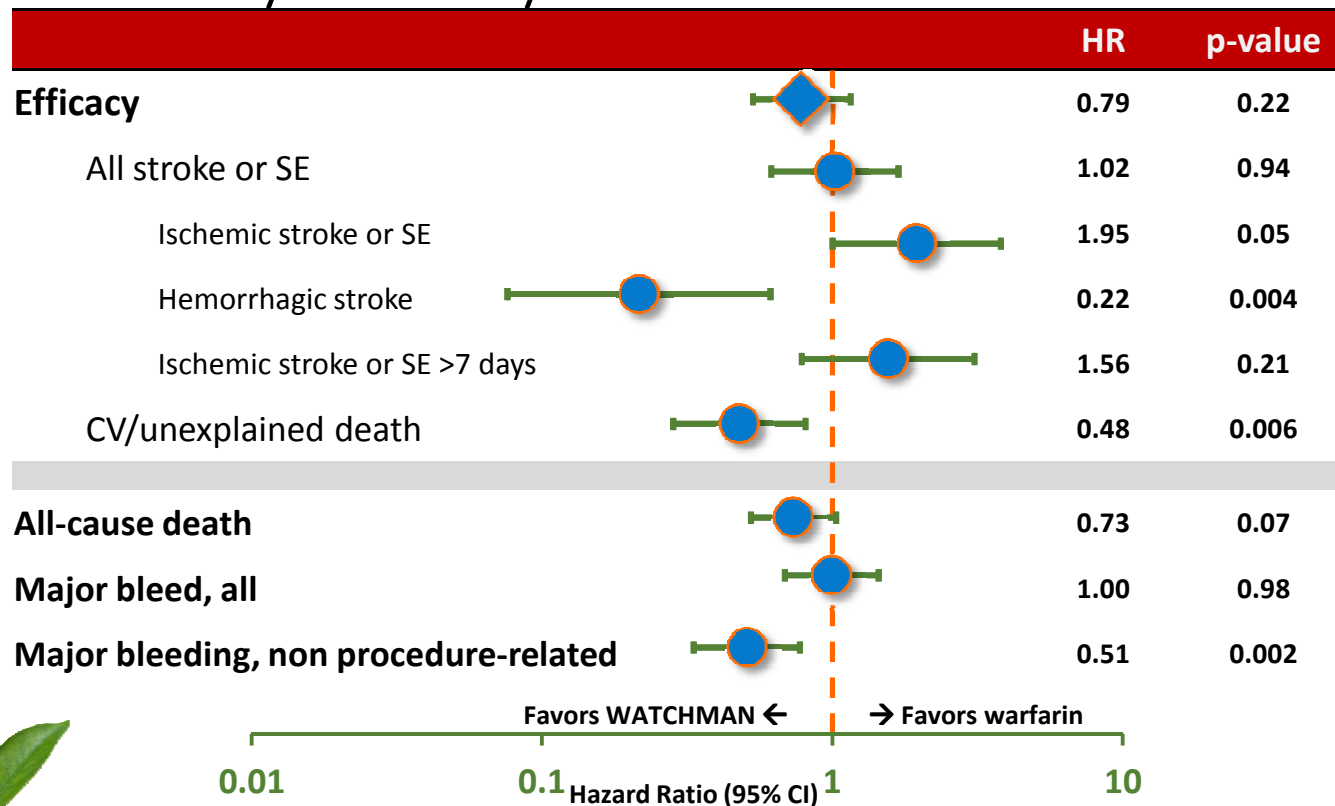
Benefit of NOACs is reduction of CNS bleed. Apixaban cuts CNS bleed in half c/w warfarin. LAA closure reduces CNS bleed 5-fold.

Watchman Long-Term Follow up

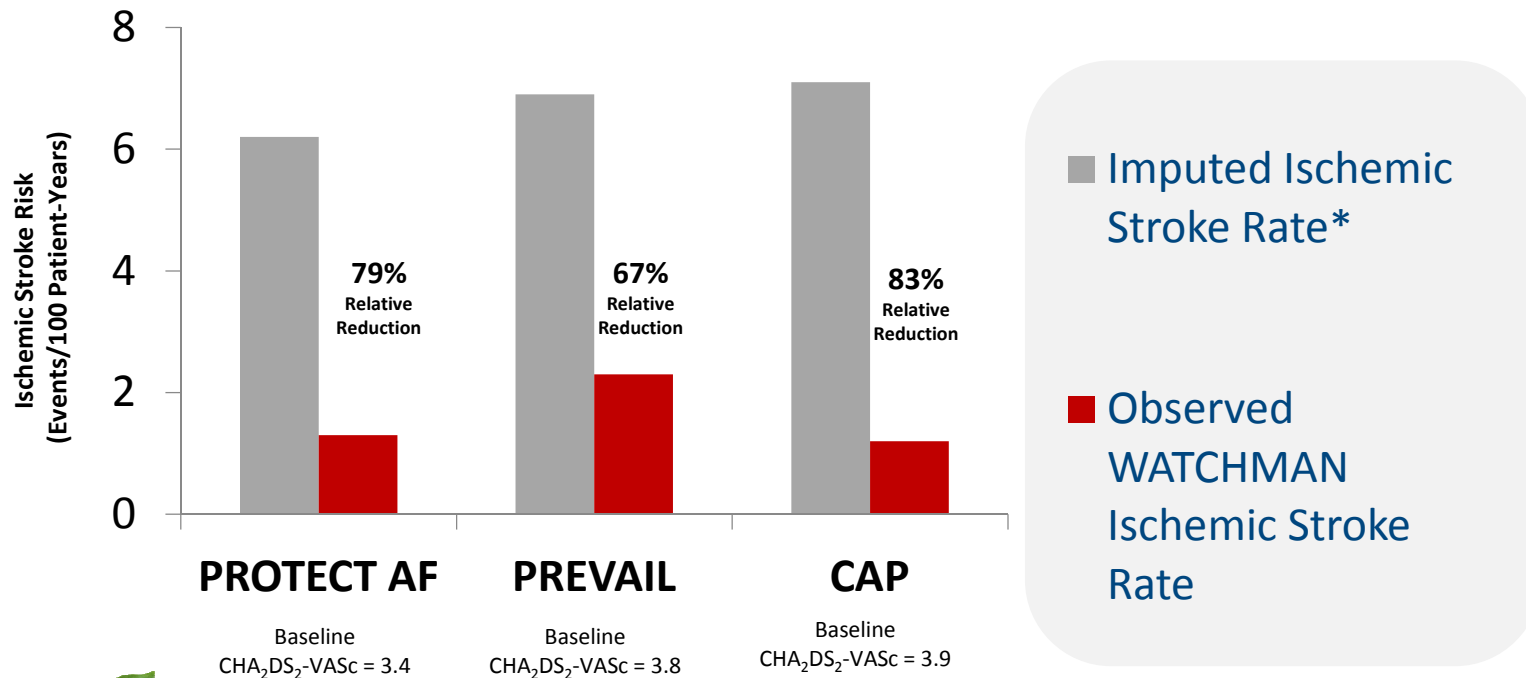
PROTECT AF 4-Year Superiority



Meta-Analysis Shows Comparable Primary Efficacy Results to Warfarin



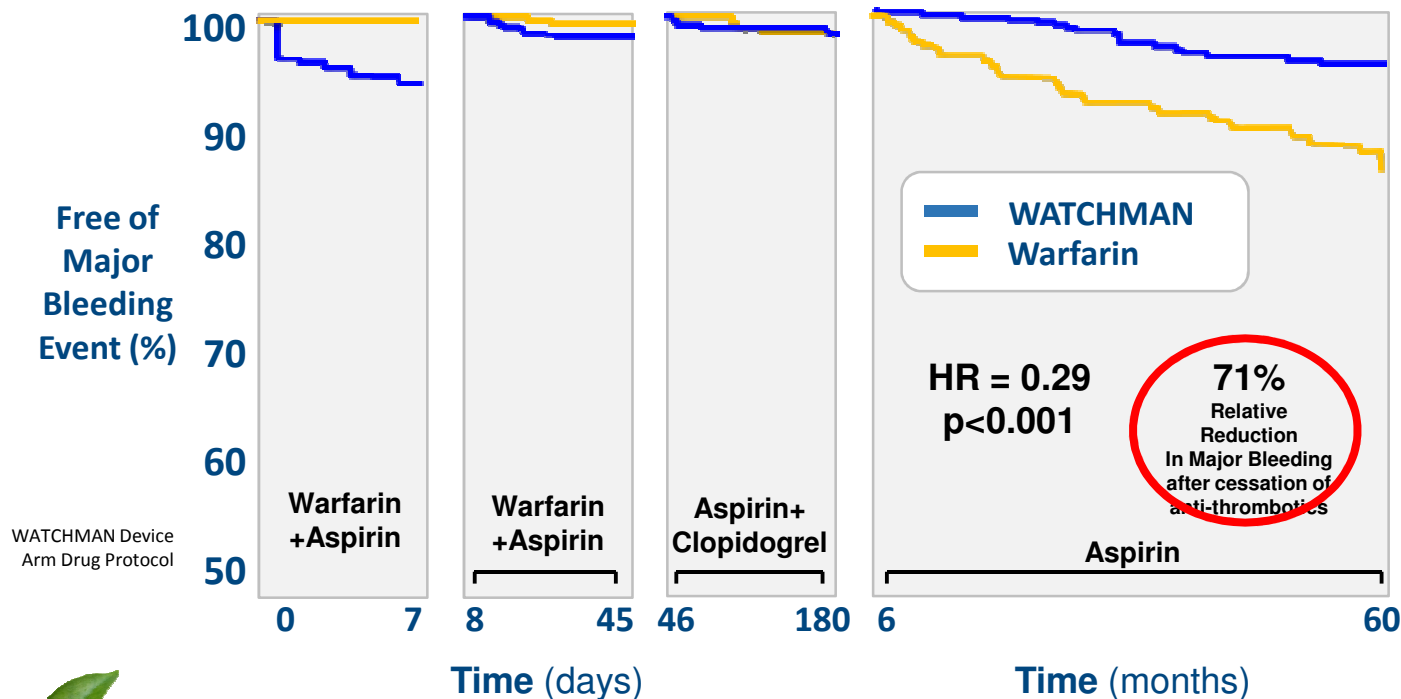
LAA Occlusion with WATCHMAN™ Reduces Ischemic Stroke Over No Therapy



* Imputation based on published rate with adjustment for CHA₂DS₂-VASc score (3.0); Olesen JB. Thromb Haemost (2011)

FDA Oct 2014 Panel Sponsor Presentation. Hanzel G, et al. TCT 2014 (abstract)

PROTECT AF/PREVAIL Pooled Analysis: Less Bleeding with WATCHMAN™ Device



Definition of bleeding: Serious bleeding event that required intervention or hospitalization according to adjudication committee

Price, M.J. Avoidance of Major Bleeding with WATCHMAN Left Atrial Appendage Closure Compared with Long-Term Oral Anticoagulation : Pooled Analysis of the PROTECT-AF and PREVAIL RCTs. TCT 2014 (abstract)

~~Hypothesis~~

Evidence

Eliminating blood flow in the LAA will reduce the risk of stroke without the inherent risks of anticoagulation



2 questions remain:

- Can you guys in the real world have similar results?
- OK, lets talk \$\$\$

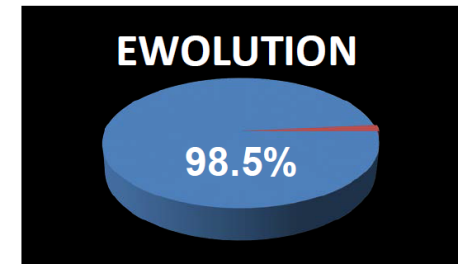
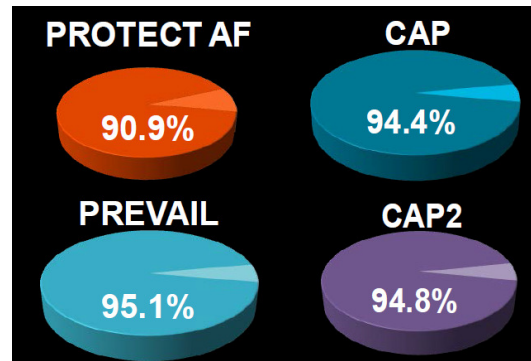


What is Happening in the “Real World”?

EWOLUTION Registry

- Prospective, Multicenter (n=47), Non-randomized Registry
- Enrollment
 - Consecutive Watchman Patients
 - 47 sites: Europe, Russia, Middle East
 - From October 2013 – May 2015
 - **Total Enrollment = 1021 pts**
- Follow-Up:
 - Normally 1-3 months post-implant
 - Annually for at least 2 years
 - Post-Implant OACs: Per Physician preference

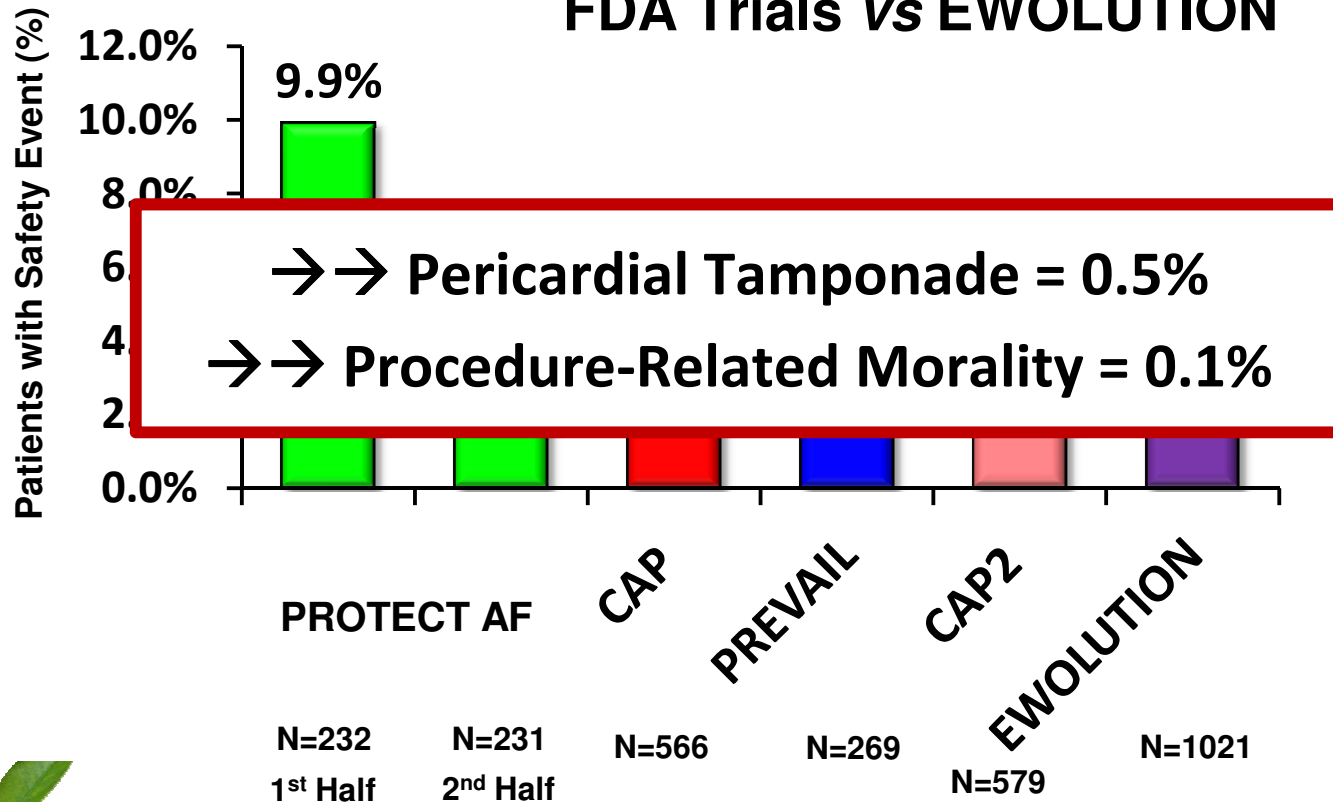
What is implant success in the “real world”?



