Update on LAA Closure Devices: Will They Get Approved?

Angioplasty Summit – TCTAP 2012

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David R. Holmes, MD
Mayo Clinic
Rochester, MN

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Presenter Disclosure Information

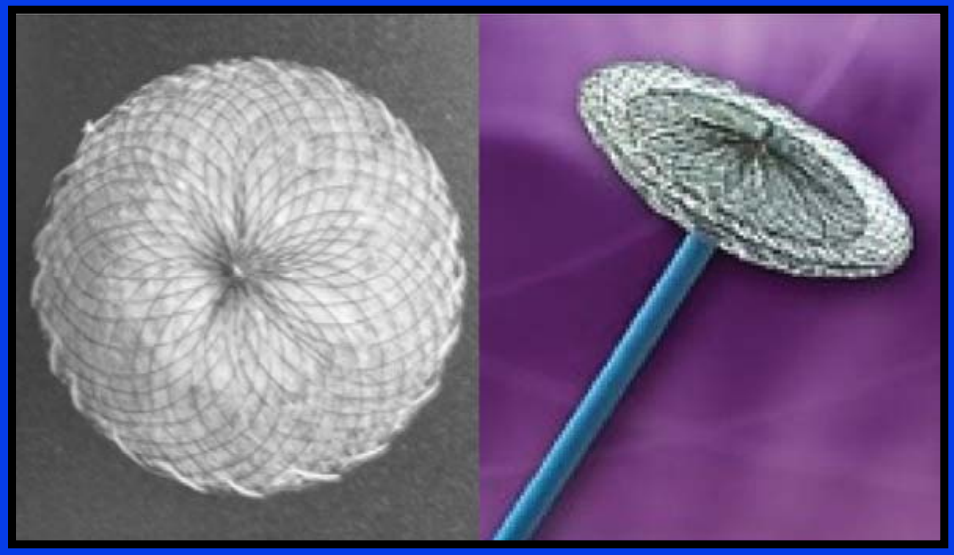
David R. Holmes, Jr., M.D.

**"Update on LAA Closure Devices:
Will They Get Approved?"**

The following relationships exist related to this presentation:

Immediate Past President ACC

Mayo Clinic and I have licensed some related technology to Atritech



Approval
Why has it taken so long?

- Huge number of patients
- Perception that drugs are better than devices (“Conservative medical therapy best”)
- Perception that new drugs have solved the problems of old drugs
- Perception that AF ablation solves the stroke issues
- AF patients are seen by EP services

LAA Devices
Will they get approved?

- Some already have been
- Others are in clinical trials
- Issues:
- Approval process
- Patient population
- Specific devices- Safety/efficacy
- Trial performance

FDA Approval

510 (K)

PMA

510 (k) Approval Process

- Classify the new product
- Identify predicate devices already cleared for sale in the US
- Determine if any special guidance documents or International Standards apply

