Growth and Importance of Transcatheter Left Atrial Appendage Closure in AF

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DISCLOSURE STATEMENT OF FINANCIAL INTEREST

In the past 12 months, I or my spouse/partner has had a financial interest/arrangement with the organization(s) listed below.

BSCI

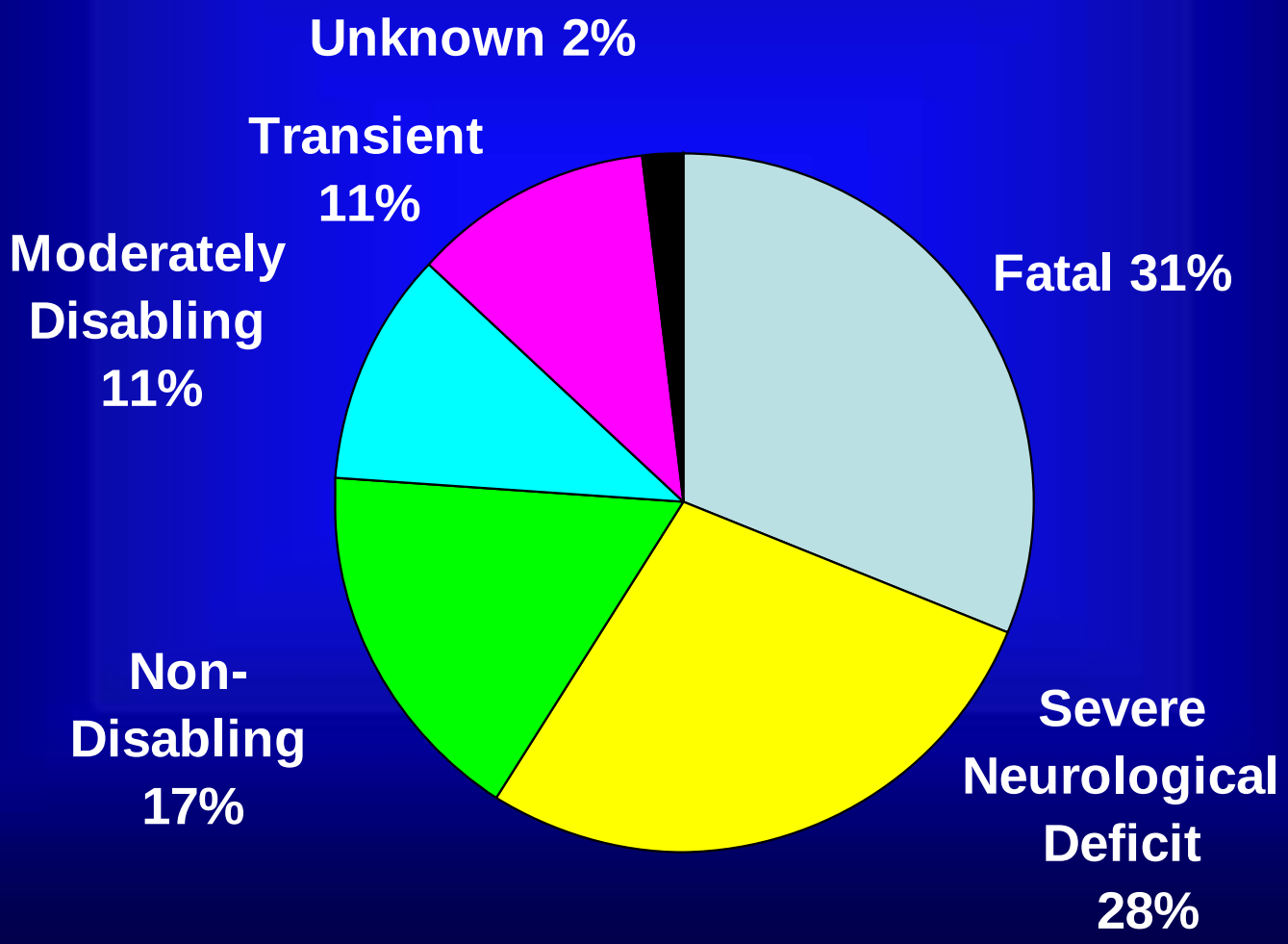
- Scientific Advisory Board Member
- Speaker Bureau
- Equity Ownership

Facts about Atrial Fibrillation (AF)

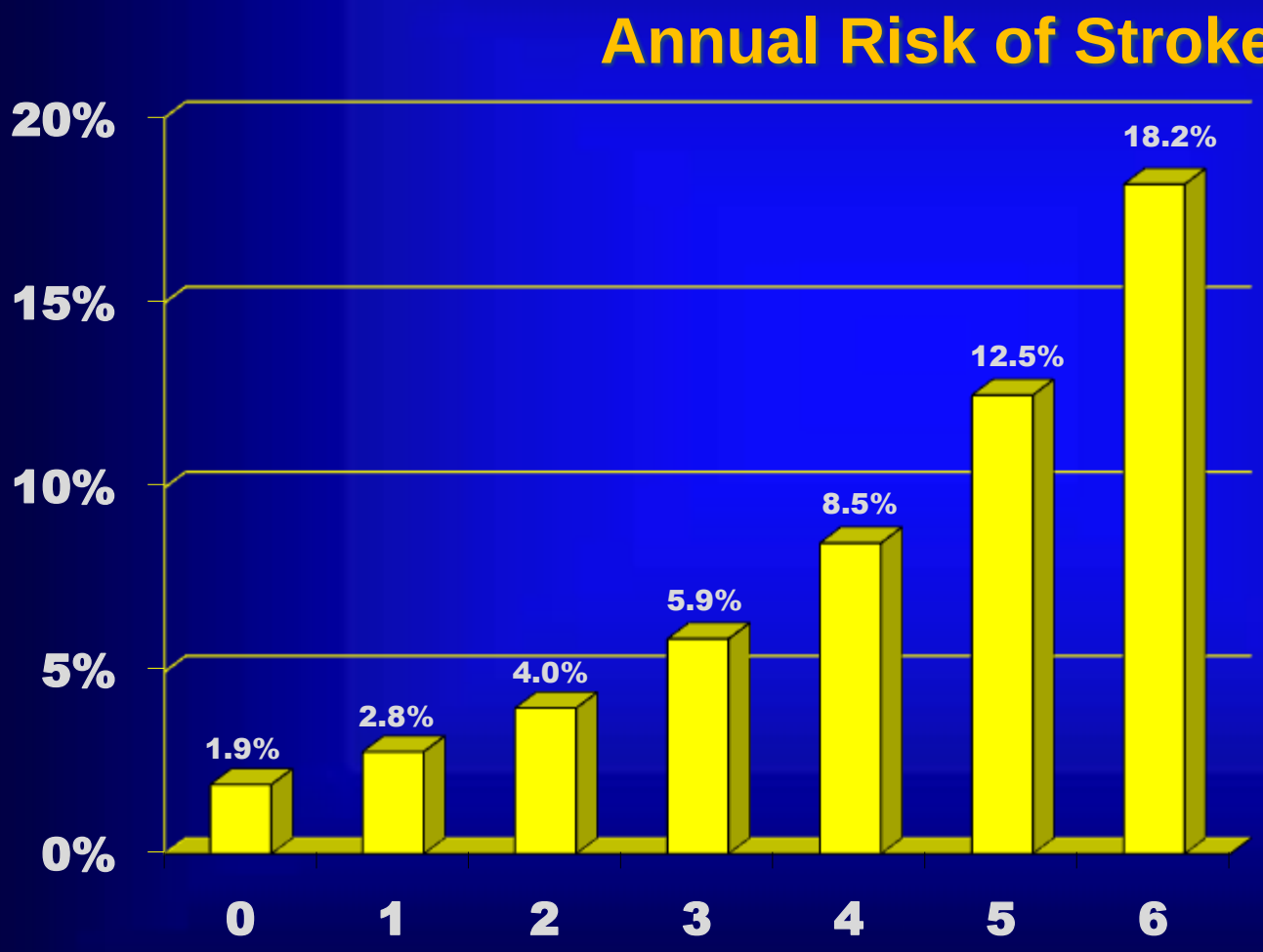
- AF is the most common cardiac arrhythmia
  - Affecting more than 3 million individuals in the US
  - Projected to increase to 16 million by 2020
- Stroke is the number one cause of long-term disability and the third leading cause of death in patients with AF

Stroke: A Life Threatening and Debilitating Disease

Functional impact of AF-related strokes



CHADS2 Score and Stroke Rate



Score	$CHADS_2$ Risk Criteria
1 point	Congestive heart failure
1 point	Hypertension
1 point	Age >75 years
1 point	Diabetes mellitus
2 points	Stroke/transient ischemic attack

Adapted from Gage et al, JAMA 2001;285:2864–2870

CHA2DS2-VASc

- **2010 ESC AF Guidelines now call for use of CHA2DS2-VASc score**
- **Recommend oral anticoagulation for score 2 or greater and either anticoagulation or aspirin for score =1**

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%

Camm et al, European Heart Journal doi:10.1093/eurheartj/ehq278

Anticoagulation and Bleeding

"An assessment of bleeding risk should be part of the patient assessment before starting anticoagulation ... It would seem reasonable to use the HAS-BLED score to assess bleeding risk in AF patients, whereby a score of ≥3 indicates 'high risk', and some caution and regular review of the patient is needed following the initiation of antithrombotic therapy,whether with VKA or aspirin."