Comparison of proportions between all studies: $p < 0.001$

Safety Events Across Trials

FDA Trials vs EWOLUTION



Post-Approval U.S. Experience With Left Atrial Appendage Closure for Stroke Prevention in Atrial Fibrillation



Vivek Y. Reddy, MD,^a Douglas N. Gibson, MD,^b Saibal Kar, MD,^c William O'Neill, MD,^d Shephal K. Doshi, MD,^e Rodney P. Horton, MD,^f Maurice Buchbinder, MD,^g Nicole T. Gordon, BSEE,^h David R. Holmes, MDⁱ

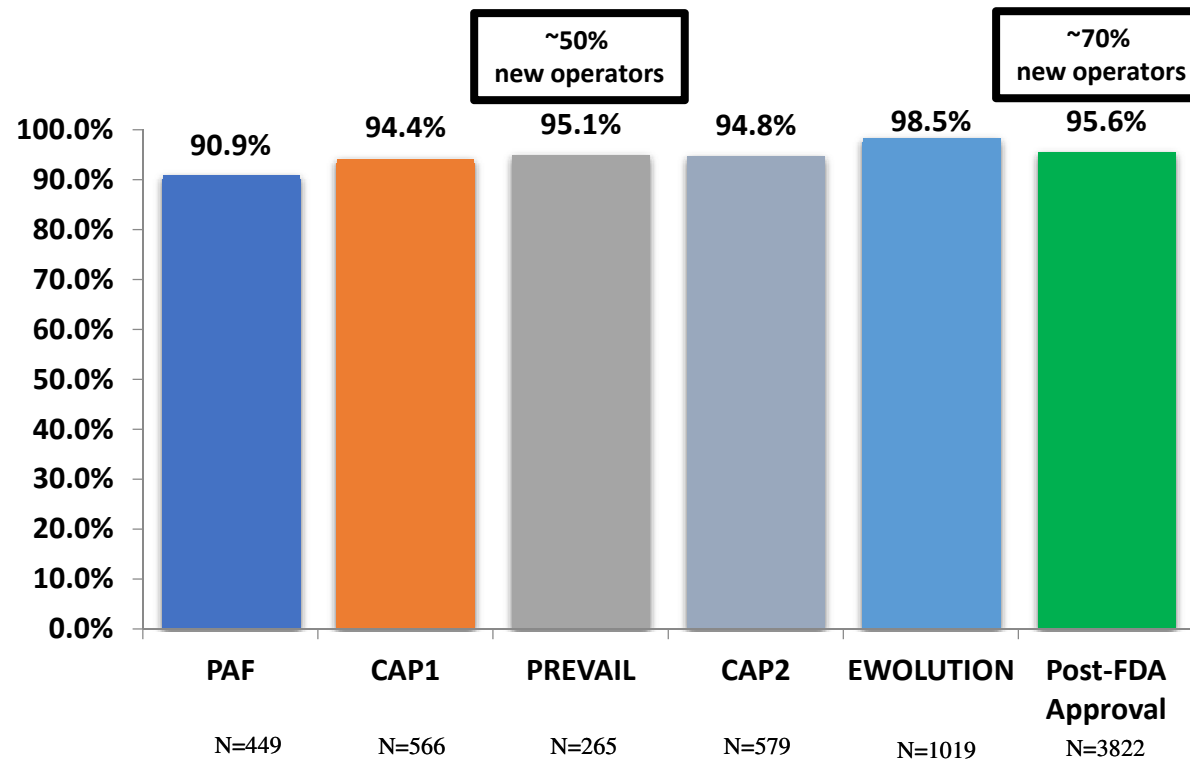
ABSTRACT

BACKGROUND Left atrial appendage closure (LAAC) was approved by the U.S. Food and Drug Administration (FDA) as a stroke prevention alternative to warfarin for patients with nonvalvular atrial fibrillation. However, clinical decision-making is confounded by the fact that although LAAC attenuates the anticoagulant-related lifetime risk of bleeding, implantation is associated with upfront complications. Thus, enthusiasm for LAAC as a treatment option has been appropriately tempered, particularly as the therapy is introduced beyond the clinical trial sites into general clinical practice.

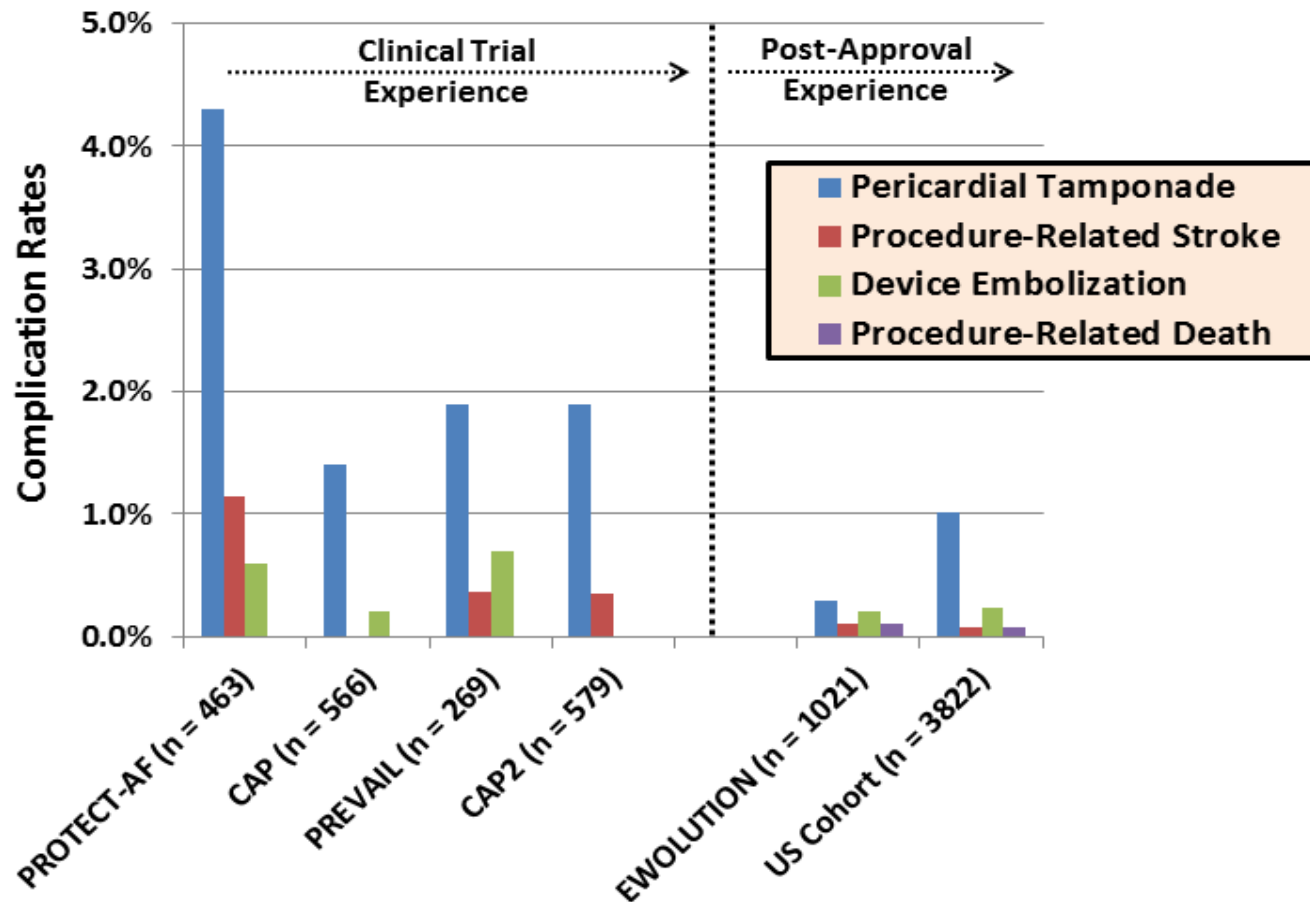
Reddy VY et al J Am Coll Cardiol 2017;69:253–61



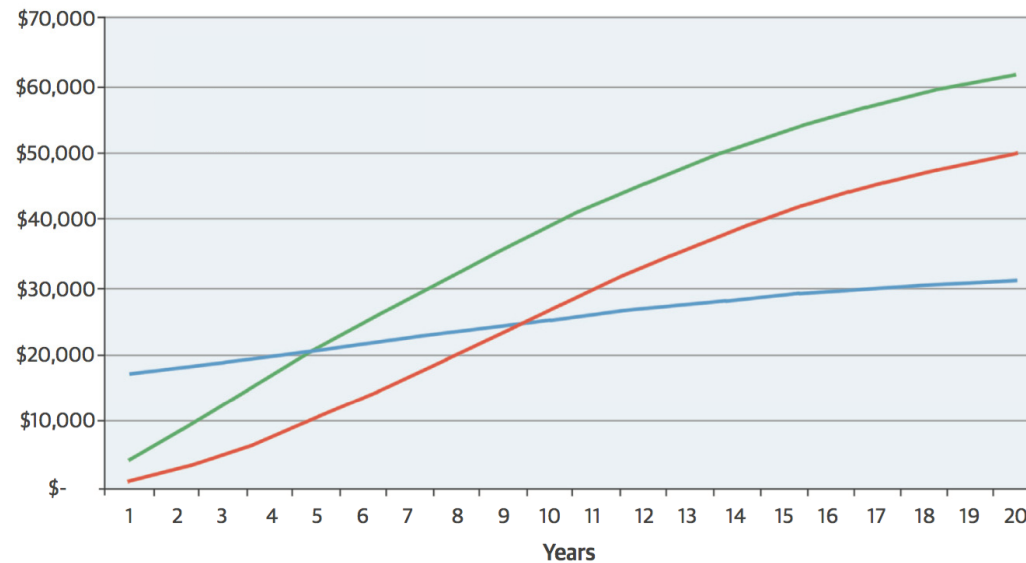
Procedural Success



Comparison of Procedural Parameters Across Watchman Studies



Cumulative Cost and Time to Cost-Effectiveness Following Treatment Initiation: Warfarin Versus NOACs Versus LAAC