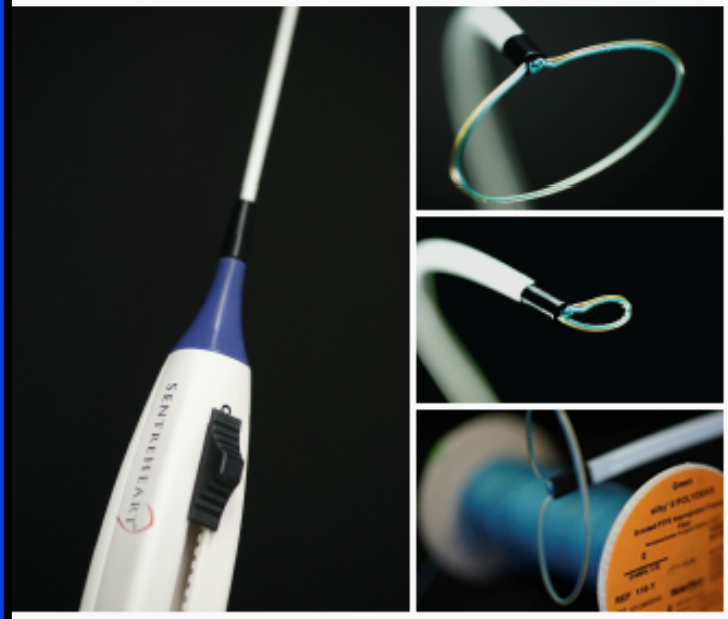
CARDIAC SURGERY / CARDIOLOGY / SURGERY

AtriCure Gets FDA OK for its AtriClip Device

by EDITORS *on* Jun 17, 2010 • 12:00 am

West Chester, Ohio based **AtriCure** has received 510(k) clearance for its AtriClip Gillinov-Cosgrove Left Atrial Appendage Exclusion system, an implantable clip for the occlusion of the left atrial appendage (LAA). AtriClip is designed to be implanted from the outside of the heart, avoiding contact with circulating blood and eliminating blood flow between the LAA and the atria. Under direct visualization and in conjunction with other open-heart cardiac procedures, the device can help reduce blood clots that could lead to strokes in patients with atrial fibrillation (AF).

LARIAT® Suture Delivery Device



The LARIAT Suture Delivery Device[1] is an elegant and intuitive solution to soft tissue closure. Innovation in catheter and suture delivery technology enables physicians with maximum flexibility in access choice and control of closure. The LARIAT was designed for optimal control to remotely deliver a 40mm pre-tied suture loop for immediate and complete closure through access as small as 4.3mm and with no metal, clips or fabrics left behind. Closure without Compromise.

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510(k) Summary

This summary of 510(k)-safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.
Date Prepared: March 10, 2006

JUN – 2 2006

Applicant Information:
SentreHeart
2468 Embarcadero Way
Palo Alto, CA 94303

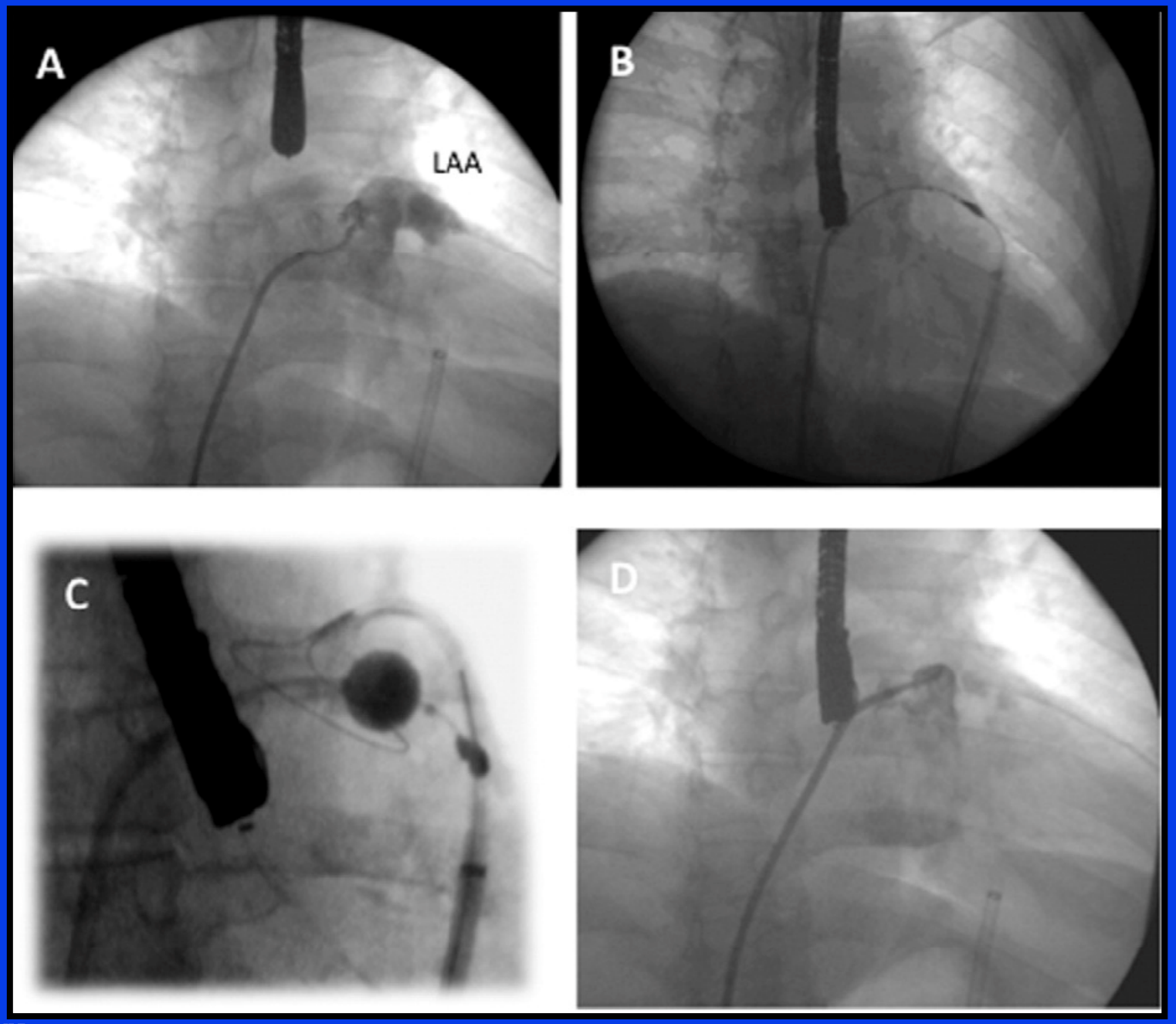
Device Information:

Trade Name:	LARIAT Loop Applicator
Classification:	Class II
Classification Name:	Suture, Non-absorbable, Synthetic

Physical Description:
The LARIAT Loop Applicator is a one piece, single-use suture delivery and deployment device with a pre-tied polyester suture loop that is pre-loaded on the device. A central lumen within the LARIAT Loop Applicator is designed for aspiration and stabilization of tissue during the delivery of the LARIAT Suture Loop.

The suture is itself a cleared medical device as a part of Pre-Market Notification K021019.

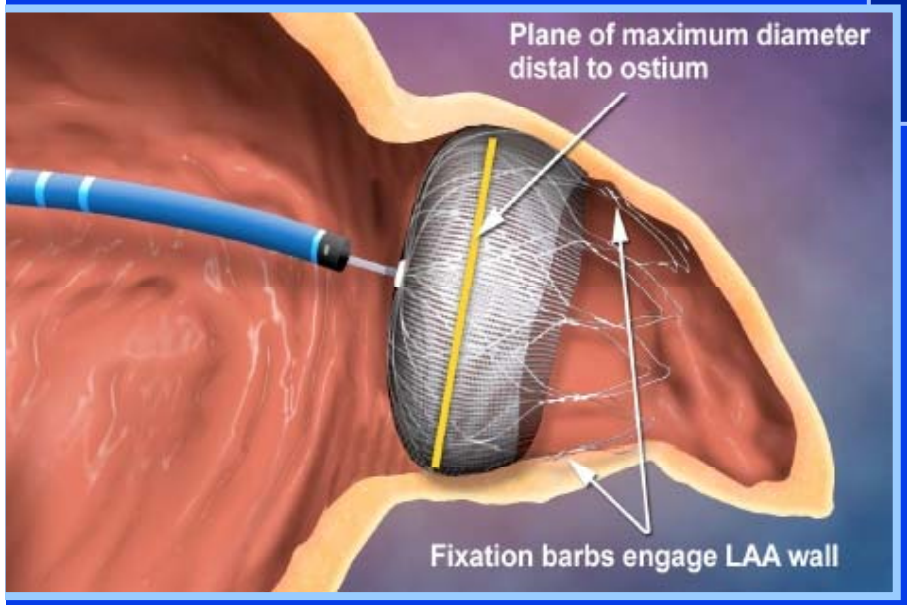
Intended Use:
The LARIAT Loop Applicator facilitates suture placement and knot tying for use in surgical applications where soft tissue are being approximated and/or ligated with a pre-tied polyester suture.