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

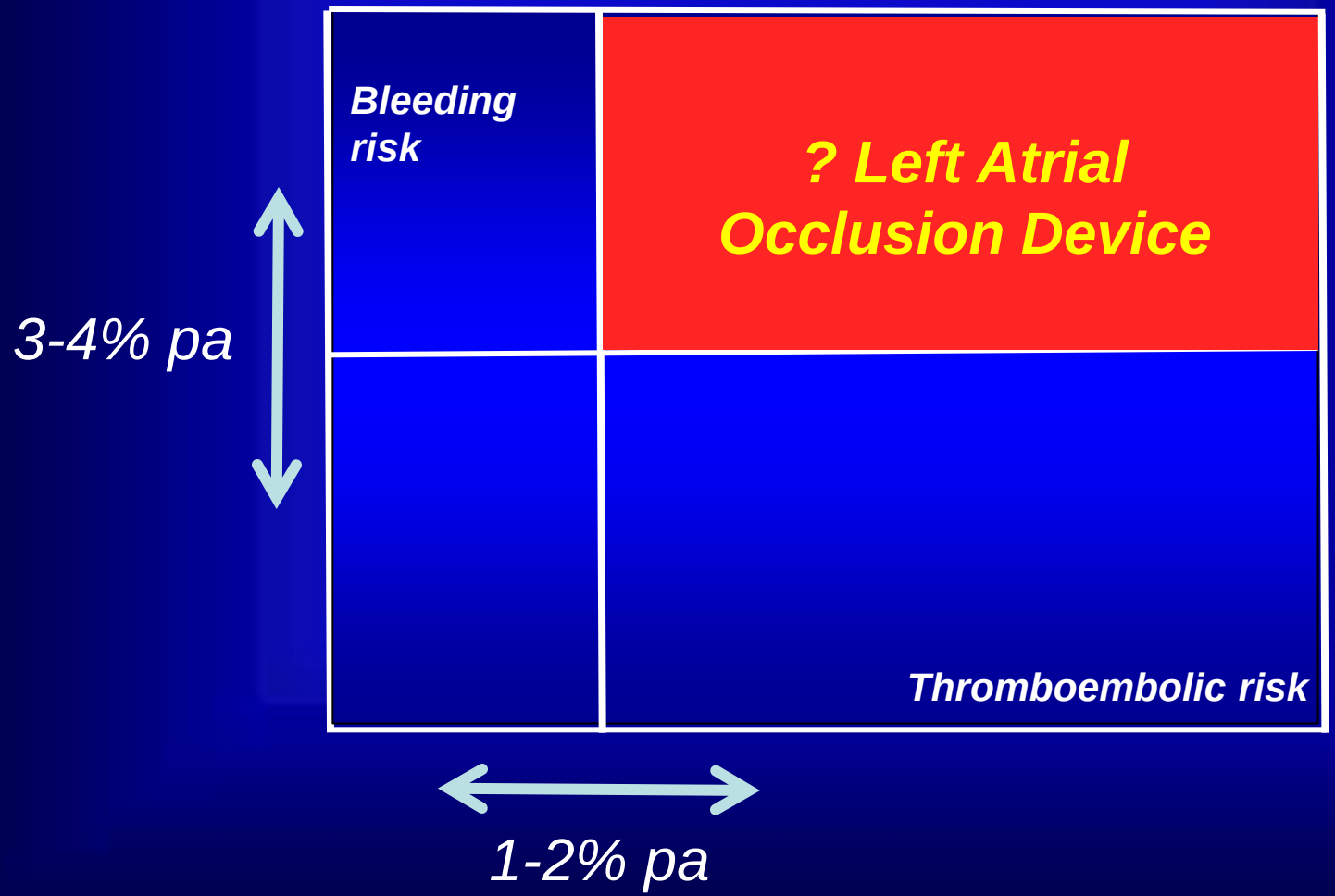
Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

According to HAS-BLED, 61% of pts currently on warfarin for AF are at "moderate" risk of bleeding and additional 19% are at "high" risk!

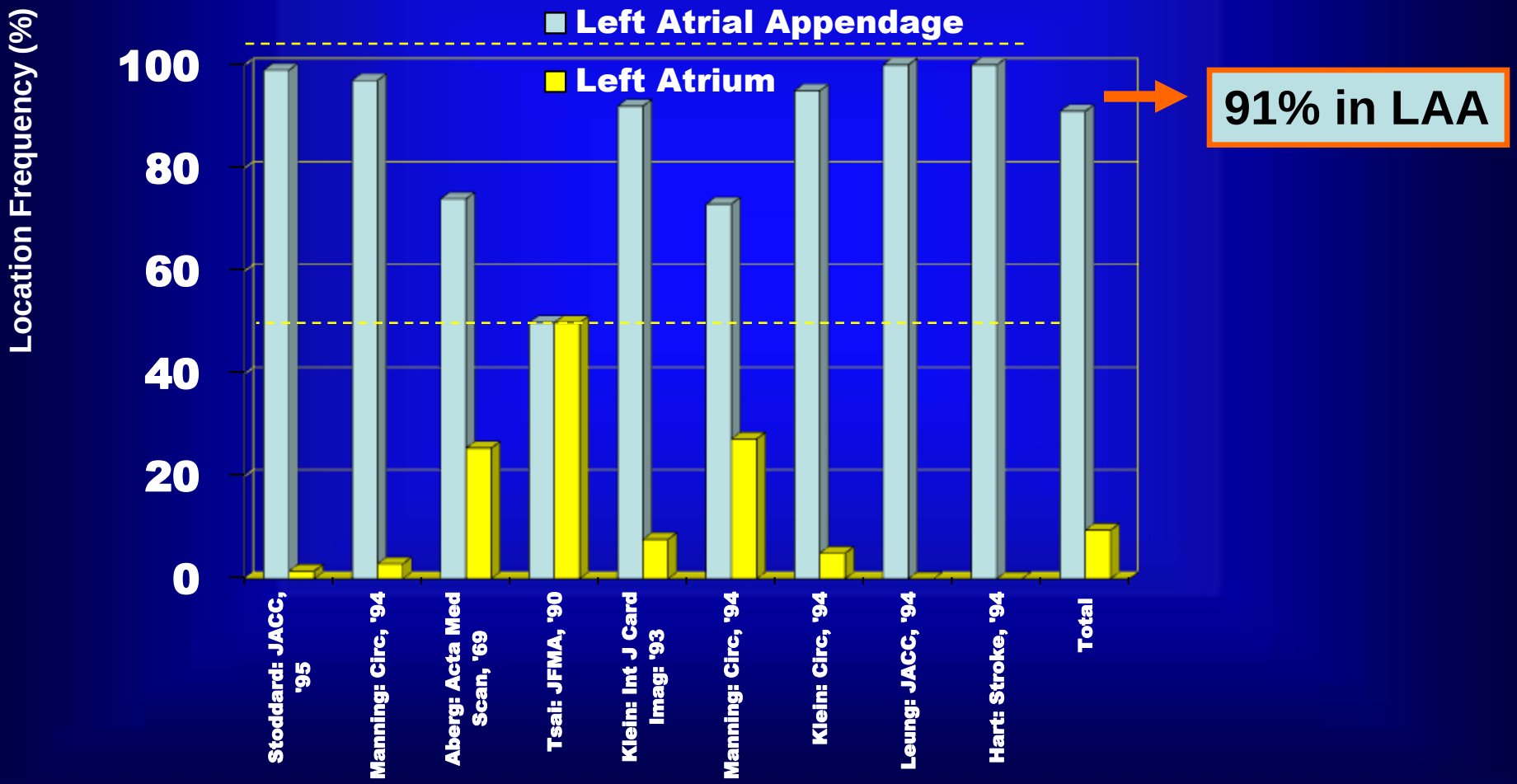
Camm et al, European Heart Journal doi:10.1093/eurheartj/ehq278

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

Thromboembolism versus Haemorrhage

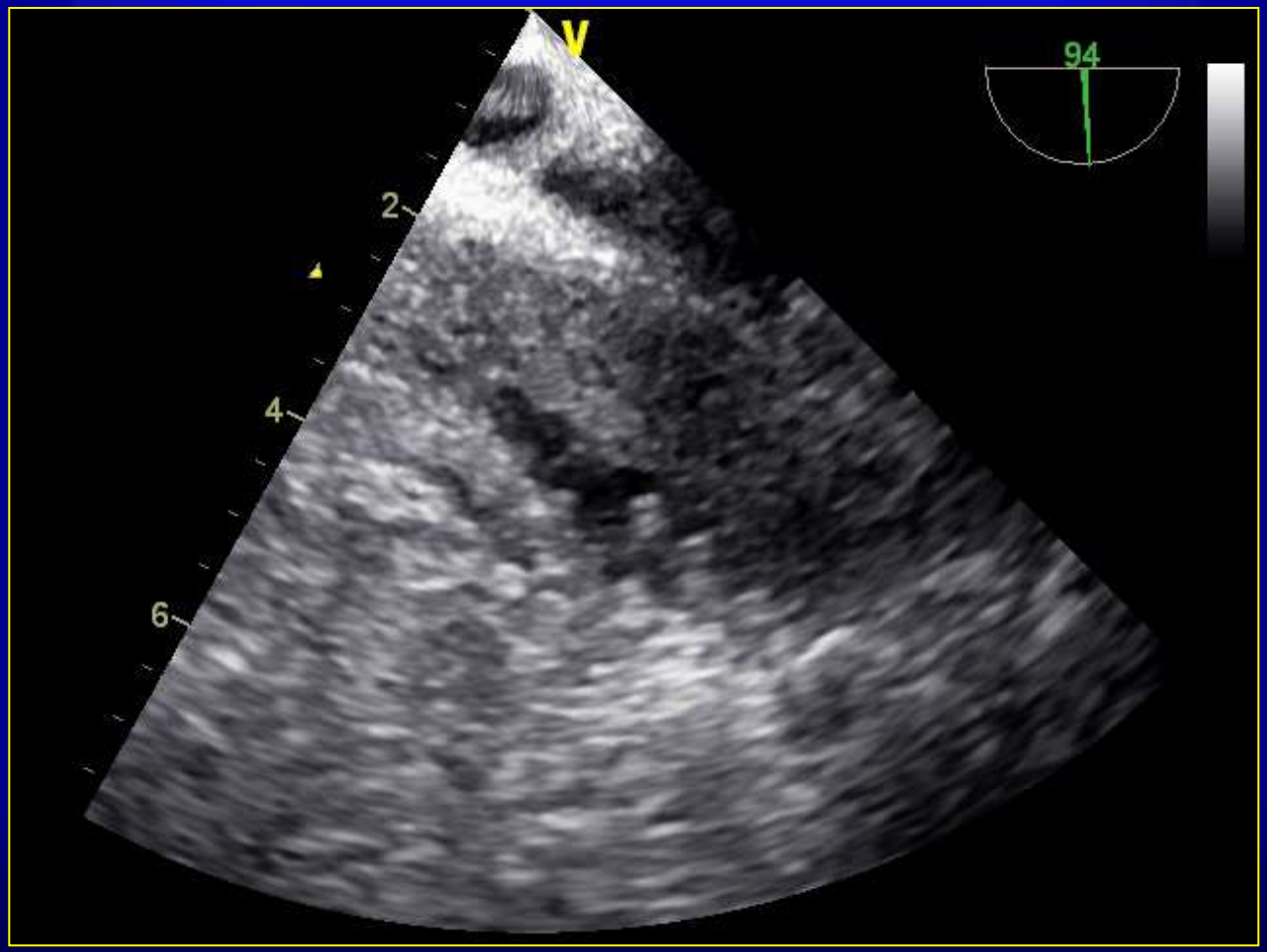


Prevalence of Thombi in the Left Atrium (in patients with AF)