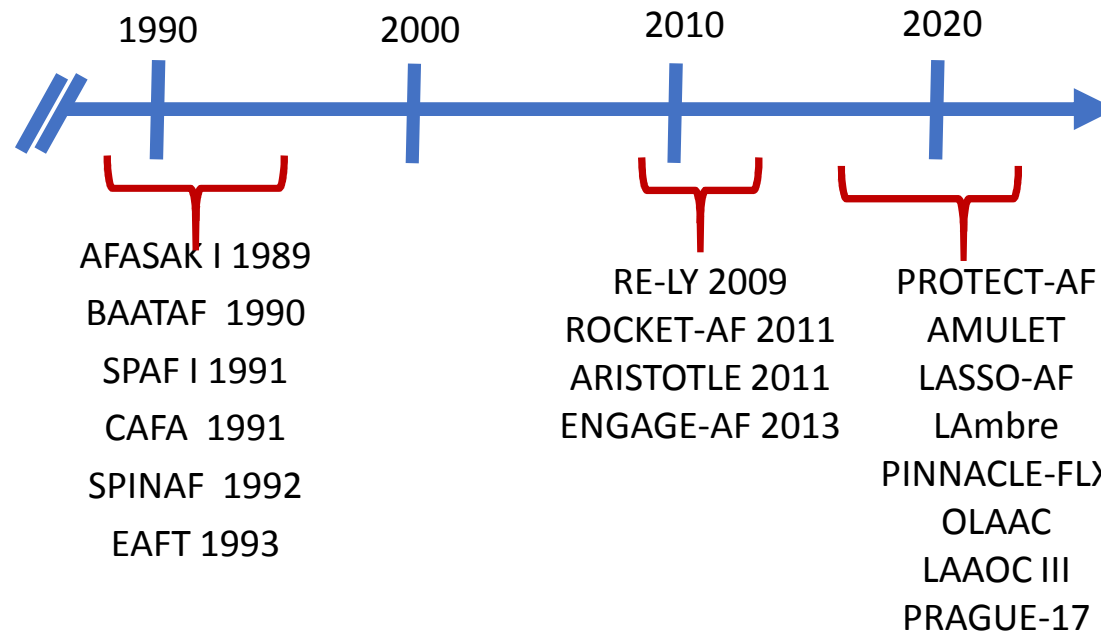
NOAC

Warfarin

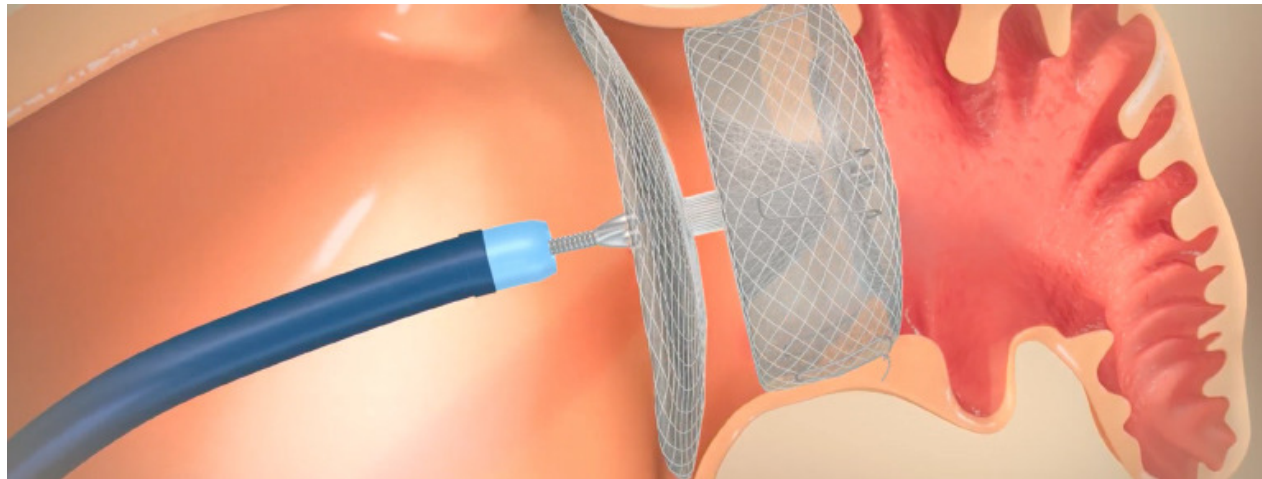
LAAC Closure

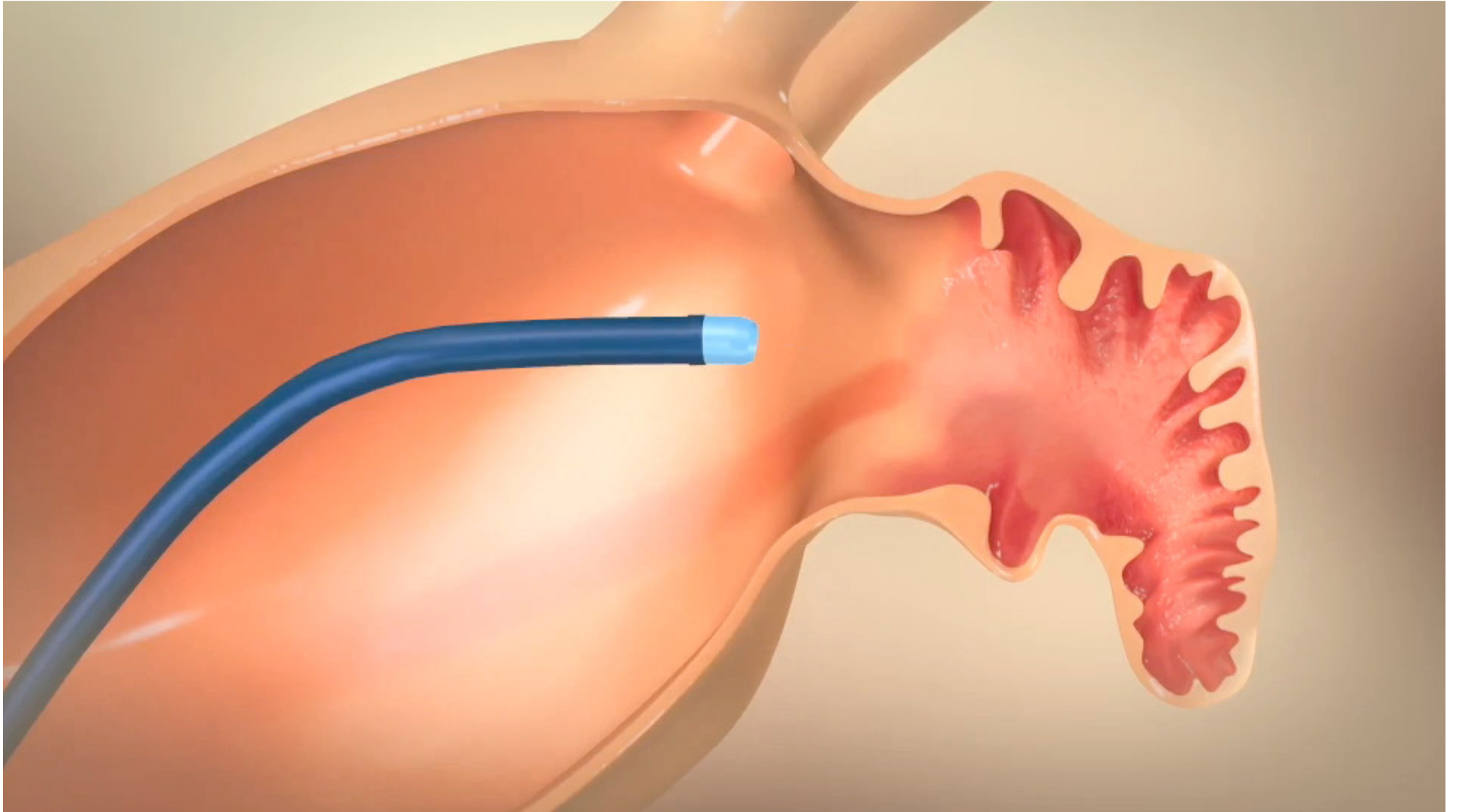
	Time to Clinical Effectiveness (Incremental QALYs)	Time to Cost-Effectiveness (Cost per QALY)	Time to Dominance (More Effective, Less Costly)
LAAC vs. warfarin	Year 3 (0.015)	Year 7 (\$42,994/QALY)	Year 10
NOACs vs. warfarin	Year 1 (0.008)	Year 16 (\$48,446/QALY)	N/A
LAAC vs. NOACs	Year 5 (0.007)	Year 5 (Dominant)	Year 5

AF Timeline

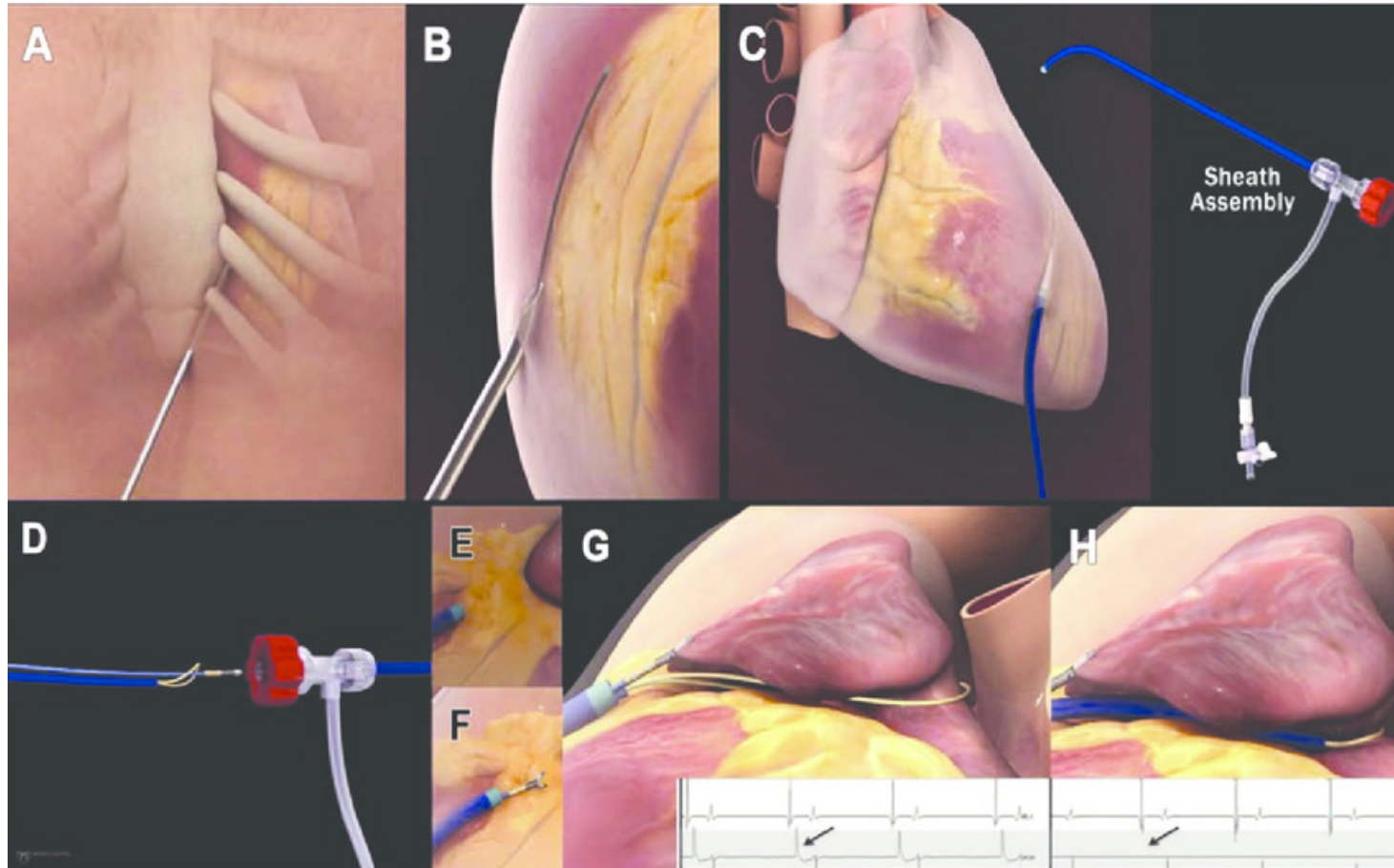


Amulet





Completely Epicardial



LAA Closure vs. Anticoagulation

Procedure

Procedural Risk
(acute bleeding/stroke)

Drugs

Drug side effects
(bleeding/time)
Adherence



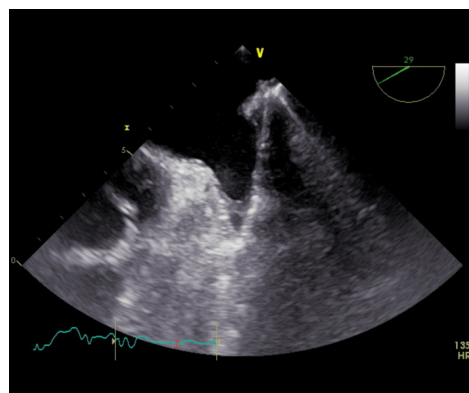
Device benefit accrues over time
Compared to ongoing drug therapy

Watchman Indication

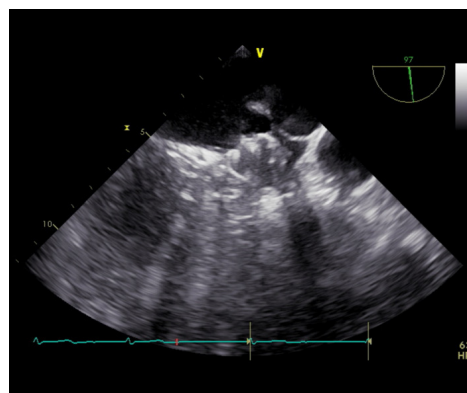
- High risk of stroke
 - CHADS₂ ≥ 2
 - CHA₂DS₂VASc ≥ 3
- Suitability for short-term warfarin but deemed unable to take long term oral anticoagulation
- A formal shared decision making interaction with an independent non-interventional physician using an evidence-based decision tool on oral anticoagulation

Mr. M

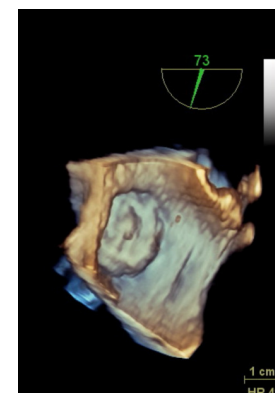
Pre



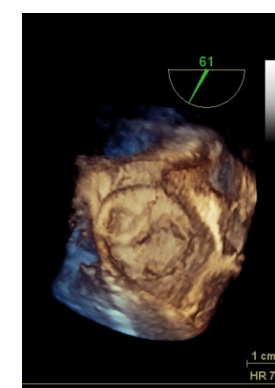
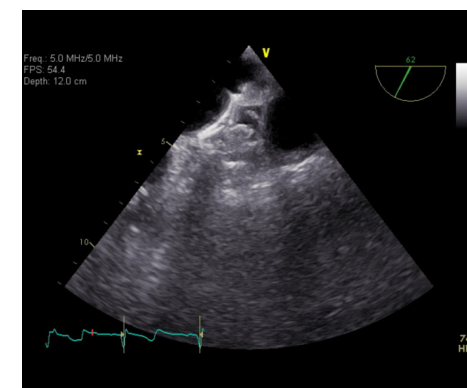
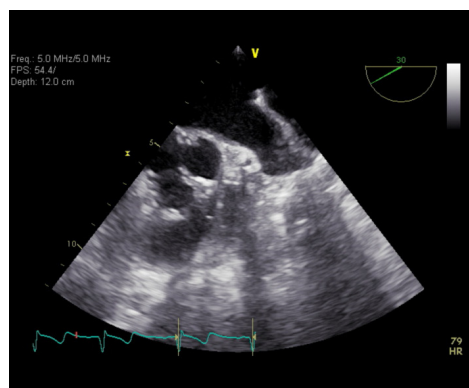
Post



3D-TEE



Mrs. M



Conclusions

- The LAA appendage is the source of 90% stroke in NVA
- Warfarin and NOACS significantly reduce risk of stroke, but increase risk of bleeds
- LAA closure reduces the risk of stroke WITHOUT increasing risk of bleed