A
LAA
B
C
D

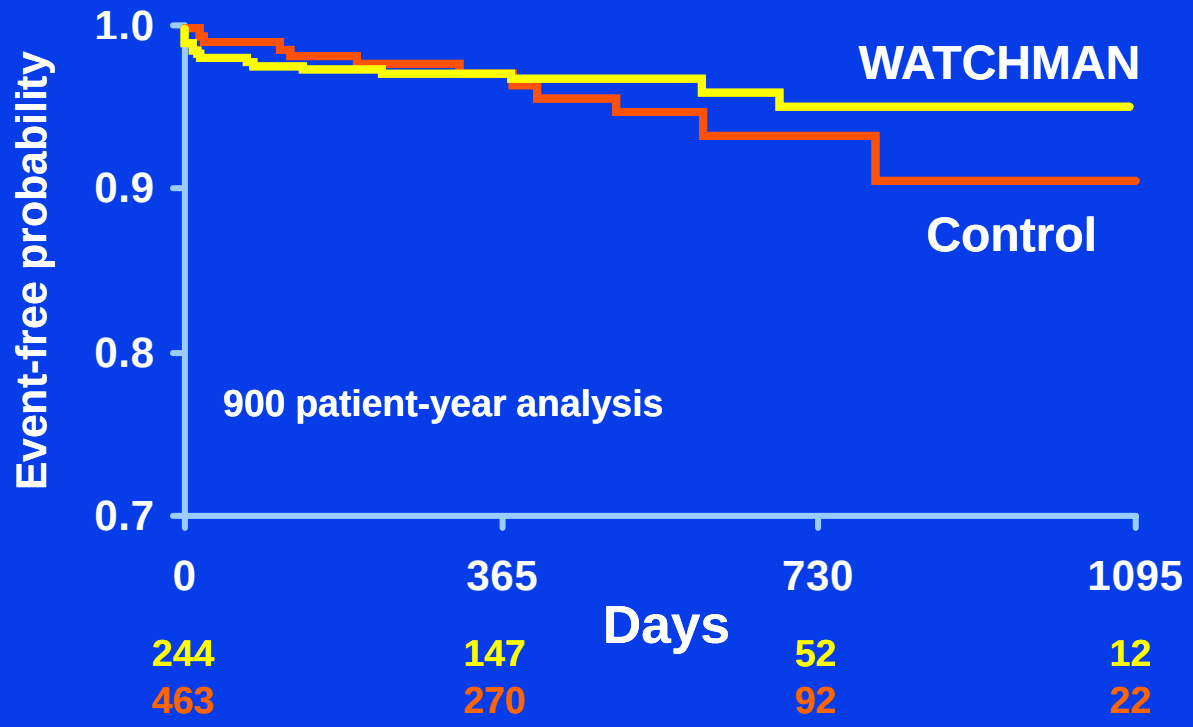
PMA

- Established by Medical Device Amendments of 1976 to the Federal Food, Drug and Cosmetic Act
- “Required process of scientific review to ensure the safety and effectiveness of Class III devices”
- A license granted to the applicant for marketing a specific medical device for a specific indication.

Proof of Concept



Intent-to-Treat
All Stroke



Randomization allocation
(2 device:1 control)

Key Implication: Confirms Role of LAA in CVA

Holmes et al, Lancet 2009

FDA

Issues

- Safety
- Safe and efficacious
- Political climate
- Recent device experience
- Panel make-up
- Alternative available

PROTECT AF
FDA Issues

- % of $CHADS_2$ patients
- Early (45 day) warfarin use in both groups
- Subsequent concomitant use of ASA + clopidogrel in both groups
- Insufficient longer-term follow-up
- Safety

Intent-to-Treat: Primary Efficacy Results

Cohort	WATCHMAN Rate (95% CI)	Control Rate (95% CI)	Rel risk (95% CI)	Posterior probabilities Noninferiority	Superiority
600 pt-yr	4.4 (2.6-6.7)	5.8 (3.0-9.1)	0.76 (0.39-1.67)	0.992	0.734
900 pt-yr	3.4 (2.1-5.2)	5.0 (2.8-7.6)	0.68 (0.37-1.41)	0.998	0.837
1,065 pt-yr	3.0 (1.9-4.5)	4.9 (2.8-7.1)	0.62 (0.35-1.25)	>0.999	0.900
1,350 pt-yr	2.9 (2.0-4.3)	4.2 (2.5-6.0)	0.69 (0.42-1.37)	>0.999	0.830
1,500 pt-yr	3.0 (2.1-4.3)	4.3 (2.6-5.9)	0.71 (0.44-1.30)	>0.999	0.846