Blackshear J.L. Odell J.A., Annals of Thoracic Surgery, 1996;61:755-759

Thrombi Formation in the LAA



Interventions for LAAC:
Ligation, Clips, and Endovascular Implant Options

LAA Clip

EXCLUDE Trial (completed)
- AtriClip Device was FDA approved in 2010 for LAA closure
  - No specific indication for Stroke Reduction

ClinicalTrials.gov identifier: NCT00779857

Surgical Ligation

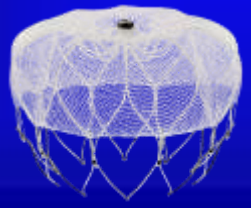
"Safety and Efficacy of Left Atrial Appendage Occlusion Devices"
Observational Study (retrospective)
- To compare LARIAT vs. WATCHMAN
- LARIAT currently does not have a specific indication for LAA Closure or Stroke Reduction

ClinicalTrials.gov identifier: NCT01695564

LAA Closure (LAAC) Devices

First LAAC device (2001- Device no longer available)

PLAATO



2 Completed Trials:
- **PROTECT AF** Trial
- **PREVAIL** Trial

ClinicalTrials.gov identifiers:
NCT00129545 (PROTECT AF)
NCT01182441 (PREVAIL)

WATCHMAN

trial begun in 2013
AMPLATZER Cardiac Plug Clinical Trial

ACP

ClinicalTrials.gov identifier:
NCT01118299

SH-178008-AA

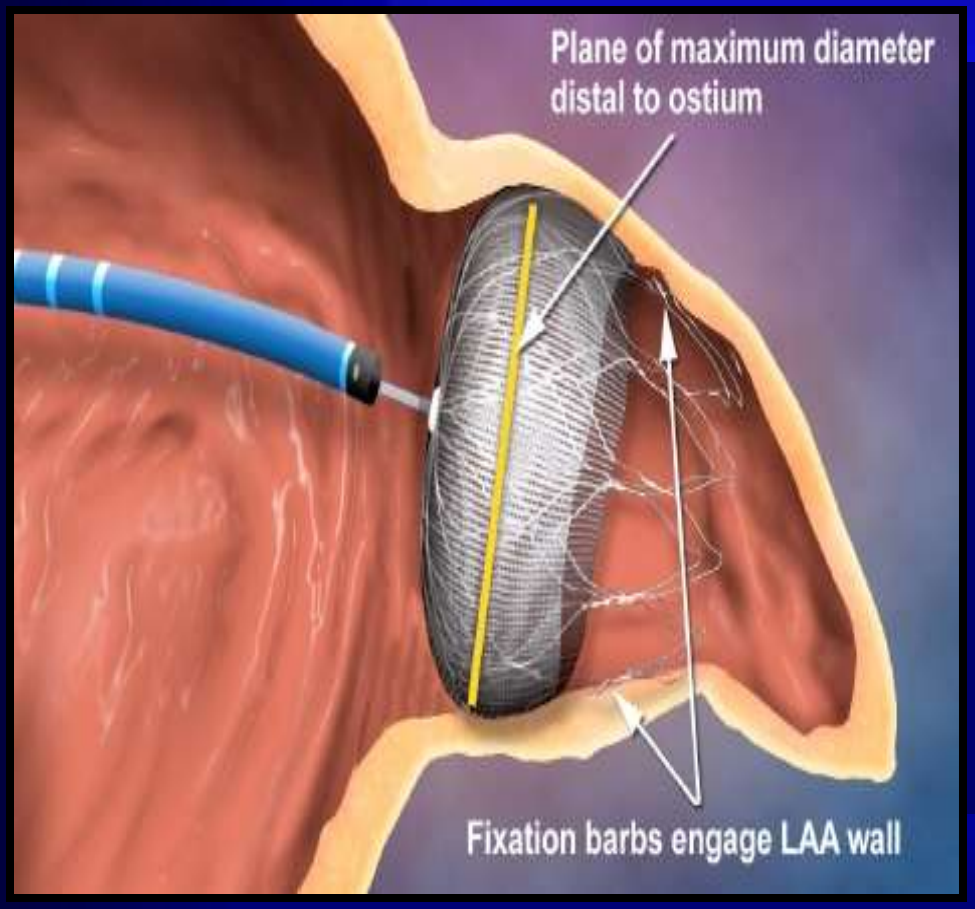
Caution: In the US, WATCHMAN is an investigational device, limited by applicable law to investigational use only and not available for sale. CE Mark 2005

WATCHMAN® Device

- Device available in various sizes:
  - 21, 24, 27, 30 and 33 mm (diameter)
  - Device diameter is measured across face of device
  - Device Length = Device Diameter

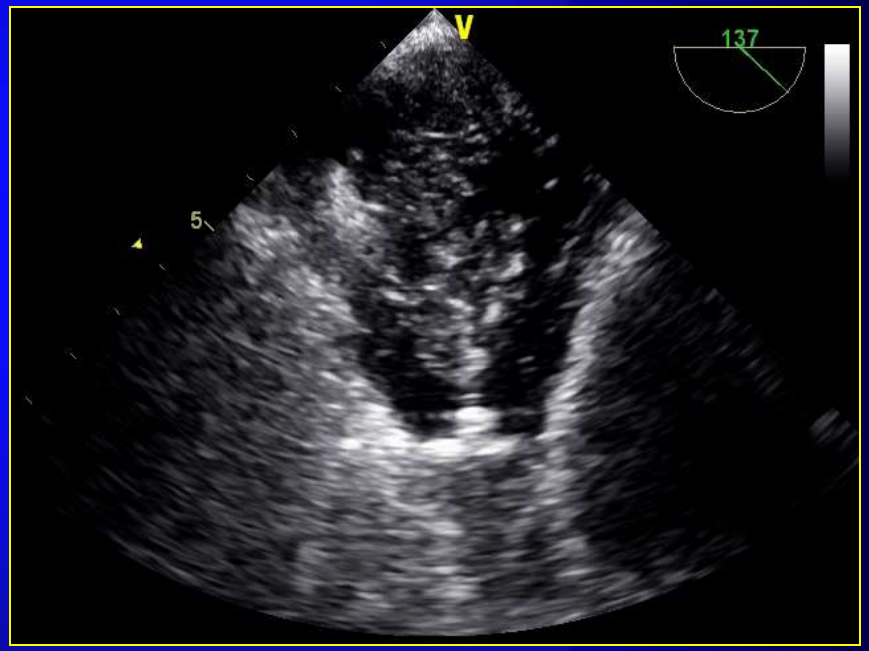
- **Frame:** Nitinol (shape memory)
  - Contour shape accommodates most LAA anatomy
  - Barbs engage the LAA tissue
- **Fabric Cap:** Polyethyl terephthalate (PET) Fabric
  - Prevents harmful emboli from exiting during the healing process

WATCHMAN® LAA closure system

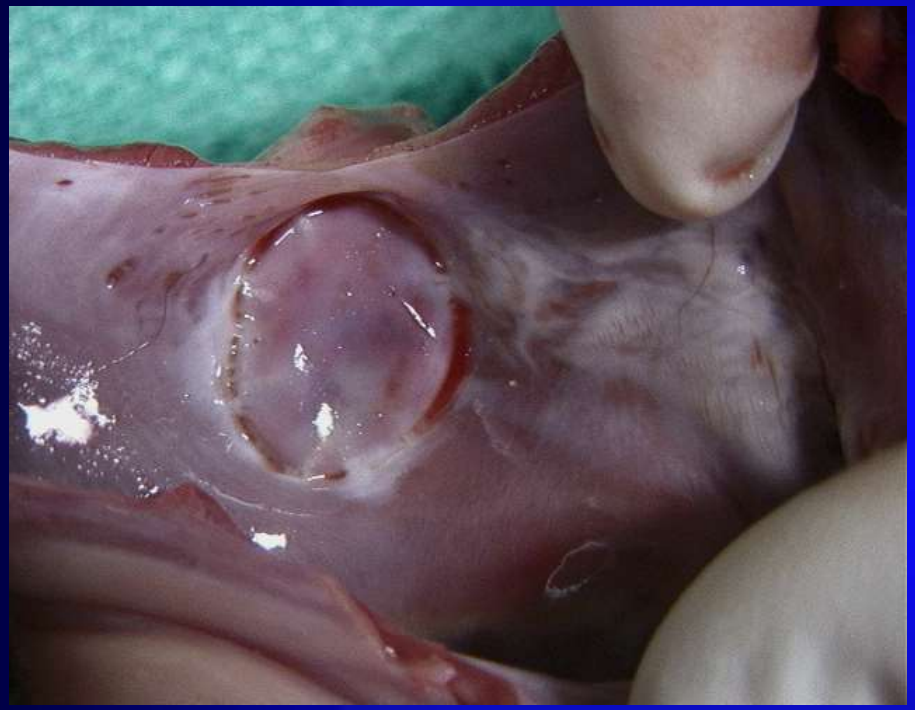


Procedure consists of percutaneous placement via transseptal of a filter device just distal to the ostium of the left atrial appendage to keep harmful sized emboli from exiting.

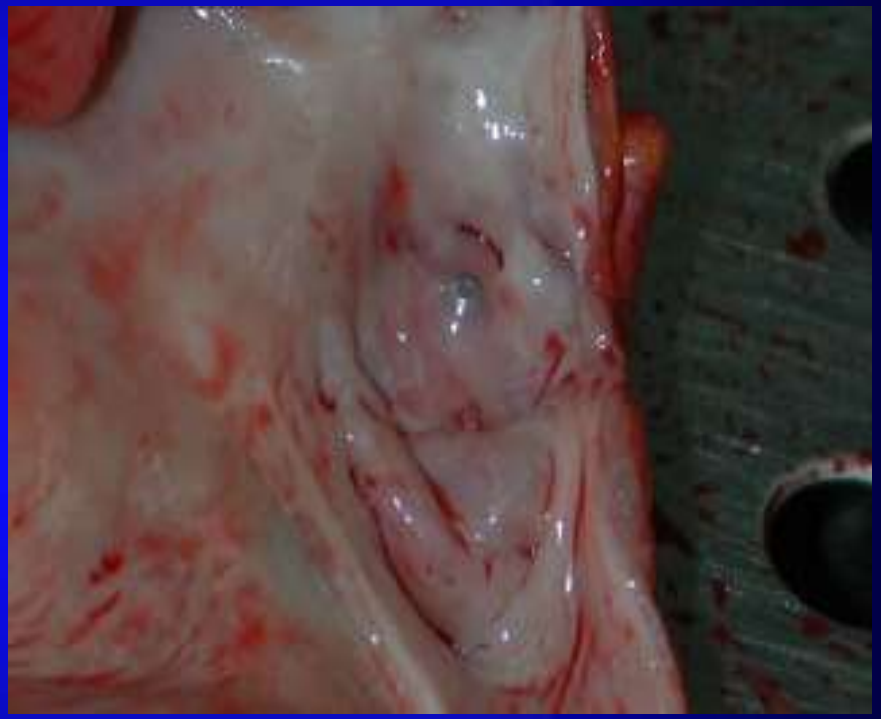
Deploying the Device



WATCHMAN® LAA System – Internal view of Complete Healing of LA



Canine – 45 days



Human @ Autopsy – 9 mos

Therapy for Stroke prevention in patient with non valvular AFib

In patients with non valvular Afib and relatively low $CHADS_2$ score (1-3):

What is the evidence for t***argeted Mechanical Therapy*** with LAAC

for prevention of stroke in A Fib ?