Device Options for Stroke Prevention in Atrial Fibrillation

David A. Sandler, MD, FACC, FHRS

Director, Heart Rhythm Service

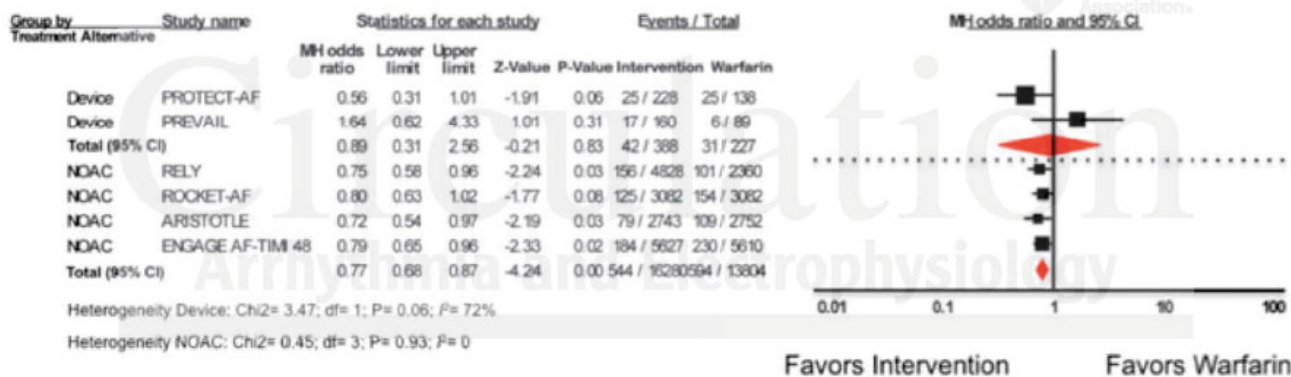
Oklahoma Heart Institute



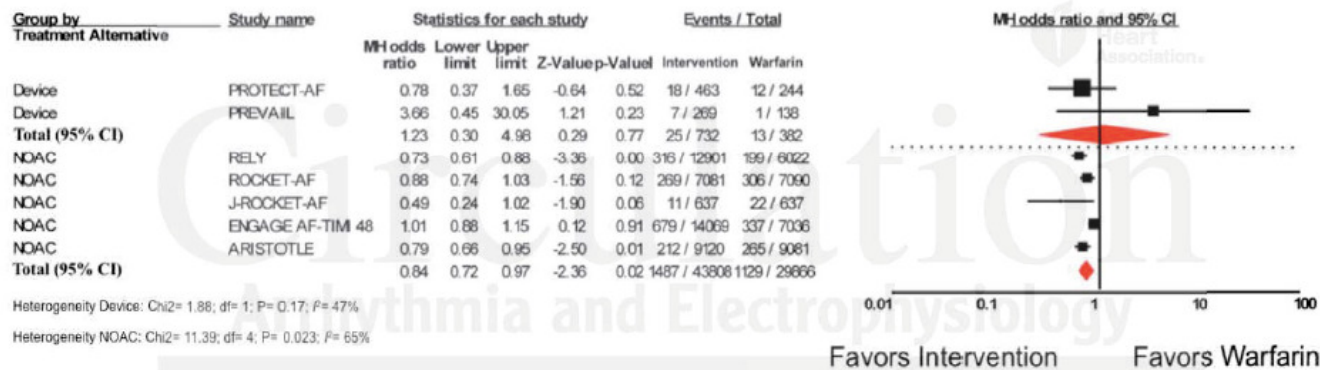
- PRAGUE-17
- LAAOS III



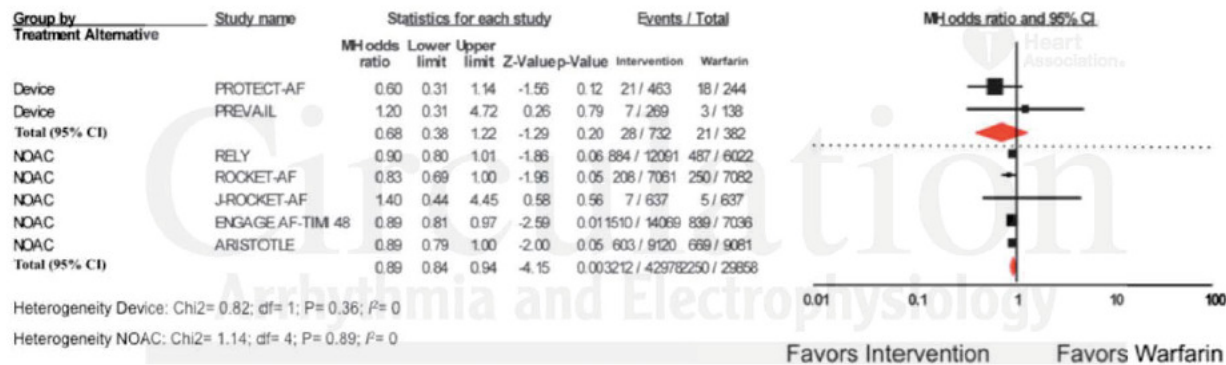
Stroke or Systemic Embolism in the Elderly



Stroke or Systemic Embolism



Mortality



Watchman

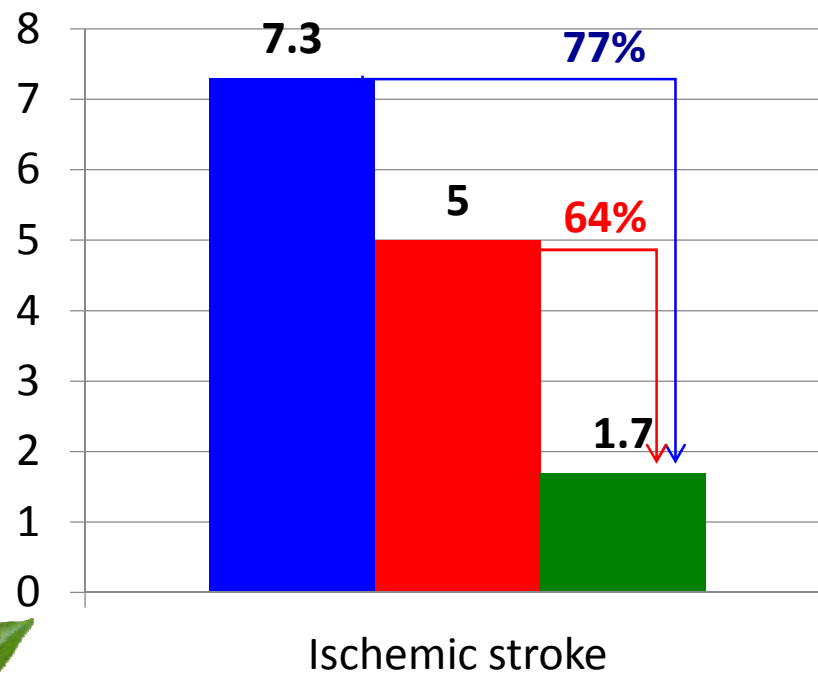
- 150 AF patients contraindicated for long-term warfarin therapy were included in the ASAP Registry
 - Average CHADS₂ = 2.8
 - Average CHA₂DS₂VASc score = 4.4
 - Mean age 72.5
 - Mean patient follow-up was 14.4 months

Most Studied LAAC Device

	PROTECT AF	CAP Registry	PREVAIL	CAP2 Registry	Totals
Enrollment	2005-2008	2008-2010	2010-2012	2012-2014	
Enrolled	800	566	461	579	2406
Randomized	707	---	407	---	1114
WATCHMAN: warfarin (2:1)	463 : 244	566	269 :138	579	1877: 382
Mean Follow- up (years)	4.0	3.7	2.2	0.58	N/A
Patient-years	2717	2022	860	332	5931



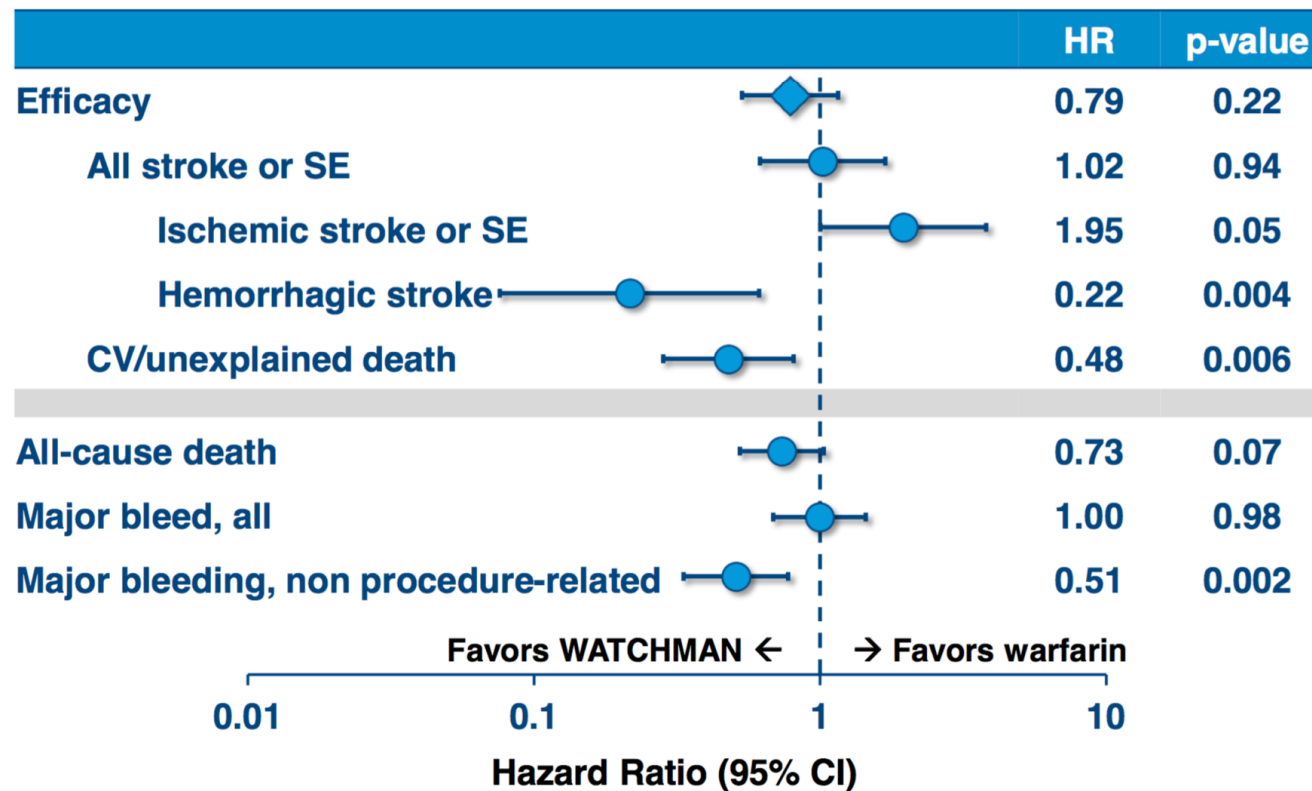
ASAP Registry



■ Expected
based on
CHADS score

PROTECT AF and PREVAIL Meta-Analysis: WATCHMAN Comparable to Warfarin

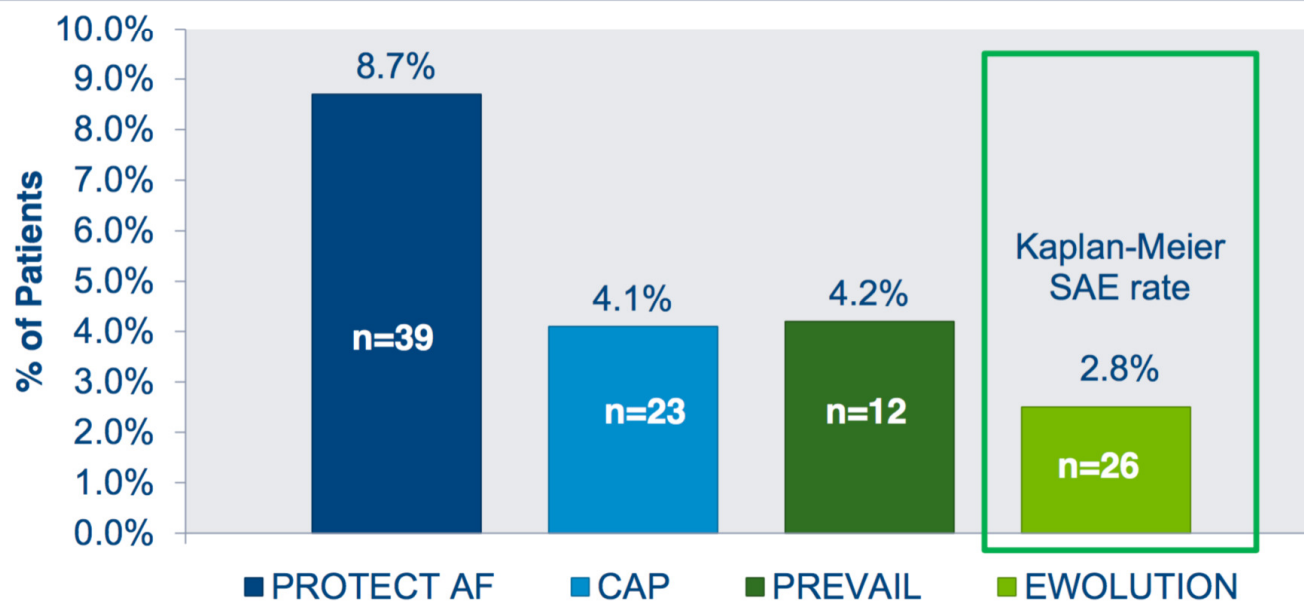
Boston
Scientific



All WATCHMAN studies: 7-Day Serious Procedure/Device Related



WATCHMAN™
LEFT ATRIAL APPENDAGE
CLOSURE DEVICE



Boston Scientific Confidential. For internal use only

Composite of vascular complications includes cardiac perforation, pericardial effusion with tamponade, ischemic stroke, device embolization, and other vascular complications including observed PE not necessitating intervention, AV fistula, major bleeding requiring transfusion, pseudoaneurysm, hematoma and groin bleeding

PROTECT AF/CAP: Reddy et al. *Circulation* 2011
PREVAIL: Holmes et al. *JACC* 2014.
Boersma L et al. *AHA* (2015)

stitute

Conclusion – last slide



The NOACs

Medication	Trial	FDA Approval
Dabigatran (Pradaxa)	RE-LY	October 19, 2010
Rivaroxaban (Xarelto)	ROCKET-AF	November 4, 2011
Apixaban (Eliquis)	ARISTOTLE AVERROES	December 28, 2012
Edoxaban (Savaysa)	ENGAGE-AF-TIMI 48	January 8, 2015

NOACs: Clinical Challenges

- No validated tests of anticoagulation intensity
- No established therapeutic range
- No confirmation of adherence
- One antidote available, others on the way.
- No long-term safety data
- **Requirement for CrCL monitoring**
- Limited cardioversion/ablation experience
- **Uncertain bridging/discontinuation information**
- Complex pharmacology
- ***No head-to-head trials***

HAS-BLED Score

	Clinical Characteristic	Score
H	Hypertension	1
A	Abnormal renal or liver function (1 each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Elderly age	1
D	Drugs or alcohol (1 each)	1 or 2
Maximum Score		9

Hypertension: SBP > 160 mmHg; Abnormal renal function: Chronic dialysis, renal transplant, serum creatinine $\geq 200\mu\text{mol/L}$; Abnormal liver function: Chronic hepatitis, bilirubin > 2x upper limit of normal (ULN) in association with AST/ALT/ALP > 3 x ULN; Bleeding: Previous history, predisposition; Labile INRs: unstable/high INRs, in therapeutic range < 60%; Age > 65 years; Drugs/alcohol: Concomitant use of antiplatelet agents, non-steroidal anti-inflammatory drugs, etc.