- Noninferiority criteria met
- 29% lower relative risk in WATCHMAN group

Intent-to-Treat: All Stroke

Cohort	WATCHMAN Rate (95% CI)	Control Rate (95% CI)	Rel risk (95% CI)	Posterior probabilities* Noninferiority	Superiority
600 pt-yr	3.4 (1.9-5.5)	3.6 (1.5-6.3)	0.96 (0.43-2.57)	0.927	0.488
900 pt-yr	2.6 (1.5-4.1)	3.5 (1.7-5.7)	0.74 (0.36-1.76)	0.998	0.731
1,065 pt-yr	2.3 (1.3-2.6)	3.2 (1.6-5.2)	0.71 (0.35-1.64)	0.993	0.769
1,350 pt-yr	2.1 (1.3-3.3)	2.7 (1.4-4.3)	0.78 (0.41-1.75)	0.989	0.685
1,500 pt-yr	2.0 (1.3-3.1)	2.7 (1.5-4.1)	0.77 (0.42-1.62)	0.995	0.728

- 23% lower relative risk in WATCHMAN group

*No adjustment made for multiple comparisons

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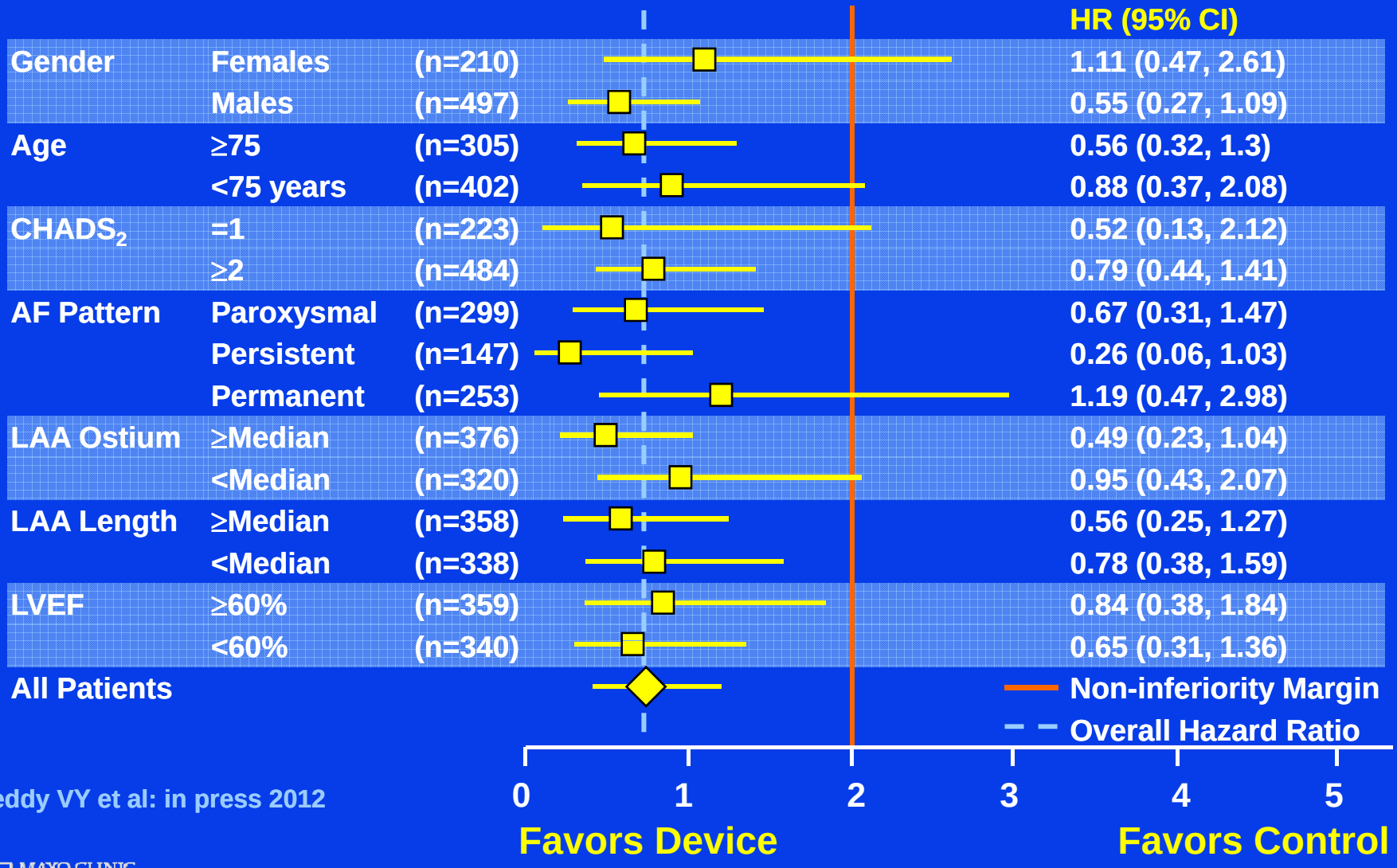
Primary Efficacy By Patient Subgroup