Clinical Trial Update

WATCHMAN
Evidence-Based Medicine

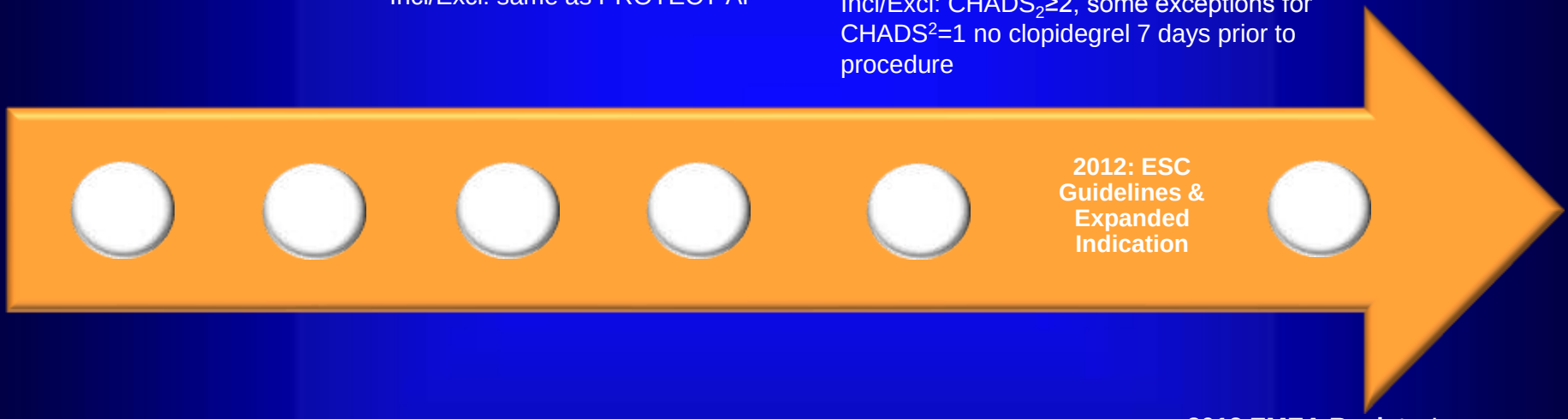
2002 – Pilot
Endpoints: Feasibility and Safety
Comparison: nonrandomzed
Incl/Excl: $CHADS_2$≥1, able to tolerate warfarin

2005 – PROTECT AF
Endpoints: Safety and Efficacy
Comparison: warfarin
Incl/Excl: $CHADS_2$ ≥ 1, able to tolerate warfarin

2008 – CAP Registry
Endpoints: Collect additional safety and efficacy data to be pooled with PROTECT AF
Incl/Excl: same as PROTECT AF

2009 – ASAP
Endpoint: Efficacy
Comparison: $CHADS^2$ score expected stroke rate
Incl/Excl: intolerant or contra-indicated for warfarin

2010 – PREVAIL
Endpoint: Safety and Efficacy
Comparison: warfarin
Incl/Excl: $CHADS_2$≥2, some exceptions for $CHADS^2$=1 no clopidegrel 7 days prior to procedure



2013 EMEA Registry*
Endpoint: Additional information in a real-world setting
Incl/Excl: All comers

WATCHMAN™ PROTECT AF 4 Year Study Overview

Study Design & Objective	Prospective, randomized (2:1), non-inferiority trial of LAA closure vs. warfarin in non-valvular Afib patients for prevention of stroke
Primary Endpoint	Efficacy: Composite end point of stroke, cardiovascular death or systemic embolization Safety: Major bleeding, device embolization or pericardial effusion
Statistical Plan	All analyses by intention-to-treat Bayesian (stratified for CHADS2 score) : Primary Efficacy and Safety endpoints Cox Proportional: All Secondary Analyses
Patient Population	n = 707 Mean CHADS2=2.2
Key Inclusion Criteria	Paroxysmal / Persistent / Permanent AF CHADS $\geq$ 1 Eligible for long-term Warfarin therapy
Mean Follow-Up	2,621 patient-years, 45 months
Number of Sites	59 in the United States and Europe Enrollment Feb 2005 – June 2008

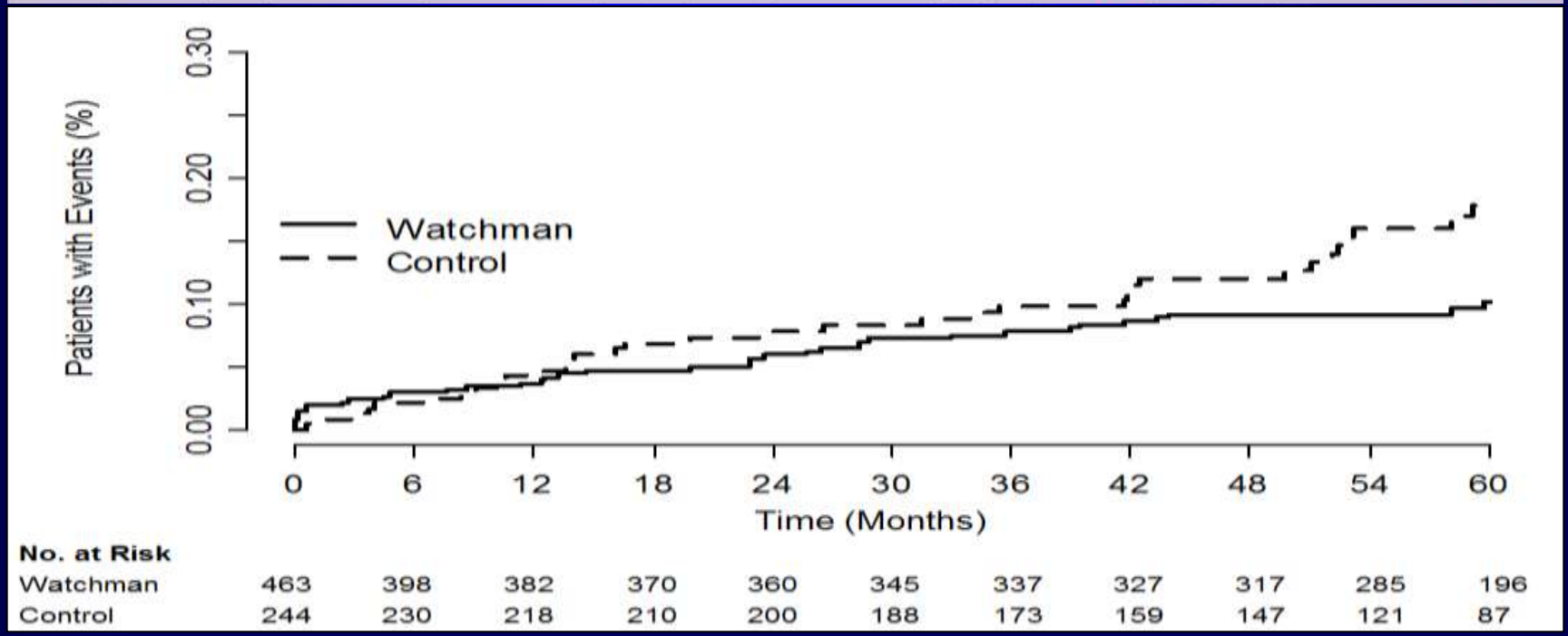
PROTECT AF
Intent-to-Treat: Primary Efficacy Results

Cohort	WATCHMAN		Control		Relative Risk (95% CI)		Posterior Probabilities	
	Rate (95% CI)		Rate (95% CI)				Non-inferiority	Superiority
600 pt-yrs	4.4	(2.6, 6.7)	5.8	(3.0, 9.1)	0.76	(0.39, 1.67)	0.992	0.734
900 pt-yrs	3.4	(2.1, 5.2)	5.0	(2.8, 7.6)	0.68	(0.37, 1.41)	0.998	0.837
1065 pt-yrs	3.0	(1.9, 4.5)	4.9	(2.8, 7.1)	0.62	(0.35, 1.25)	>0.999	0.900
1350 pt-yrs	2.9	(2.0, 4.3)	4.2	(2.5, 6.0)	0.69	(0.42, 1.37)	>0.999	0.830
2621 pt-yrs	2.2	(1.7,3.2)	3.8	(2.5, 4.9)	0.60	(0.41, 1.05)	>0.999	0.960

- Non-inferiority criteria met
- 32% relative risk reduction in ischemic stroke in the WATCHMAN Group

PROTECT AF 4 Year Follow Up:
Primary Efficacy Endpoint

Event	Watchman Group (n = 463) Events/ Patient-Years	Watchman Group (n = 463) Observed Rate (Events per 100 Patient-Years) (95% CrI)	Warfarin Group (n = 244) Events/ Patient-Years	Warfarin Group (n = 244) Observed Rate (Events per 100 Patient-Years) (95% CrI)	Rate Ratio (Watchman/Warfarin) (95% CrI)	Posterior Probabilities Non-inferiority	Posterior Probabilities Superiority
Primary Efficacy Endpoint	39/1720.2	2.3 (1.7, 3.2)	34/900.8	3.8 (2.5, 4.9)	0.60 (0.41, 1.05)	>0.999	0.960