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Pisters R, et al. *Chest*, 2010;138:1093-100



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HAS-BLED

Bleeding Risk Classifications

Score	Bleeding Risk Classification (% bleeds per 100 patient-years)
0-1	Low Risk (1.1%)
2	Intermediate Risk (1.9%)
≥ 3	High Risk (4.9%)

The Dilemma

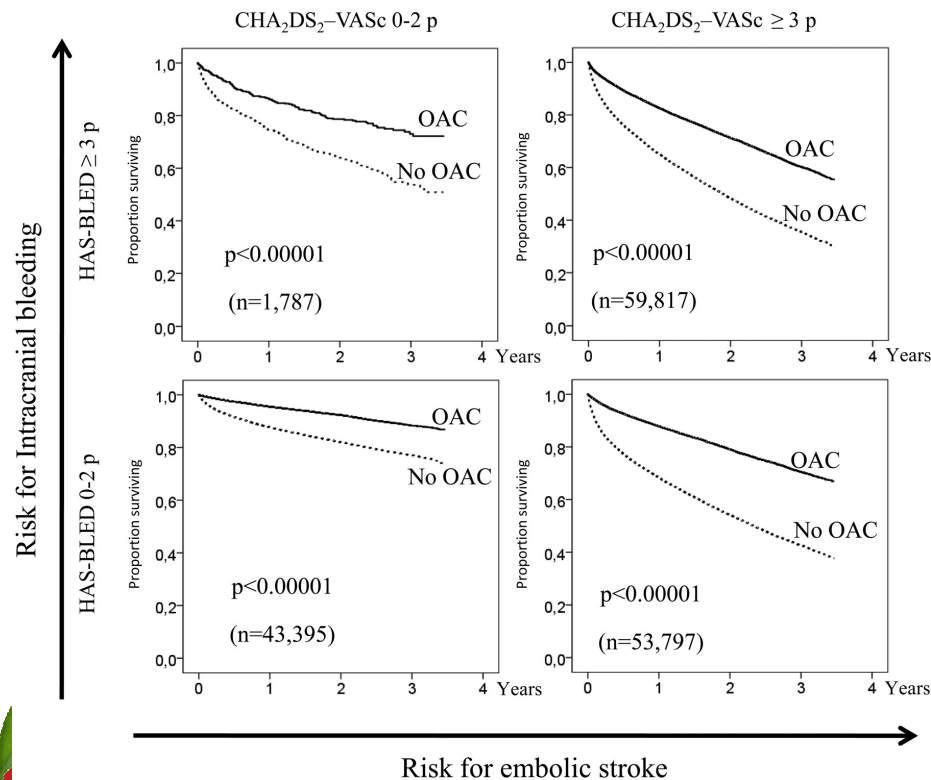
HAS-BLED

Clinical Characteristic	Score
Hypertension	1
Abnormal renal/liver function	1 or 2
Stroke	1
Bleeding	1
Labile INR	1
Elderly age	1
Drugs or alcohol (1 each)	1 or 2

CHA₂DS₂VASc

Clinical Characteristic	Score
Congestive Heart Failure	1
Hypertension	1
Age > 75	2
Diabetes	1
Stroke/TIA	2
Vascular Disease	1
Age > 65	1
Sex (female gender)	1

Net Clinical Benefit of Warfarin in AF



"In almost all patients with AF, the risk of ischemic stroke without OAC treatment is far higher than the risk of ICH with OAC."

CHA₂DS₂-VASc score was more sensitive than the CHADS₂ score in identifying patients who were 'truly low risk' in whom anticoagulation may be associated with a net disadvantage

CLINICIAN UPDATE



Use of the CHA₂DS₂-VASc and HAS-BLED Scores to Aid Decision Making for Thromboprophylaxis in Nonvalvular Atrial Fibrillation

Deirdre A. Lane, PhD; Gregory Y.H. Lip, MD

“HAS-BLED should not be used as an excuse not to prescribe anticoagulation, but rather to highlight those patients in whom caution with such treatment and regular review is warranted”

– Circulation 2012;126:860



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2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

January CT et al. *Circulation* 2014; 130: e199-e267

Antithrombotic therapy based on shared decision-making, discussion of risks of stroke and bleeding, and patient's preferences

CHA₂DS₂-VASc score recommended to assess stroke risk

Warfarin recommended with mechanical heart valves.
Target INR intensity should be based on the type and location of prosthesis

If end-stage CKD (CrCl<15 mL/min) or on hemodialysis, it is reasonable to prescribe warfarin for OAC [NOACs not recommended]

CHA₂DS₂-VASc ≥2

OAC, either VKA or NOAC (Class I)

CHA₂DS₂-VASc=1

No antithrombotic therapy, OAC, or aspirin (Class IIb)

CHA₂DS₂-VASc=0

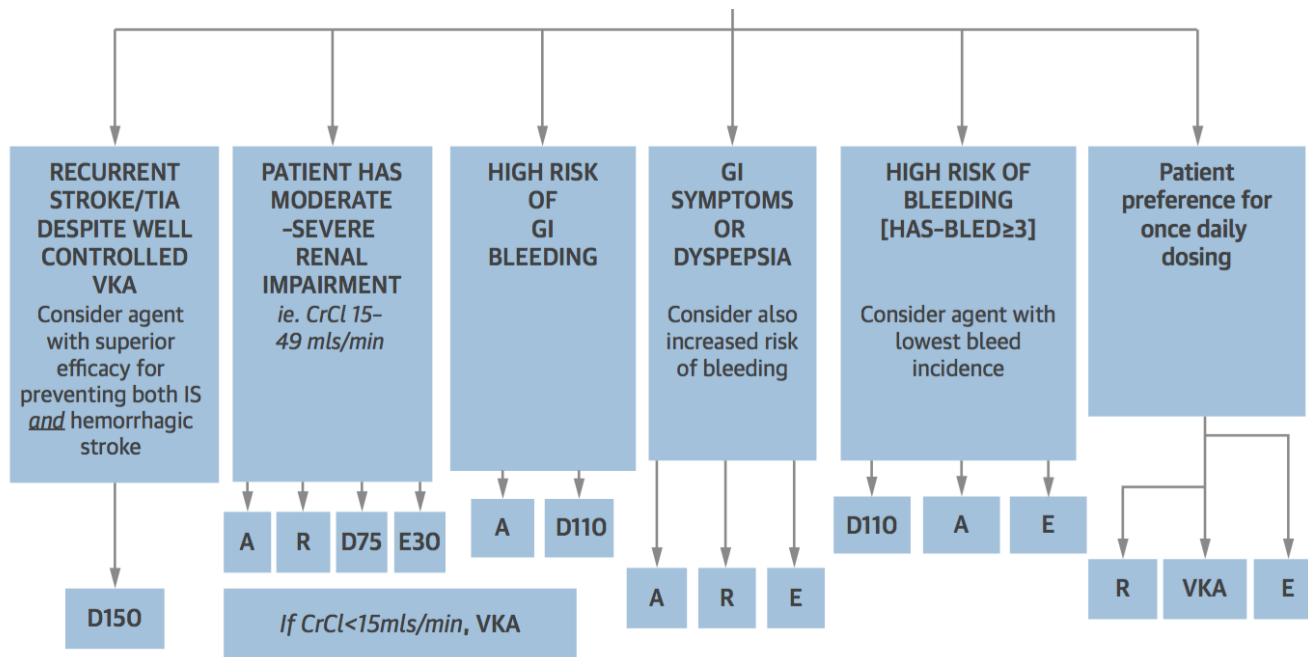
No antithrombotic Rx (Class IIa)

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Choose the OAC considering the patient profile and/or preferences



A = apixaban

D = dabigatran

E = edoxaban

R = rivaroxaban

VKA = vitamin K antagonist

Lip GYH and Lane DA *JACC* 2015;66(21):2282-4

Thank You



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Low use of AC

References

1Hsu J, Maddox T, Kennedy T, et al. Oral anticoagulant therapy prescription in patients with atrial fibrillation across the spectrum of stroke risk. Insights from the NCDR RINNACLE registry. *JAMA Cardiol* 2016;

DOI:10.1001/jamacardio.2015.0374. [Article](#)

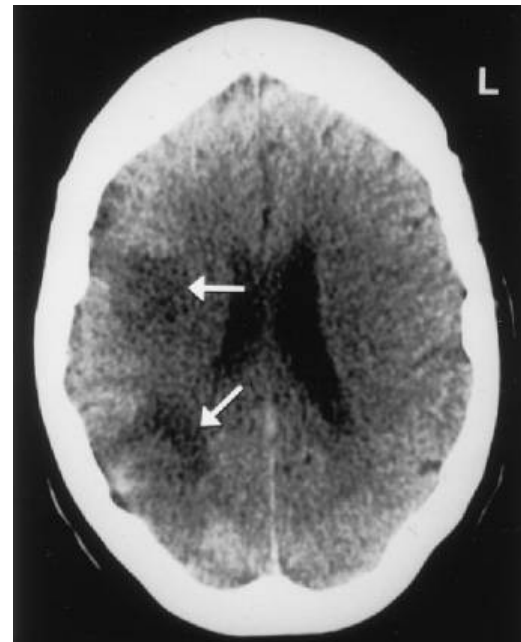
2Piccini Sr J, Fonarow G. Preventing stroke in patients with atrial fibrillation—a steep climb away from achieving peak performance. *JAMA Cardiol* 2016;

DOI:10.1001/jamacardio.2015.0374. [Editorial](#)



Atrial Fibrillation and Stroke

- Atrial fibrillation is responsible for 1/5 strokes
- In the US between 75,000 and 95,000 strokes per year are caused by atrial fibrillation



Hart, Halperin 2001
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- From 6252 citations, they used 12 published studies (10 randomized controlled trials [RCTs] or pooled RCTs and two prospective observational cohort studies) with almost 100,000 patients for their analysis.
- The pooled unadjusted estimate for the risk of thromboembolism in NPAF patients was 2.2% annually (95% CI 1.81%–2.53%) vs 1.5% annually (95% CI 1.23%–1.76%) in PAF patients. This translated to a 36% higher risk of thromboembolism in NPAF relative to PAF (HR 1.36, 95% CI 1.17–1.57; $P<0.001$), a difference that persisted in an analysis adjusted for other variables.
- The authors found similar relationships with all-cause mortality. Using six of the 12 studies (45,570 patients) that reported mortality, the pooled unadjusted estimate for mortality rate in NPAF was 3.9% per year (95% CI 3.04%–4.74%) vs 2.8% per year (95% CI 2.11%–3.47%). This led to a 46% higher mortality rate for NPAF relative to PAF. After adjustment for risk factors, the mortality risk in NPAF was 22% higher relative to PAF (HR 1.22, 95% CI 1.09–1.37; $P<0.001$).
- Bleeding rates did not differ between NPAF and PAF patients.
- In secondary analyses, the authors explored the effect of oral anticoagulant (OAC) treatment in the two types of AF. In three studies that did not include patients on OAC, the relative risk of thromboembolism in NPAF vs PAF was 1.69 (95% CI 1.15–2.48, $P=0.007$). In five studies where all patients received OAC (either warfarin or a new OAC), the unadjusted RR of stroke or systemic embolism in NPAF vs PAF was 1.27 (95% CI 1.15–1.41, $P<0.001$).



Ganesan AN, Chew DP, Hartshorne T, et al. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: A systematic review and meta-analysis. *Eur Heart J* 2016; DOI:10.1093/eurheartj/ehw007. <https://doi.org/10.1093/eurheartj/ehw007>. Abstract available at www.all heart.org.



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Patient Risk Factors Across Trials

Characteristic	PROTECT AF N=707	CAP N=566	PREVAIL N=407	CAP2 N=579	p-value
CHADS ₂ Score	2.2 ± 1.2	2.5 ± 1.2	2.6 ± 1.0	2.7 ± 1.1	<0.0001
CHADS ₂ Risk Factors (% of Patients)					
CHF	26.9	23.3	19.1	27.1	0.004
Hypertension	89.8	91.4	88.8	92.5	0.15
Age ≥ 75	43.1	53.6	51.8	59.7	<0.001
Diabetes	26.2	32.4	24.9	33.7	0.001
Stroke/TIA	18.5	27.8	30.4	29.0	<0.0001
CHA ₂ DS ₂ -VASc	3.5 ± 1.6	3.9 ± 1.5	4.0 ± 1.2	4.5 ± 1.3	<0.0001

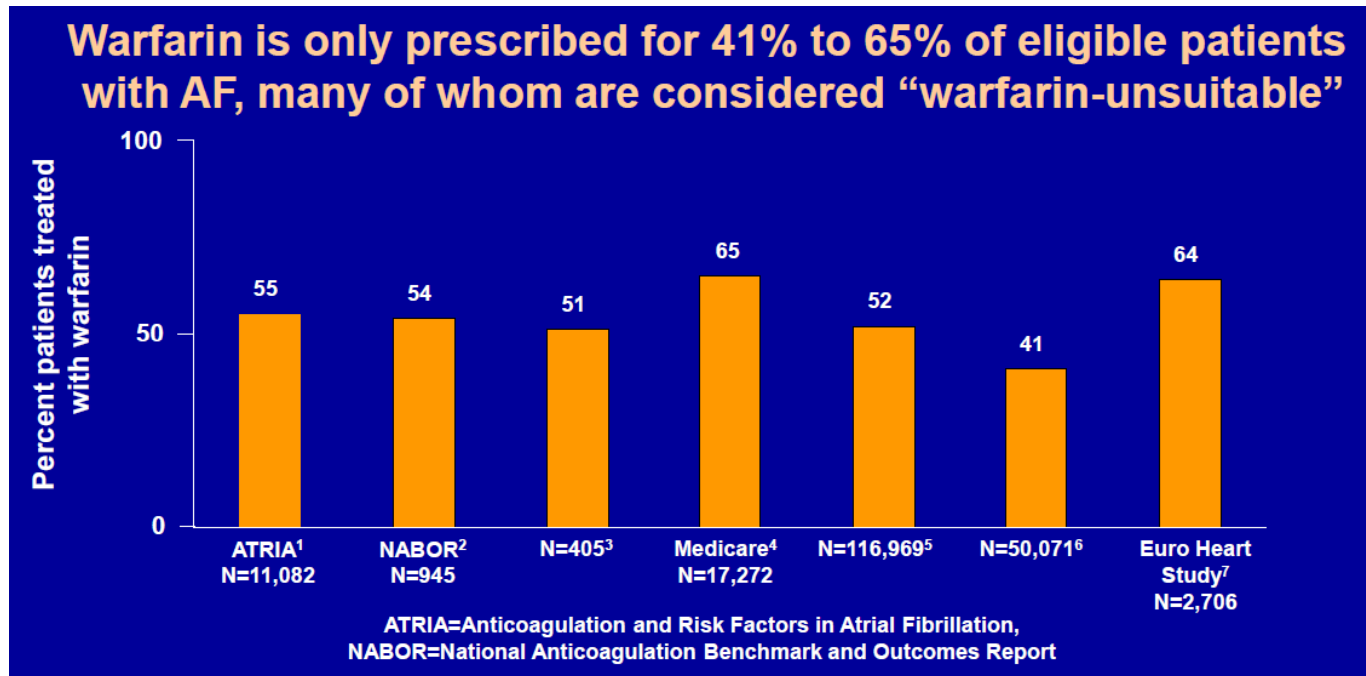


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Eligible AF Patients Receiving Warfarin Therapy