Reddy VY et al: in press 2012

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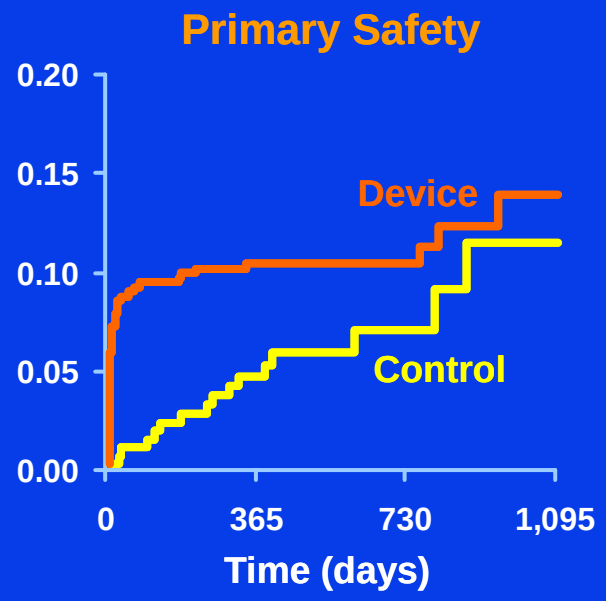
PROTECT AF Trial
What are the Analysis Issues

1. How do you deal with safety endpoints which are also primary efficacy endpoints?
2. How do you deal with early procedural safety risks (seen with all invasive interventional procedures) vs late primary efficacy endpoints?
3. How do you deal with a strategy of warfarin started immediately and indefinitely versus an invasive approach that also requires 45 days of warfarin (?double jeopardy)
4. How do you factor in procedural learning curve?

Primary Safety Results: Intent-To-Treat

Cohort 1,050 pt yr	WATCHMAN Rate (events/100 pt yr)		Control Rate (events/100 pt yr)		Relative risk	95% CI
Intention-to-treat	7.4	49/658.8	4.4	16/364.2	1.69	0.96, 2.97



Pericardial effusion/tamponade

- 22 requiring Tx (4.8% of pt)
  - 15 treated percutaneously
  - 7 underwent surgical intervention
- Extended hospitalization
- No death or long-term disability

Effect of operator experience

- ~2% (CAP registry)

Reddy et al: Circulation 123:417, 2011

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Watchman Approval Process Outcome
Personal Reflections

- New device category
- Anticipation of new anti-coagulants
- Small sample size vs drug trials
- Confusion about guidelines and patient selection
- Stroke a safety and efficacy endpoint
- Boundary and statistical analysis felt to be unusual
- Panel member issues

LAA Devices
Will they get approved?