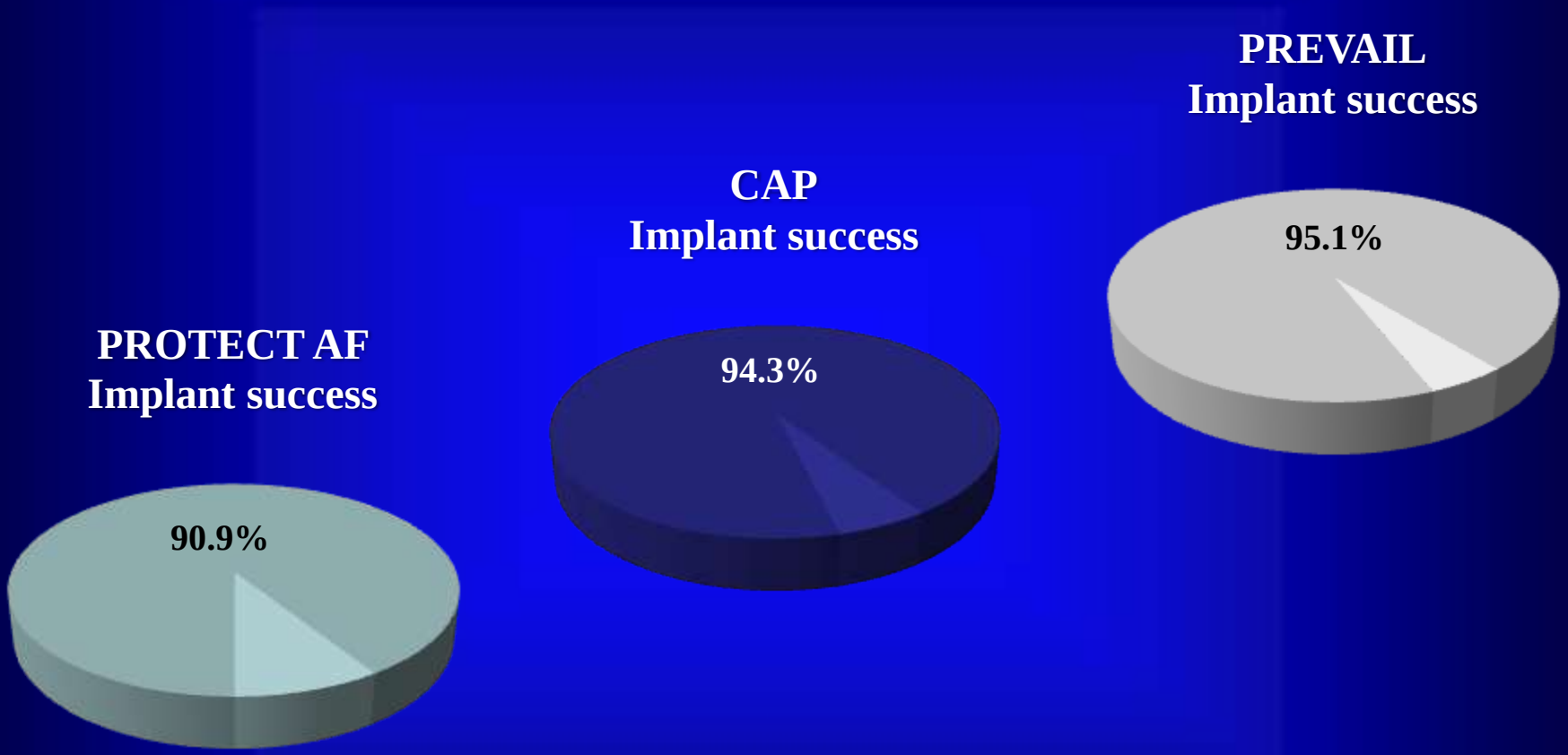


PROTECT AF
Four Year Follow Up: Summary

In the PROTECT AF Four Year follow up, “Local” therapy with WATCHMAN achieved statistical superiority to Warfarin

- 40% reduction of stroke / systemic embolism / CV death
- 60% reduction in Cardiovascular Mortality
- 34% reduction in All-Cause Mortality

Procedure Implant Success

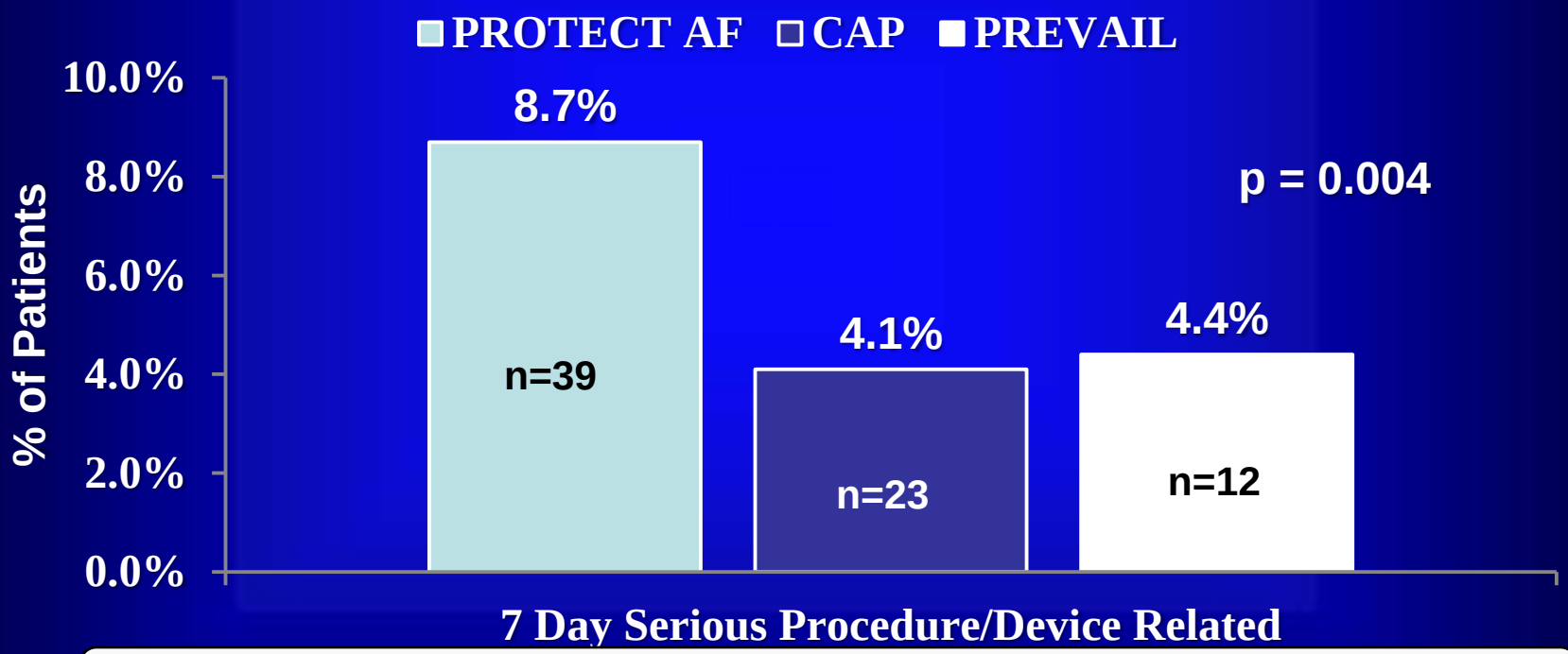


Implant success defined as deployment and release of the device into the left atrial appendage

PROTECT AF and CAP data
from Reddy, VY et al. *Circulation*. 2011;123:417-424.

Vascular Complications

- **Composite of vascular complications includes cardiac perforation, pericardial effusion with tamponade, ischemic stroke, device embolization, and other vascular complications[1]**

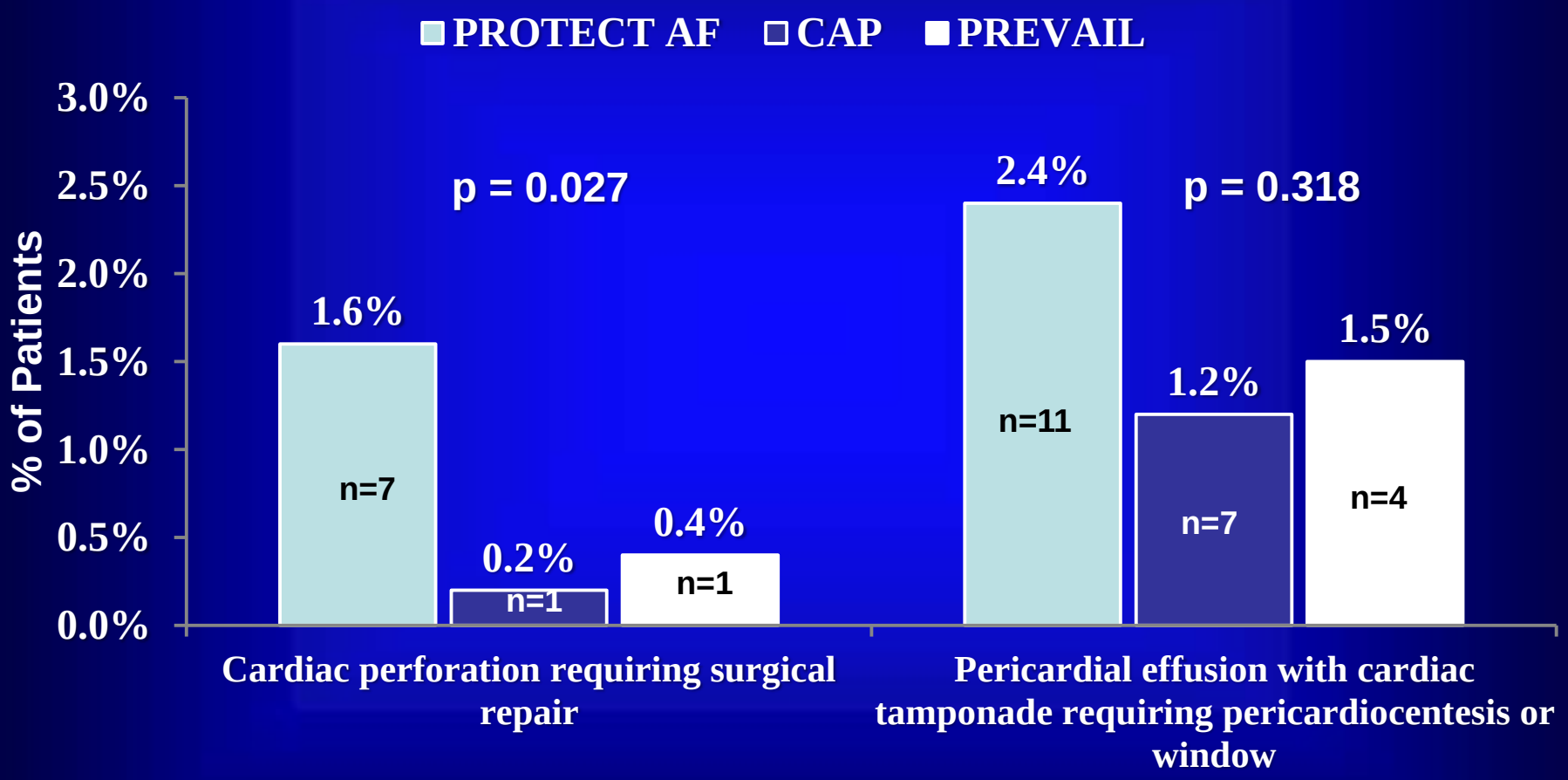


No procedure-related deaths reported in any of the trials

PROTECT-AF and CAP data from Reddy, VY et al. *Circulation*. 2011;123:417-424.