1. Go AS et al. *Ann Intern Med.* 1999;131:927-934.

2. Waldo AL et al. *J Am Coll Cardiol.* 2005;46:1729.

3. Hylek EM et al. *Stroke.* 2006;37:1075-1080.

4. Boriani G et al. *Stroke.* 2006;37:1070-1074.

5. Walker AM, Bennett D. *Heart Rhythm* 2008;5:1365.

6. Williams CJ et al. American College of Cardiology 58th Annual Scientific Session; March 29-31, 2009.

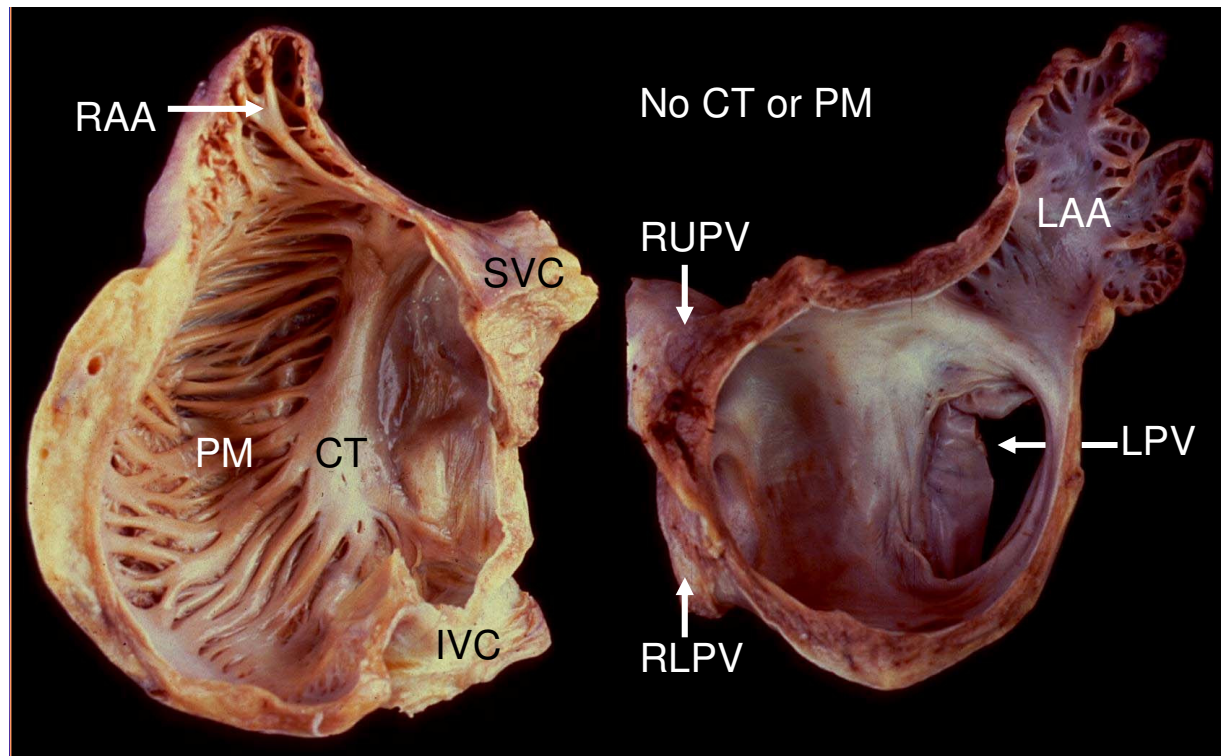
7. Nieuwlaat R et al. *Eur Heart J.* 2006;27:3018-3026.

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One Heart at a Time

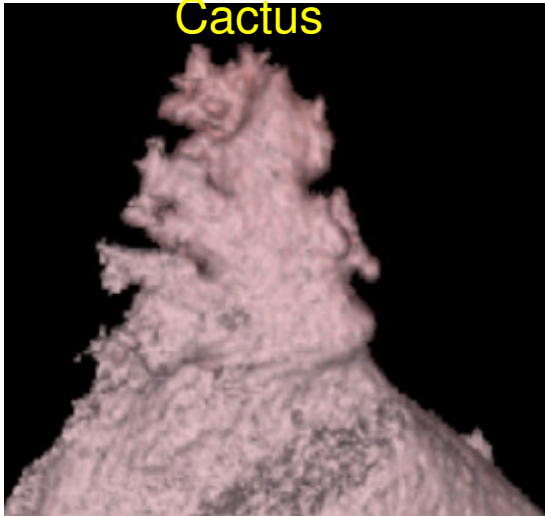
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oklahoma heart

Right Atrium

Left Atrium



Cactus



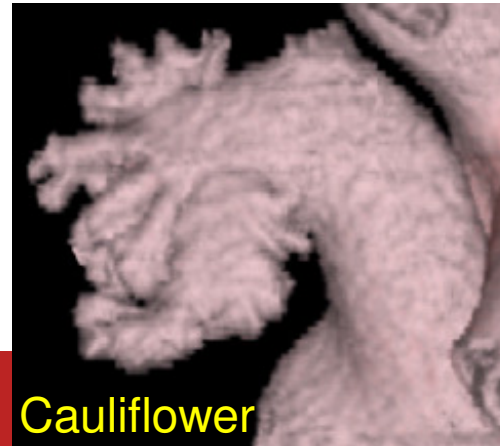
Chicken Wing



Windsock

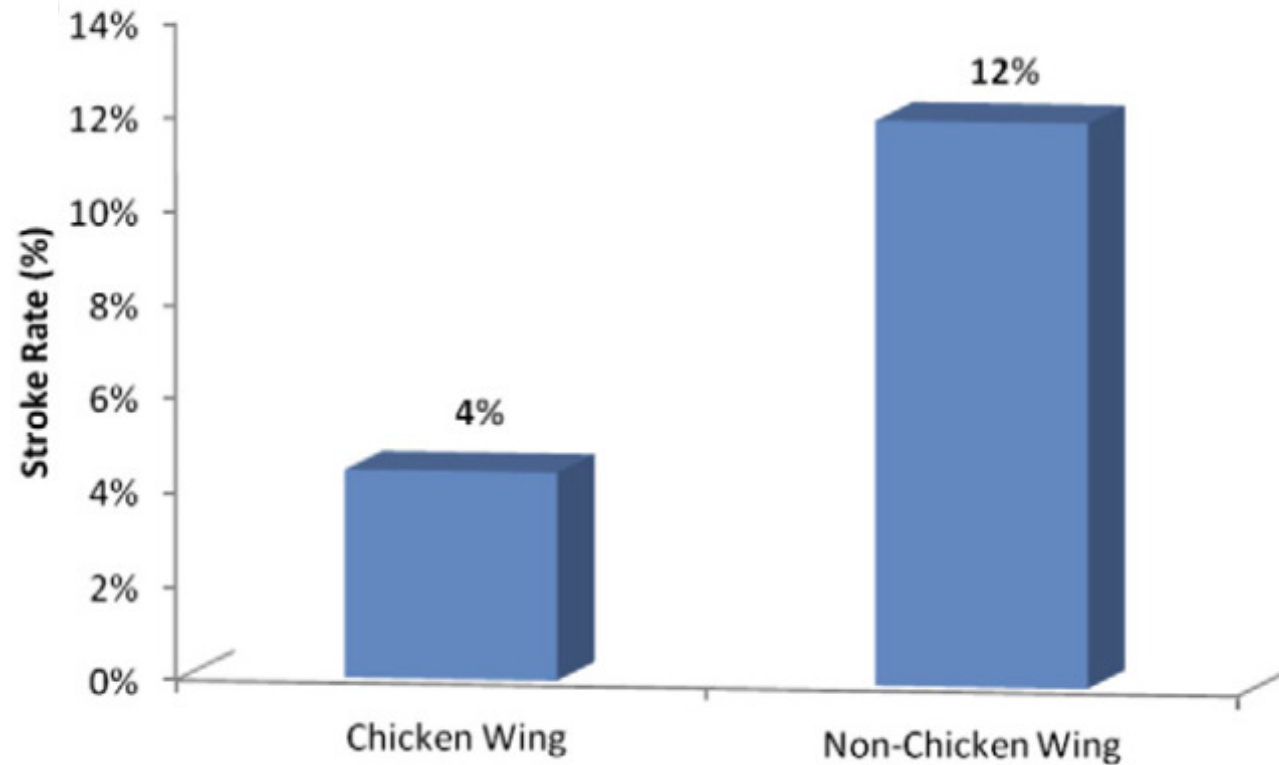


Cauliflower



Di Biase L et al.
Circulation 2012 Aug
125(8):e115-23.
doi:10.1161/CIRCULATION.111.211111

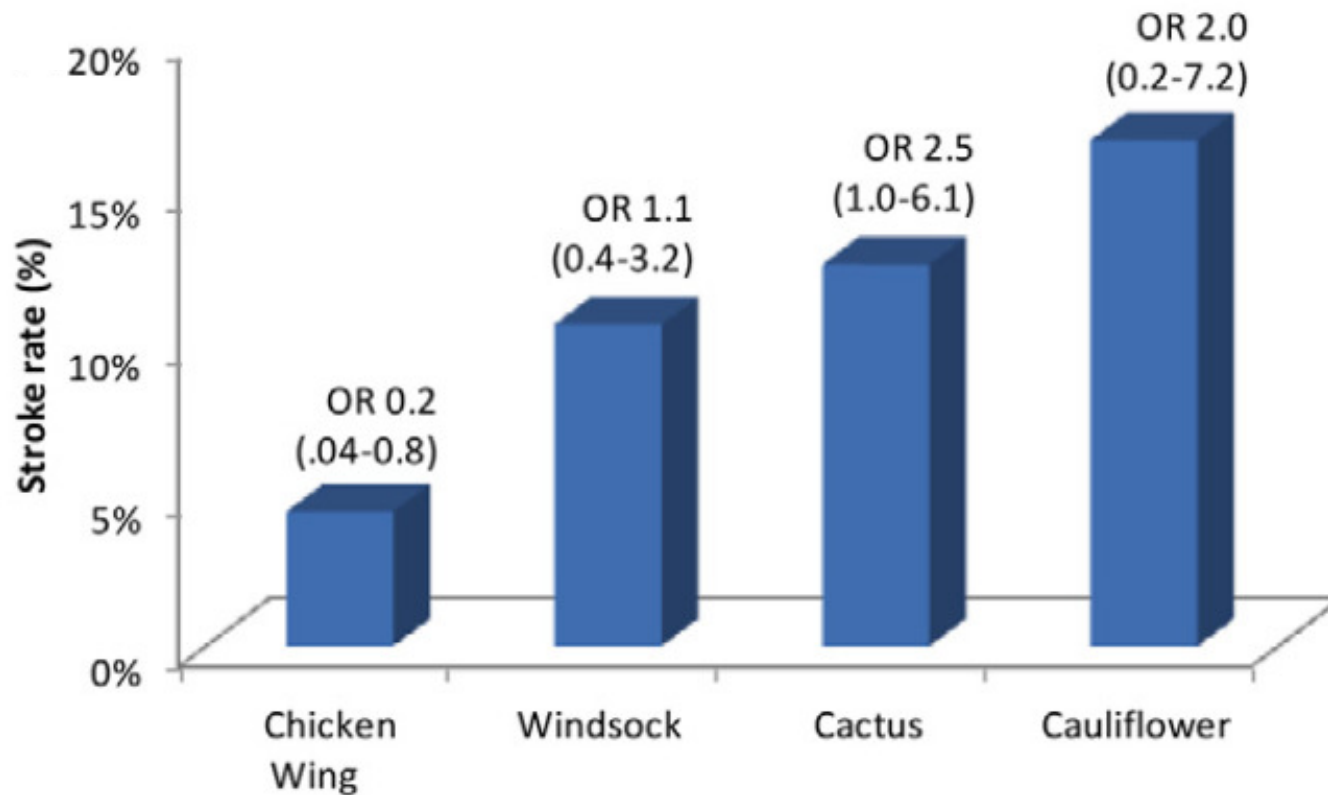
LAA Morphology and Risk of Stroke



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Di Biase L et al. JACC 2012 Aug 7;60(6):531-8. Oklahoma Heart Institute

LAA Morphology and Risk of Stroke



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Di Biase L et al. JACC 2012 Aug 7;60(6):531-8.

Importance of Left Atrial Appendage



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Blackshear, Odel. Ann Thorac Surg. 1996;61:755-759.