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- Issues:
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- Patient population
- Specific devices- Safety/efficacy
- Trial performance

LAA Devices
Patient Populations

- Low CHADS-2 score
- Suitable for anticoagulant therapy
- Higher risk for anticoagulant therapy
- Anticoagulants contraindicated
- Thrombus in LAA
- Candidates for AF Ablation

LAA Devices
Trial Performance

- Patient population
- Treatment given in control group
- Superiority vs non inferiority
- Boundaries of statistics
- Primary endpoint:
- Composite versus single
- All Stroke or specific stroke
- Bleeding-access vs other
- Anticoagulation for other reasons

LAA Devices
Trial Performance

- Treatment given in control group
- Coumadin or New agent in patients who can take AC therapy
- ASA or Plavix alone or in combination
- “Usual care”

Pivotal Trial #2
PREVAIL

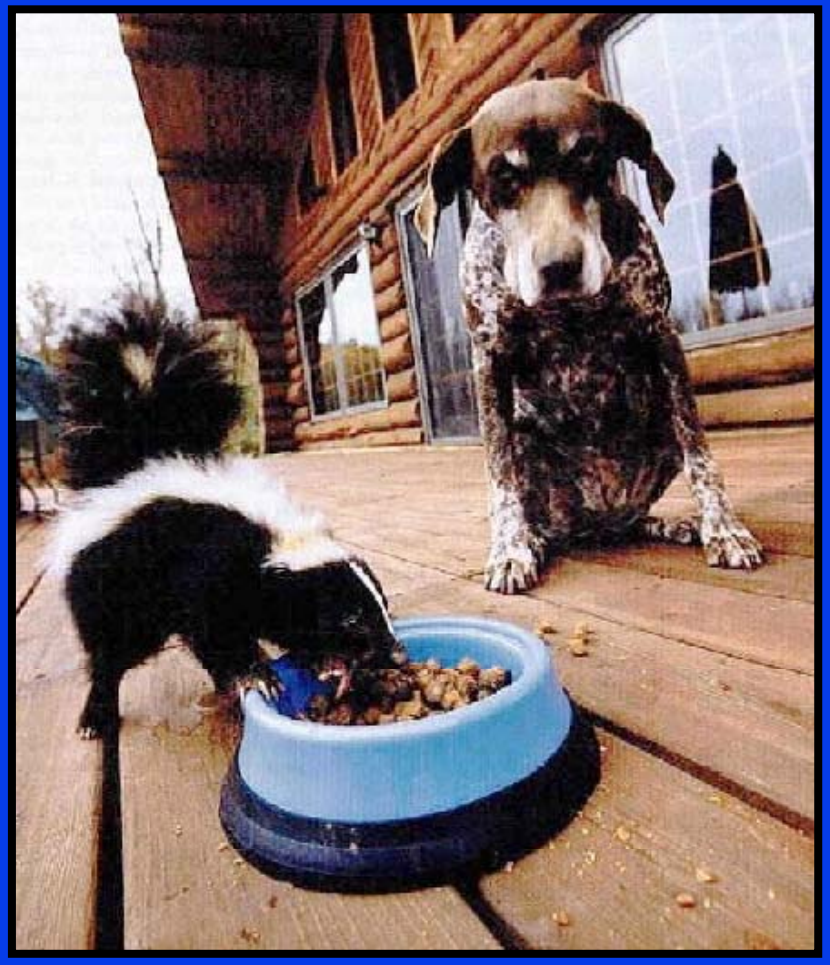
- Multicenter randomized trial of 475 patients with nonvalvular AF and similar inclusion criteria to PROTECT AF
- 2:1 randomization
- Primary endpoint:
  - Hemorrhagic stroke
  - Ischemic stroke
  - Systemic embolism
  - CV/unexplained death
- Adaptive study design, Bayesian piecewise exponential model, noninferiority

LAA Devices

What will it take for approval?

- One additional RCT (now underway for Watchman)
- Other RCT's for other devices
- Other RCT's for other patient groups

- It will happen but the Road is Winding and Long



Two of the greatest qualities in life are:

Patience and Wisdom

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