[11]Includes observed PE not necessitating intervention, AV fistula, major bleeding requiring transfusion, pseudoaneurysm, hematoma and groin bleeding

Pericardial Effusions Requiring Intervention



PROTECT AF and CAP data
from Reddy, VY et al. *Circulation*. 2011;123:417-424.

Growth of Transcatheter Left Atrial Appendage Closure in AF

Number of Worldwide Implants

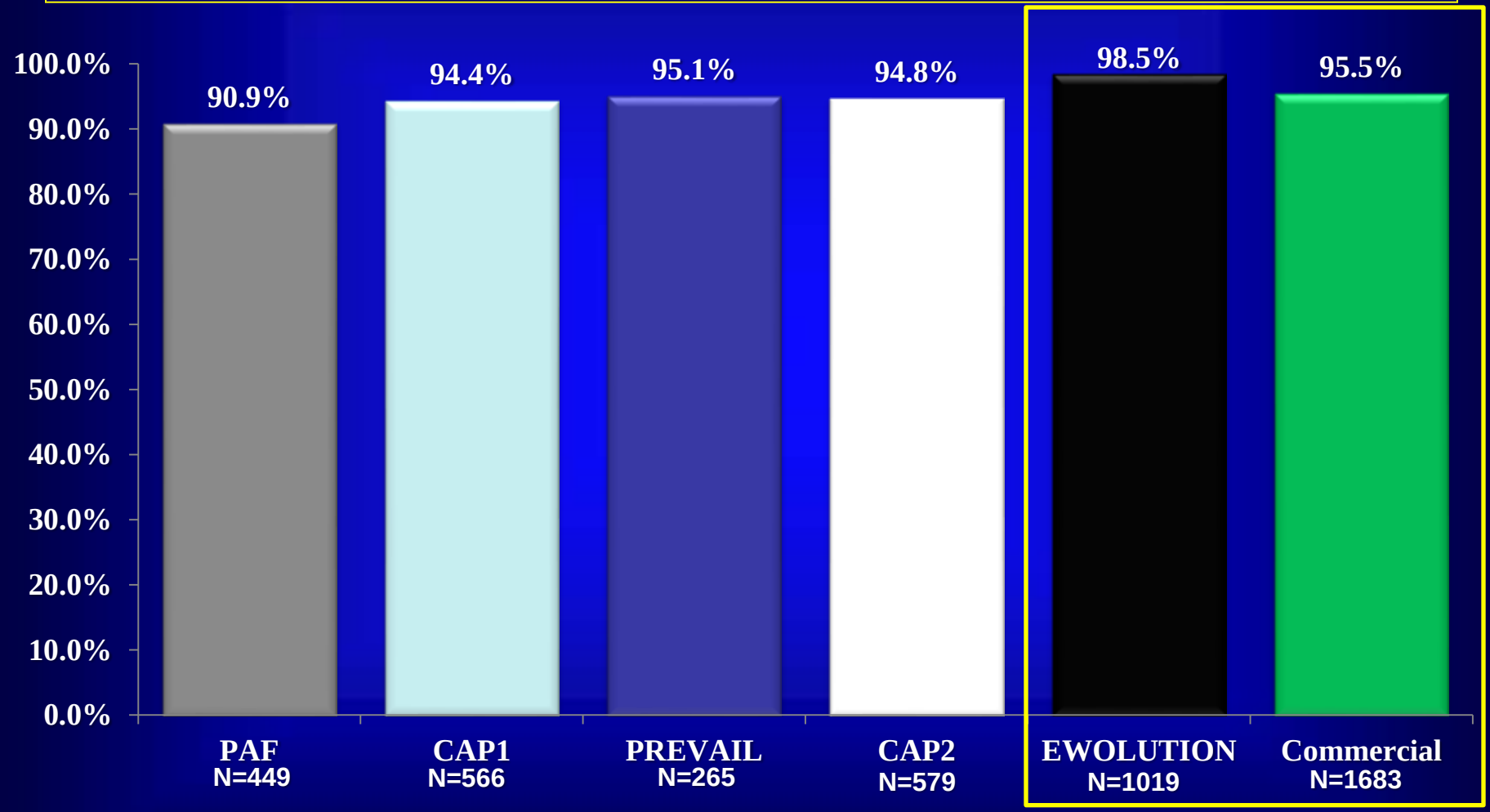
WATCHMAN Available Countries

Commercial US Registry since approval (March 2015)

- 1,700 patients have undergone clinically indicated Watchman placement accordingly to FDA IFU selection criteria
- 74 Active sites
- 200 Physicians were trained to perform LAAC Procedures performed by physicians trained in LAAC
- 20% of procedures were proctored by a physician while the remaining 80% were performed with trained Watchman clinical specialists in attendance
- Details of each procedure recorded on standardized forms

Holmes, DR et al. ACC 2016. Chicago, IL USA.

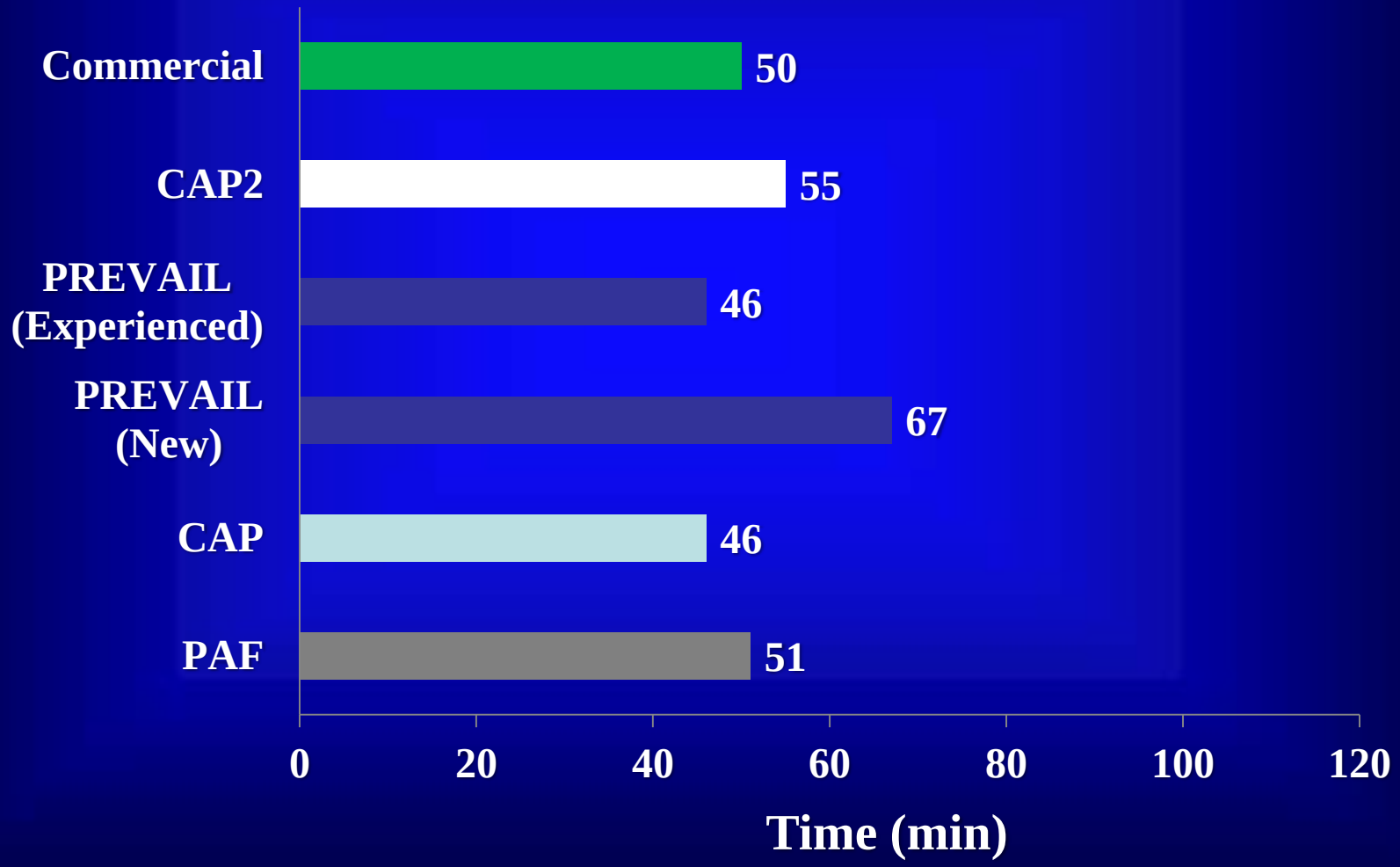
Procedural Success



Implant success defined as deployment and release of the device into the LAA; no leak ≥ 5 mm

Holmes, DR et al. ACC 2016. Chicago, IL USA.

Procedure Duration



Holmes, DR et al. ACC 2016. Chicago, IL USA.