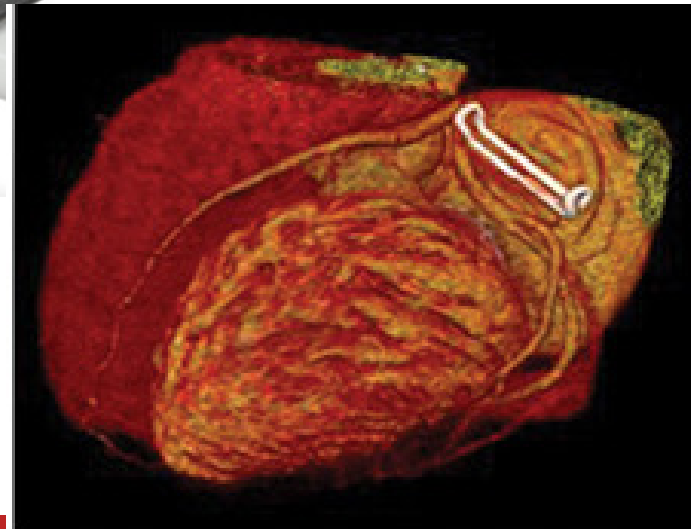


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Minimally Invasive Surgical LAA Exclusion

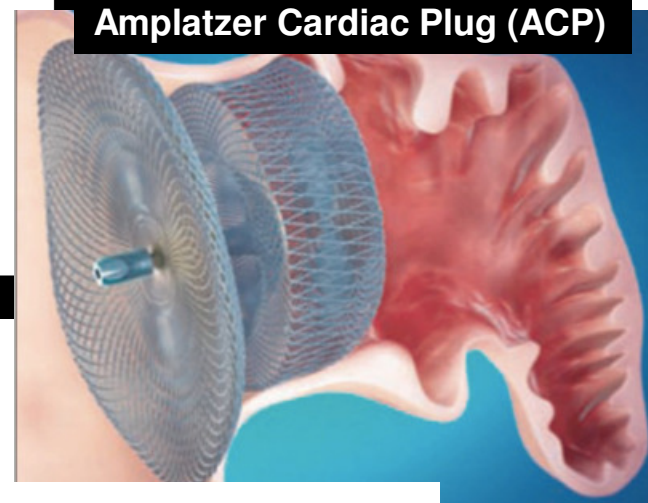
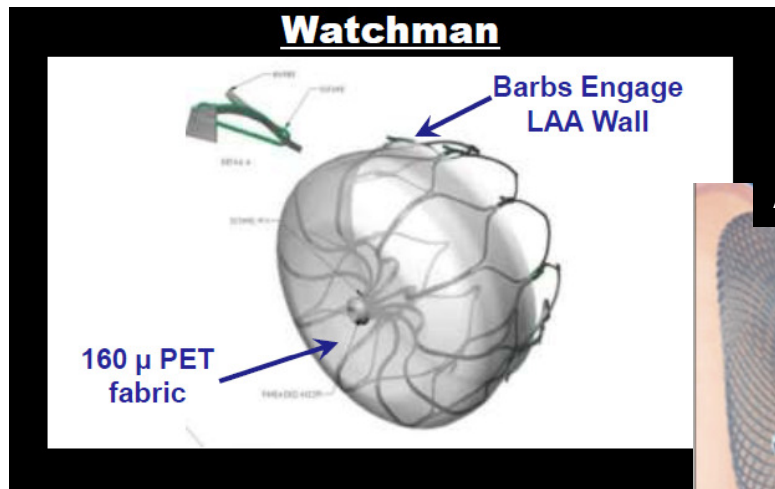
AtriCure Gets FDA OK for its AtriClip Device

Filed under: [Cardiac Surgery](#), [Cardiology](#), [Surgery](#)



CT confirmation scan

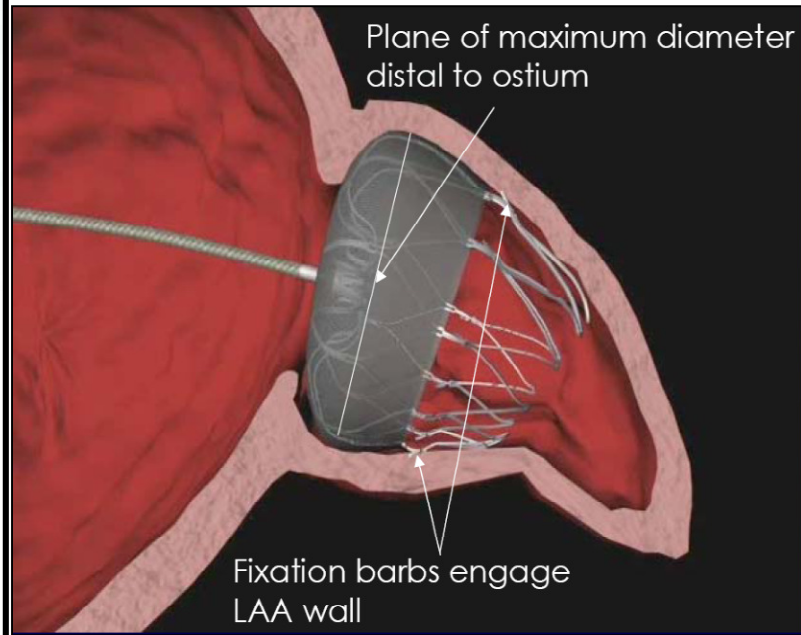
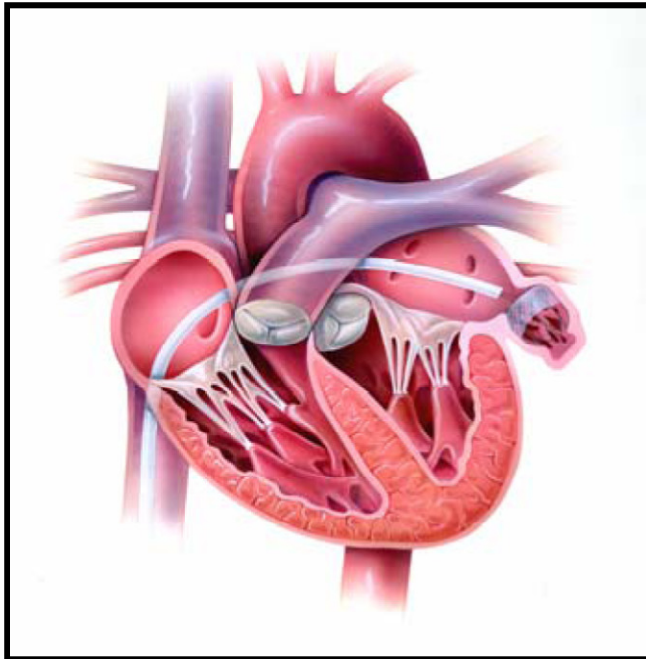
Percutaneous LAA Exclusion



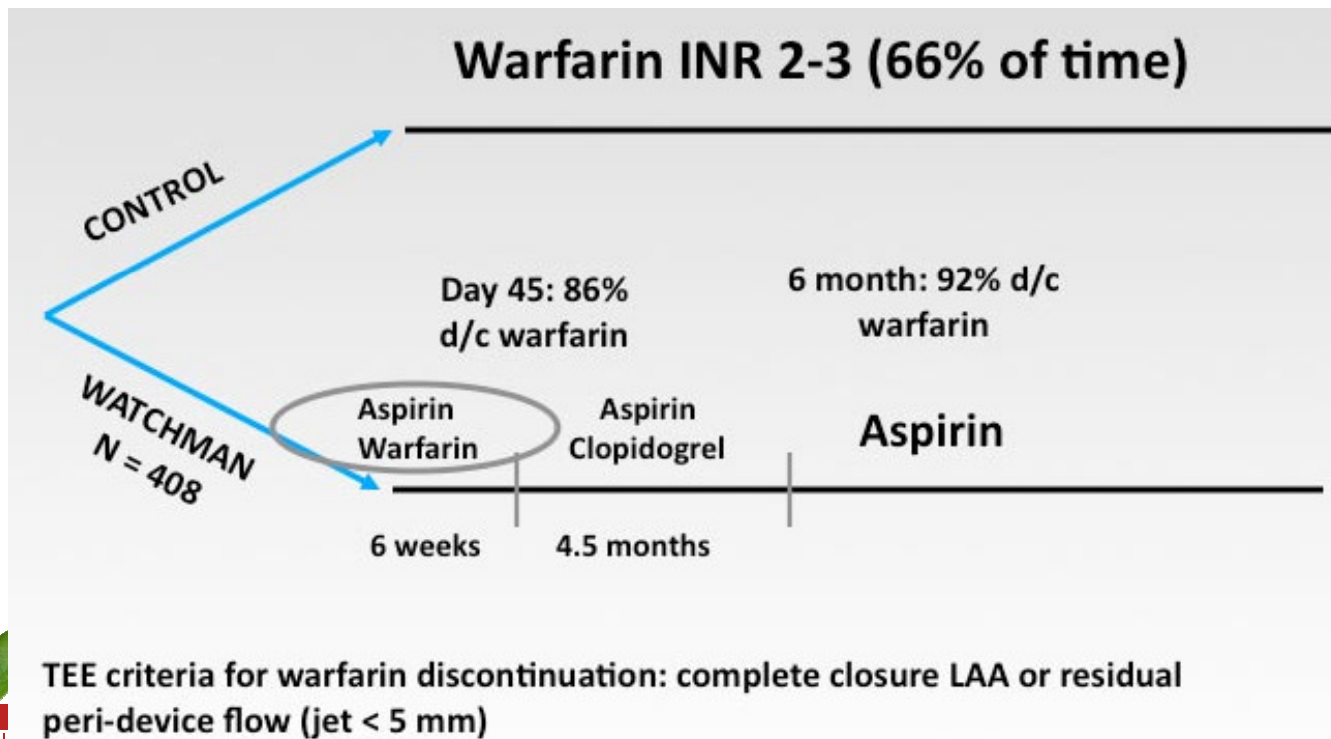
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Watchman Device

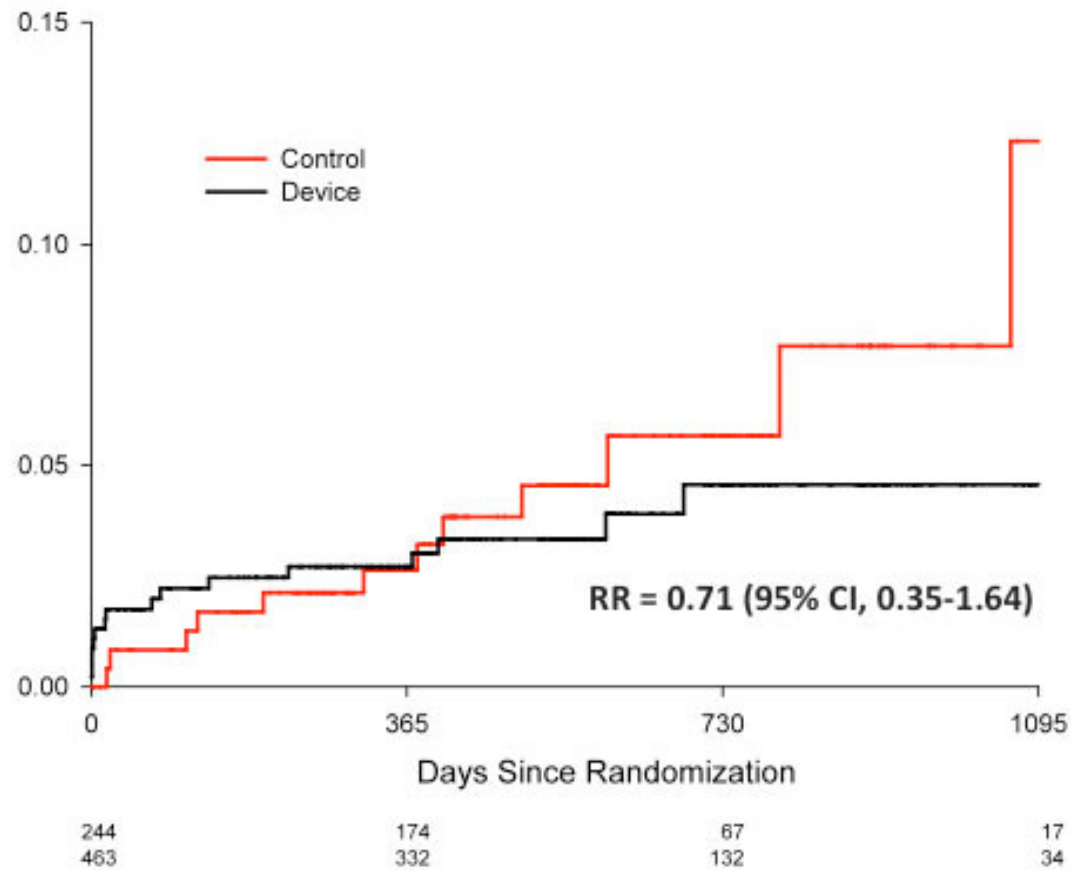
Endocardial Left Atrial Appendage Exclusion



PROTECT-AF: Methods



PROTECT-AF: All Stroke

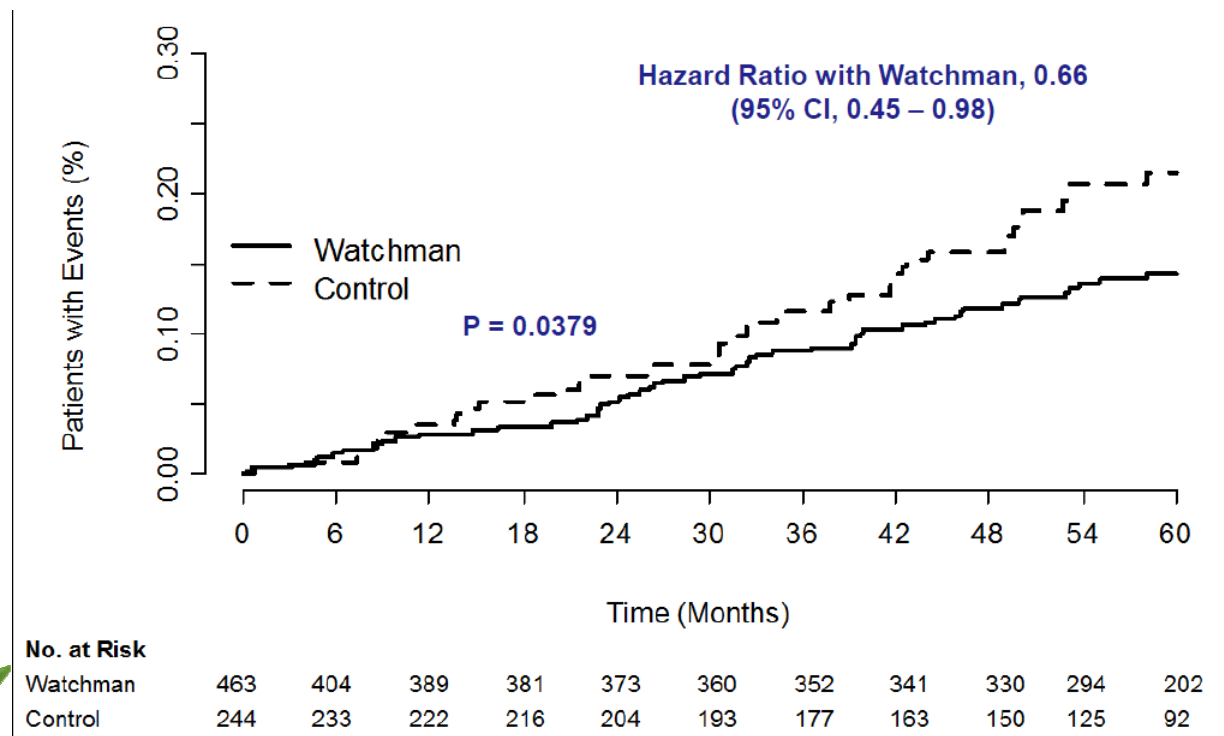


Cha
Live
@ H10

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Longterm Results of PROTECT-AF