Growth of Transcatheter Left Atrial Appendage Closure in AF

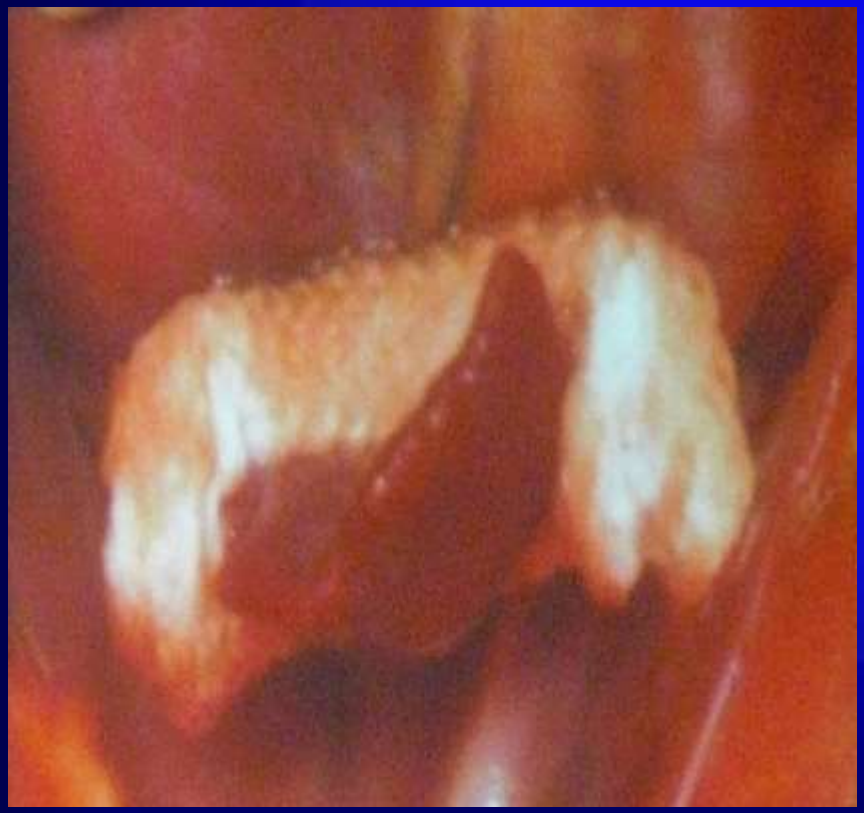
Number of New Devices

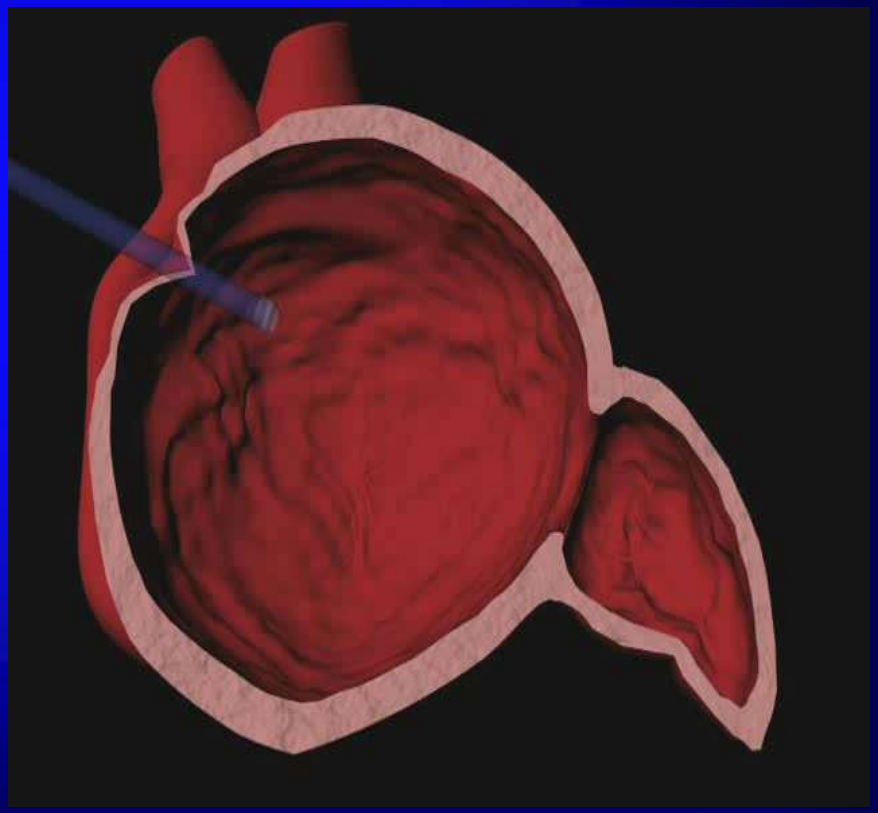
Fast Followers!

New Approaches

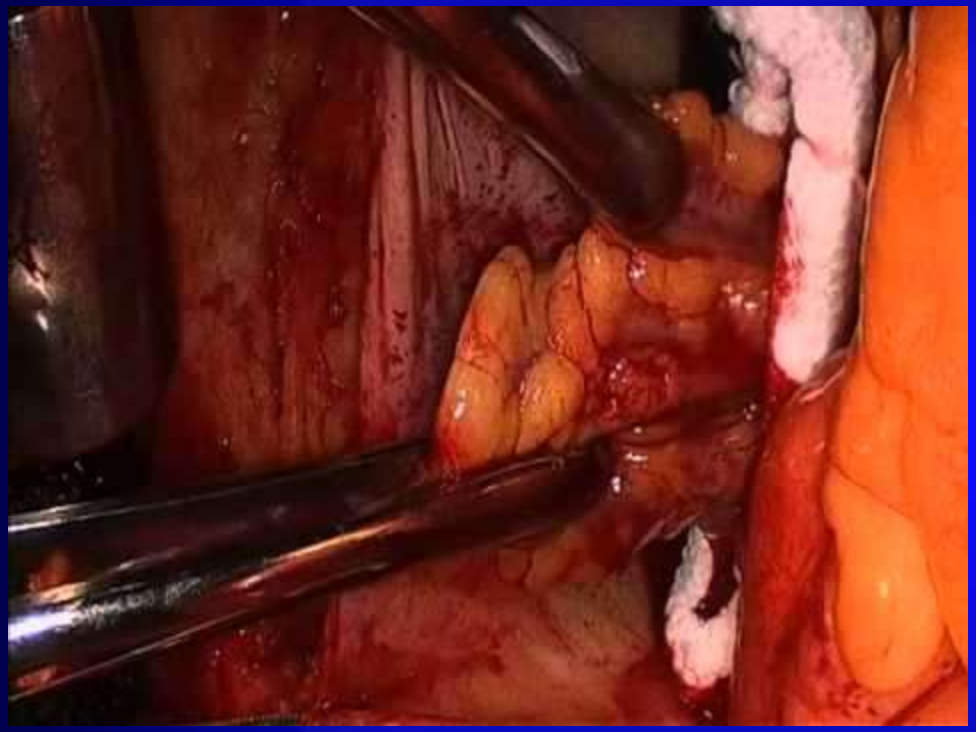
Epicardial

Endocardial



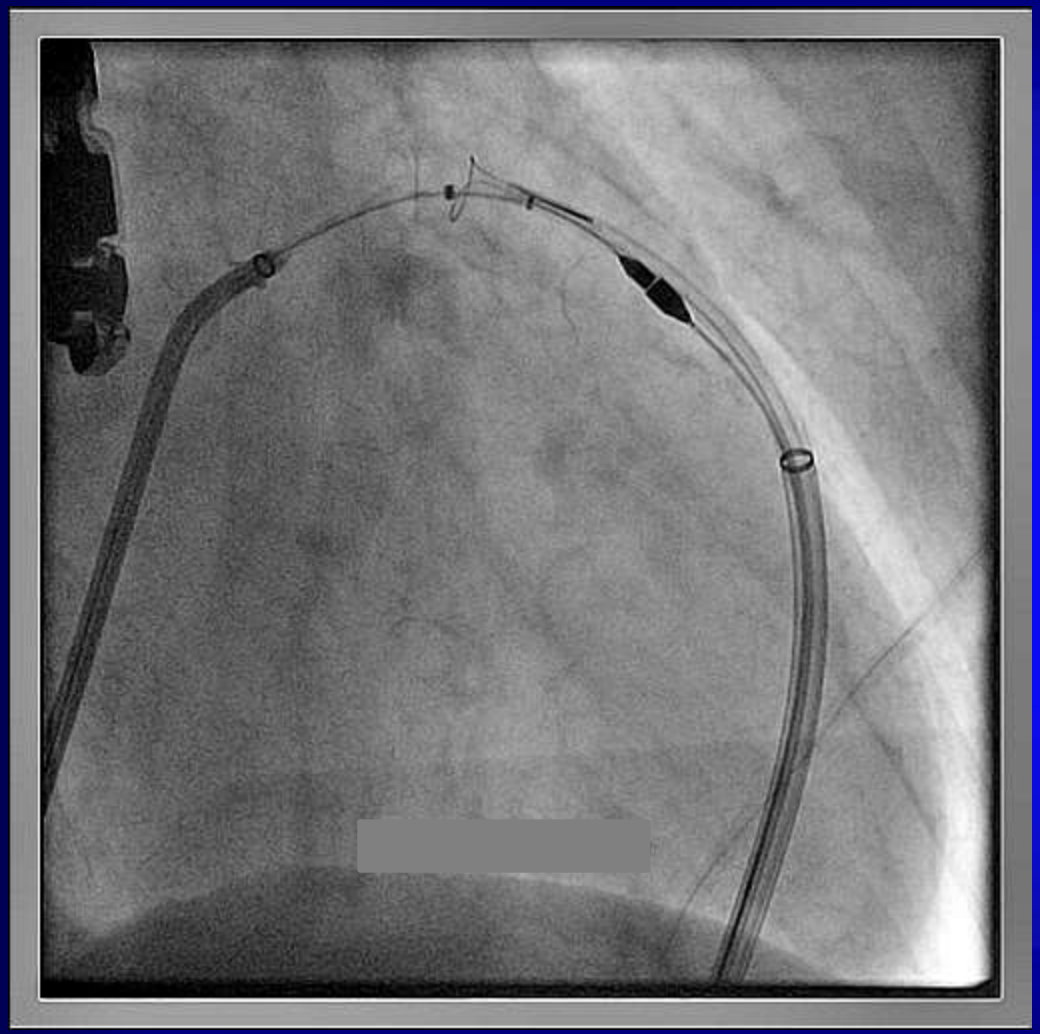


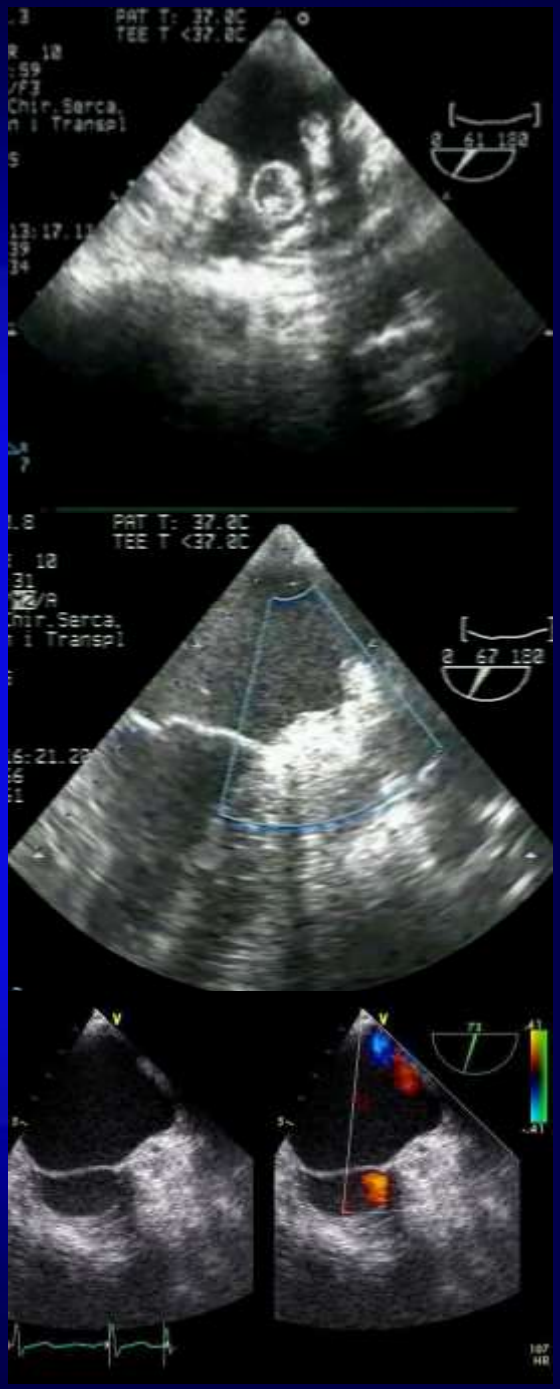
Atricure AtraClip™



- Titanium tubes with nitinol springs
- Urethane covering
- Polyester sheath

Lariat (Senter Heart)





Endocardial

- Watchman Flex™
- St. Jude Medical ACP, Amulet
- Occlutech
- Coherex
- Liftech
- Custom Medical Devices and *others*

What has changed?

Current Watchman

Watchman-Flex

The new Watchman –Flex is 10-20% shorter

What has changed?

Current Watchman

10 Fixation Anchors

Watchman-Flex

12 Fixation Anchors

What has changed?

Current Watchman

Watchman-Flex

80% more struts which increases conformability

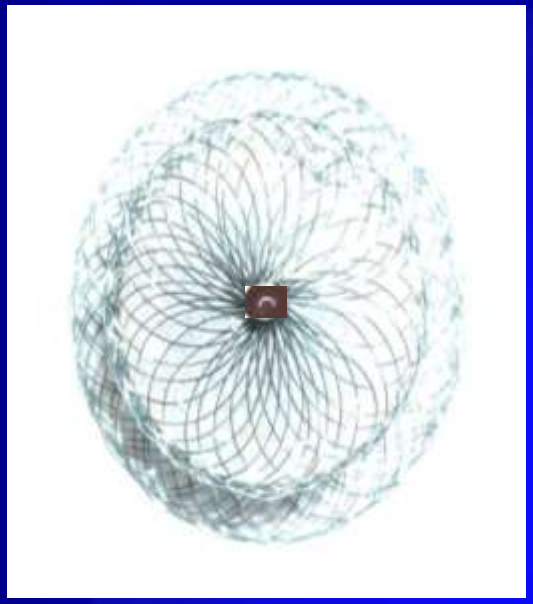
AMPLATZER™ Amulet

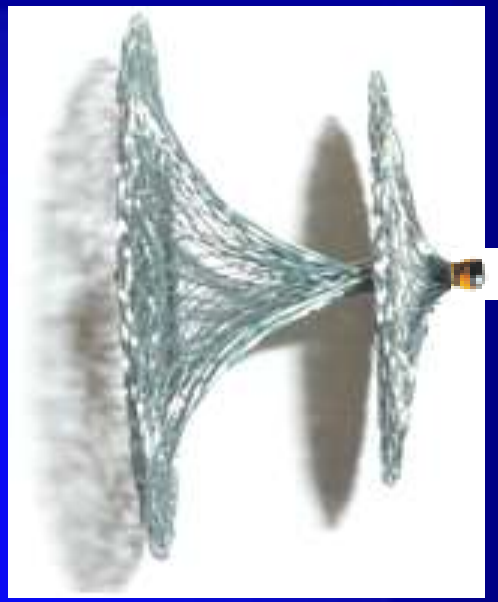
Second generation device

- Leverages the design and clinical history of the ACP
- Easier to use
- Expands the size range to treat larger appendage
- Incorporate modifications to improve device performance (less thrombus, more stability)

CE Marked Jan 2013 – Not approved in USA - Special Access Program in Canada

Occlutech



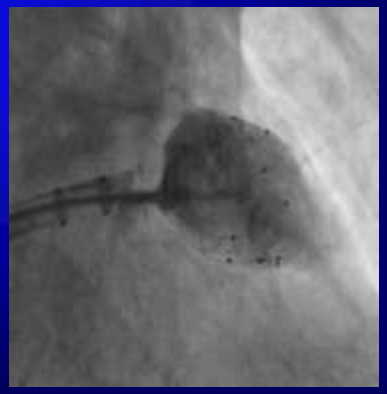


- Self-expanding flexible nitinol meshwork
- Patch to close the LAA
- The new Occlutech Connector
- Clinical trial?

Coherex WaveCrest™ LAA Occluder

Key Design Features Include:

1. **Retractable anchors**
2. **ePTFE Occluder material is occlusive and non-thrombogenic**
3. **Anchors distributed around perimeter of distal occluder edge**
4. **Distal contrast injection**
   - **Assess stability**
   - **Assess occlusion**
   - **Angio based implant**
5. **3 sizes (22mm, 27mm, 32mm)**



The Coherex WAVECREST I Trial

Primary Efficacy Endpoint
Core Lab Adjudicated Closure

	intent to treat (n = 73)	per protocol[1] (n=69)
45 day closure	**67 (92%)**	**67 (97%)**

1) *per protocol: successful device implant & 45 day transesophageal echo suitable for interpretation by echo core lab*
2) *closure: no residual flow >3 mm*

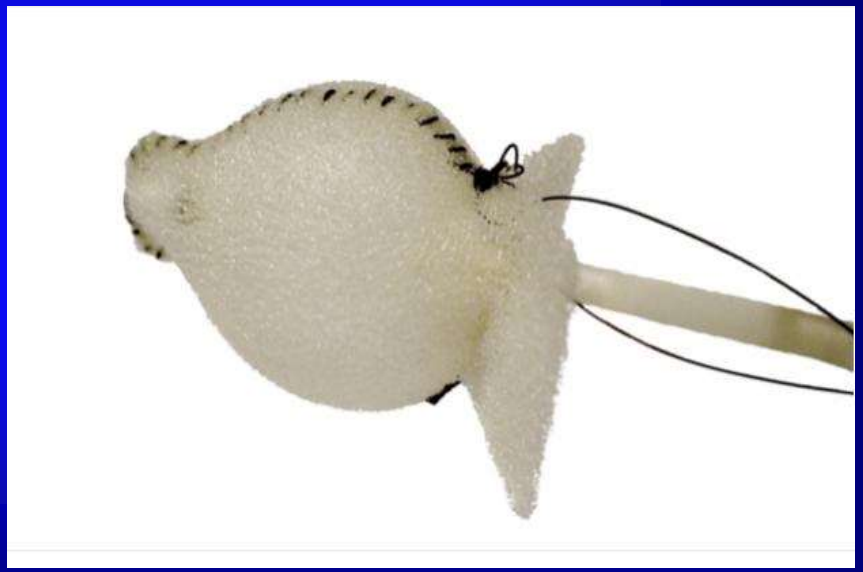
Lifetech LAmber Occluder

- Coated Nitinol
- PET membrane
- Double-membrane design
- Distal anchors
- Barbs
- Recessed hub
- 8-10 F sheath
- Retrievable/ Repositionable

And *many more!*

Custom Medical Devices

- Balloon inflatable deployment method
- Wireless design
- Allows a single patch to take the size and shape of any LAA
- Soft device
- Cannot cause perforations
- Bioabsorbable material
- Prevents chronic erosions
- CE Mark

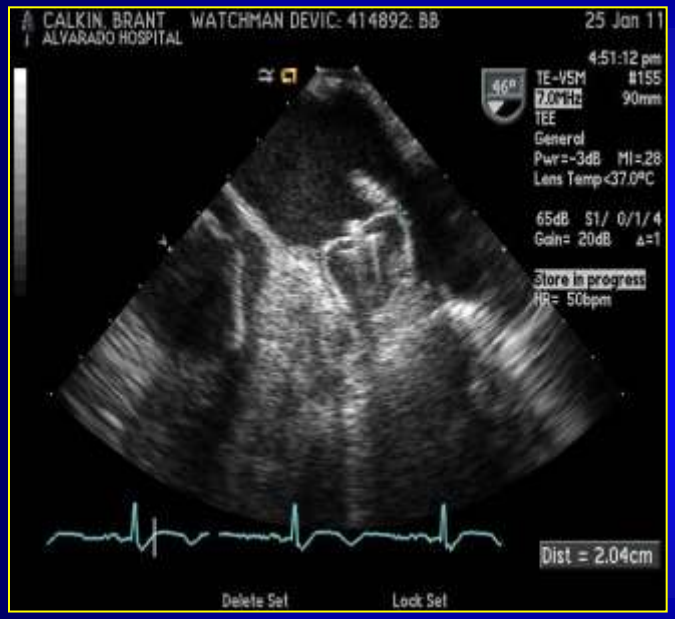


In summary
Which would you prefer!

Standard Oral Anticoagulation
(warfarin or NOACs)

- Continued dependency on drugs:
  100%
- Risk of Bleeding (per anum)
  3-3.5%
- Stroke risk (per anum)
  2-2.5%
- Hemorrhagic stroke (often fatal)
  1-1.5%
- Cost: $3,744/year (rivaroxaban)

Left Atrial Appendage Closure



- Implant Success 95%
- Stroke Risk 2%
  (over 4 years)
- Procedural Risk 4%
- Need for long term
  anti-coagulation <5%
- Ability to stop anti-coagulants
  6 weeks post implant >90%
  FOREVER

THANK YOU!