All-Cause Mortality



Longterm Results of PROTECT-AF

Conclusions

- The LAA is critical to the pathogenesis of stroke
- “Local” therapy with Watchman is superior to Warfarin
 - 40% reduction of stroke / systemic embolism / CV death
 - 60% reduction in Cardiovascular Mortality
 - 34% reduction in All-Cause Mortality
- Safety event rate similar, but bimodal distribution
- Event rate diminishes with operator experience
 - 2.2% (CAP Registry)
 - 1.9% (PREVAIL: 40% New Operators)

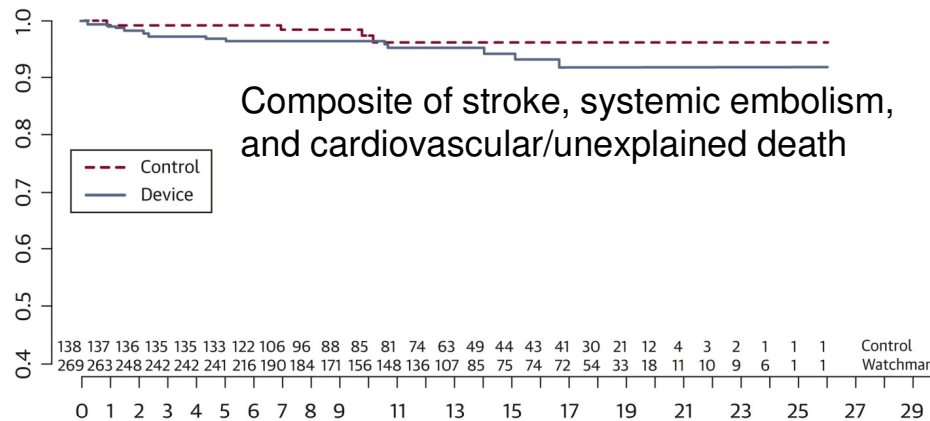
Rationale for PREVAIL

- Concerns with early PROTECT AF safety results
 - High initial rate of pericardial effusions and procedure related strokes
 - Some WATCHMAN patients did not receive their assigned treatment (i.e., implant failures)
 - Safety outcome of procedures performed by new operators
- CAP study demonstrated improved outcomes with operator experience
- Second randomized trial to confirm late PROTECT AF and CAP safety results (PREVAIL)

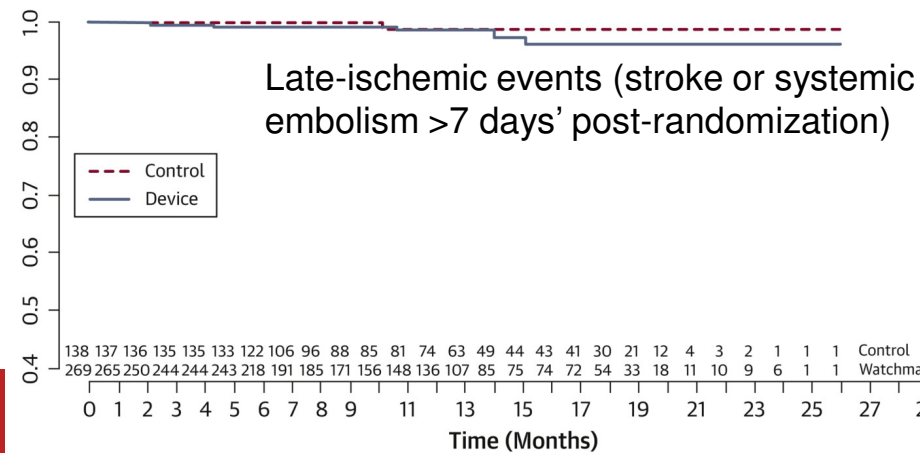
PREVAIL Trial

- 407 patients randomized (2:1) to either LAA closure or warfarin therapy
 - 25% treated by new operators
- Preliminary results:
 - 95.1% implant success
 - Achieved safety endpoints
 - 4.4% vascular complication rate
 - Watchman achieved two of three primary efficacy endpoints despite over-performing control (Warfarin) group.

PREVAIL Trial



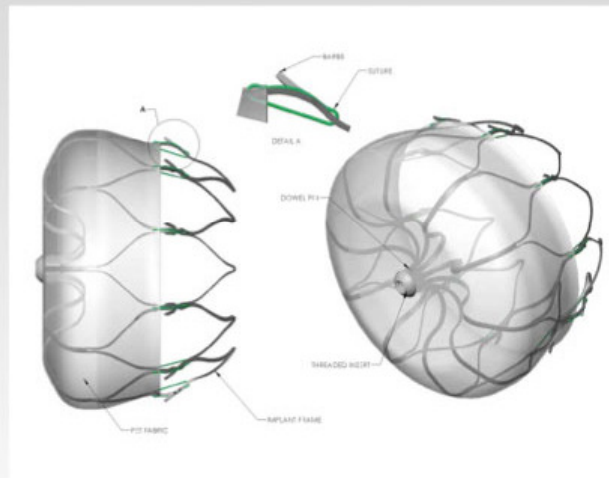
Time (Months)



Time (Months)

Await Watchman Approval

Watchman® LAA Closure Device



This is an investigational device.

An FDA advisory panel recommended approval on 4/24/09.

In March 2010, the FDA requested that a confirmatory study be conducted to further substantiate the safety and efficacy of this device.

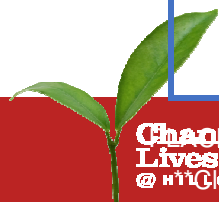
Await Watchman Approval

“In 2010 [the FDA issued a complete response letter](#) following the first advisory panel. Last year a scandal broke out when [the American College of Cardiology cancelled a prestigious late-breaking clinical trial presentation of the PREVAIL trial](#) after the company broke an embargo by giving trial results to investors. Last December the FDA’s Circulatory System Devices Panel [voted 13-1 in favor of the device](#), but as I reported at the time the lopsided vote did not provide a full indication of lingering concerns about the device by panel members. In particular, panel members repeatedly expressed concern about the potential for overuse of the device. They also had trouble interpreting the major clinical trials with the device. A date has not yet set a date for the third panel. The company now anticipates approval of Watchman in the first half of 2015.”



Efficacy = Closed

# Pts			
Intent-to-Treat			
Acute Closure			
30d Closure			
90d Closure			
ONE Year Closure			
Access Requirement			



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@ 11108887 = ≤ 1mm

Safety & Efficacy Study, JACC 2012


|| Closure defined as “complete” would = 71%
 * Retrospective analysis of Registry data - No closure data included



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Safety

	Device Related	Other Complications	All
LARIAT ^I			
Watchman ^{II}			
Amplatzer ^{III}			
 Changing Lives @ HHS n=125 Registry	PA Puncture	1 (0.9%)	

Lariat

Watchman

- No anticoagulation
- No prior cardiac surgery
- LAA anatomy restrictions
- Data?



Lariat Candidates

- AF Patients at risk for thromboembolic complications ($\text{CHADS}_2 \geq 1$) who are unable to take chronic anticoagulation
 - No prior cardiac surgery
 - Anatomy appropriate for device (as determined by CT angiography)
 - Widest point of LAA < 4 cm
 - LAA not behind pulmonary artery
 - No thrombus within left atrial appendage at time of procedure



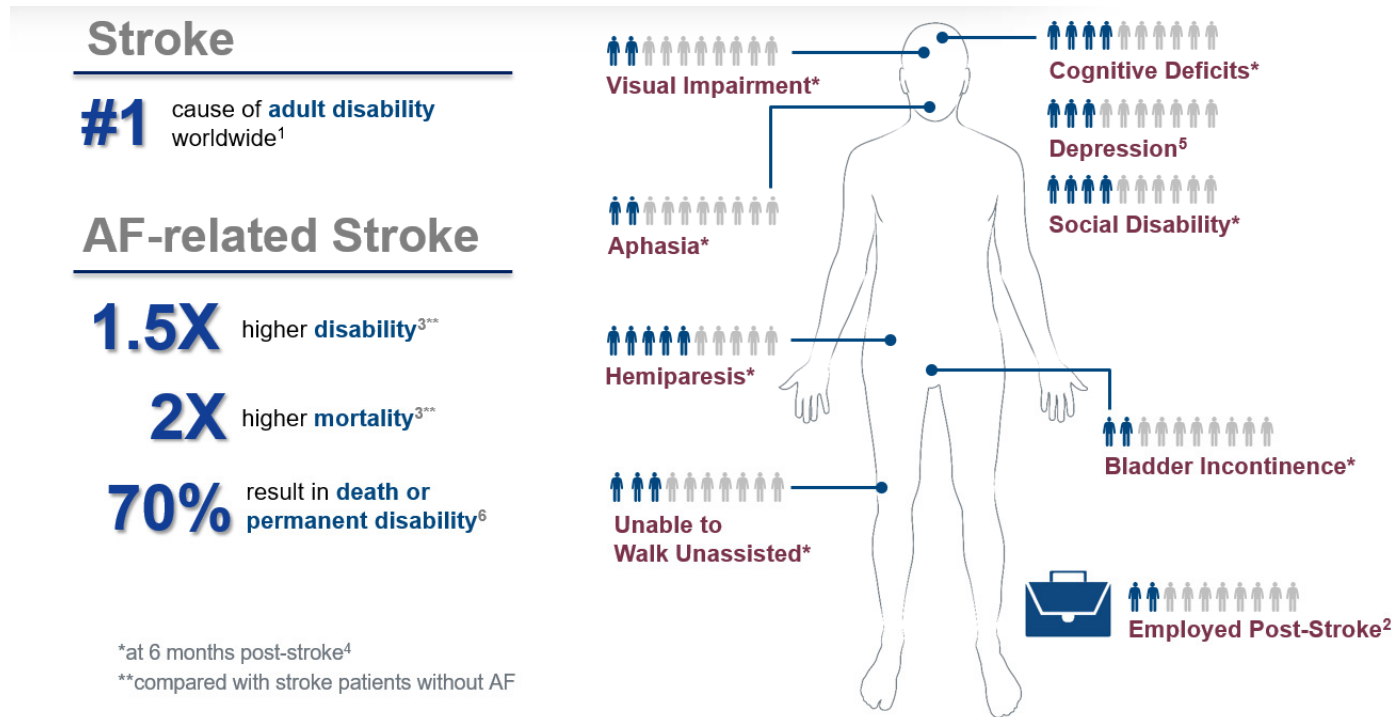
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Anticoagulation only required during transseptal catheterization



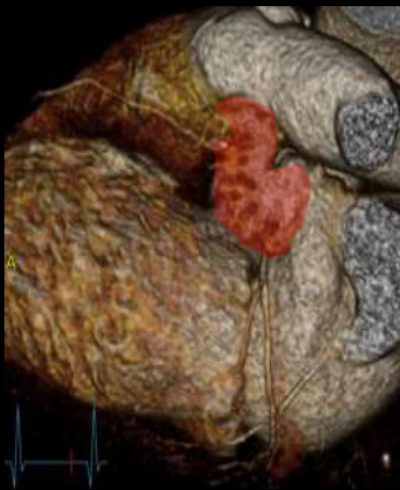
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AF related strokes are debilitating

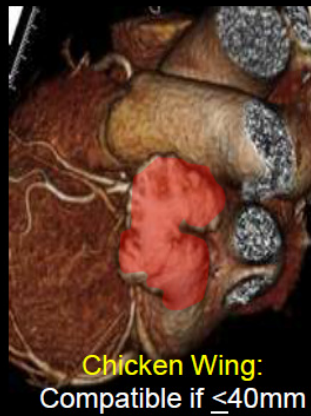


¹Chee and Tan. *Med J Malaysia* 69.3 (2014): 119-23. ²Sreedharan et al. *Journ of the neurological sciences* 332.1 (2013): 97-101. ³Lamassa et al. *Stroke* 32.2 (2001): 392-398. ⁴Kelly-Hayes et al. *Journ of Stroke and Cerebrovascular Diseases* 12.3 (2003): 119-126. ⁵Loo and Gan. *International Journ of Stroke* 7.2 (2012): 165-167. ⁶Holmes DR. *Seminars in Neurology* 2010;30:528-536.

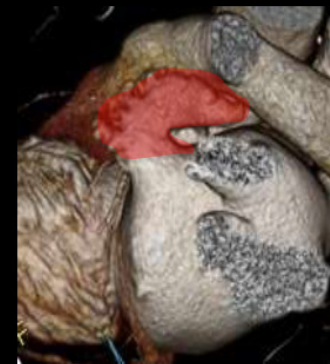
Pre-Screening



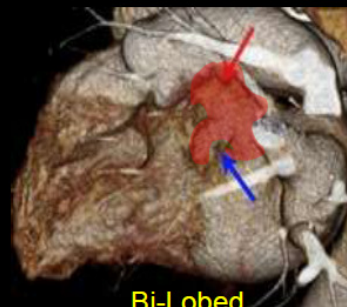
Typical
Compatible if $\leq 40\text{mm}$



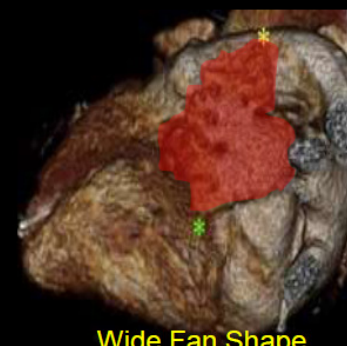
Chicken Wing:
Compatible if $\leq 40\text{mm}$



Not Compatible



Bi-Lobed
Compatible if $\leq 40\text{mm}$



Wide Fan Shape
Compatible if $\leq 40\text{mm}$

Site of Thrombus in Atrial Fibrillation

Non-Rheumatic

Setting	No. of Patients	LA Appendage	LA Cavity
TEE ^a	317	66	1
TEE	233	34	1
Autopsy	506	35	12
TEE	52	2	2
TEE	48	12	1
TEE and Operation	171	8	3
SPAF III TEE Study	359	19	1
TEE	272	19	0
TEE	60	6	0
Total	1,288	201	21

90%

Blackshear JL and Odell JA. AnnThorac Surg 1996;61:755