LAA Closure is Here: *Now What?*

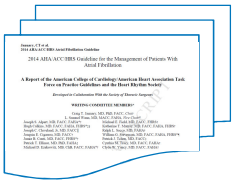
Craig S. Cameron, MD, FACC, FHRS

Oklahoma Heart Institute

No Disclosures Relevant to This Talk

Stroke Prevention

- Assess stroke risk with CHA_2DS_2-VASc score
  - Score 1: Annual stroke risk 1%,oral anticoagulants or aspirin may be considered
  - Score ≥2: Annual stroke risk 2%-15%, **oral anticoagulants are recommended**
- Balance benefit vs. bleeding risk



2014 AHA/ACC/HRS Guideline for the Management of Patients with AF

January, CT. et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. JACC. 2014; doi: 10.1016/j.jacc.2014.03.022

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CHA_2DS_2-VASc

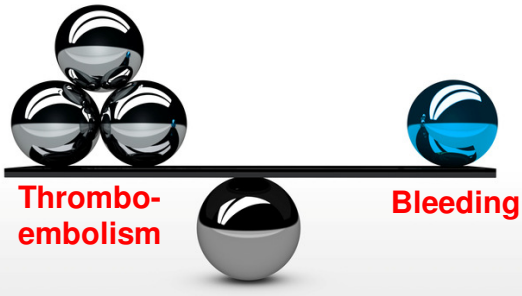
	Risk Factor	Score
C	Congestive Heart Failure	1
H	Hypertension	1
A_2	Age > 75 years	2
D	Diabetes Mellitus	1
S_2	Stroke/TIA/TE	2
V	Vascular Disease	1
A	Age 65 – 74 years	1
Sc	Female	1
	Maximum Score	9

HAS-BLED

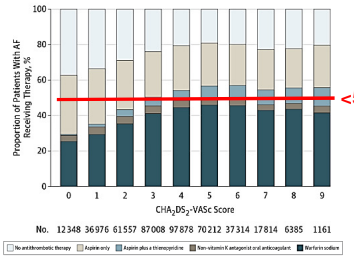
	Risk Factor	Score
H	Hypertension	1
A	Abnormal renal or liver function (1 each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Elderly Age (>65 years)	1
D	Drugs or alcohol (1 each) (antiplatelet, NSAIDS)	1 or 2
	Maximum Score	9

Camm AJ, et al. *Eur Heart J.* 2010:31;2369-2429

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



Use of OACs in AF Patients peaks at ~50%, use declines with increasing risk



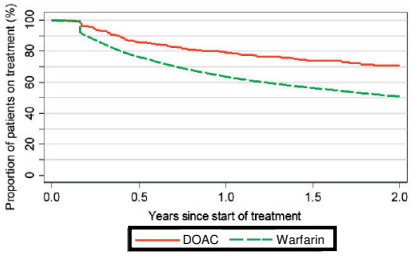
Warfarin
- Bleeding risk
- Daily regimen
- High non-adherence rates
- Regular INR monitoring
- Food and drug interaction issues
- Complicates surgical procedures

<50%

Direct Oral Anticoagulants (DOACs)
- Bleeding risk
- Daily regimen
- High non-adherence rates
- Complicates surgical procedures
- Lack of reversal agents
- High cost

Hsu, J et al. *JAMA Cardiol.* Published online March 16, 2016. doi:10.1001/jamacardio.2015.0374

Anticoagulant Discontinuation Rates



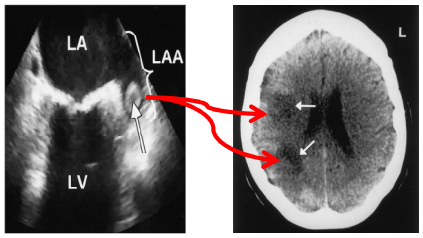
30% of patients stop DOAC at 2 years

50% of patients stop warfarin at 2 years

Martinez C, et al. Therapy Persistence in Newly Diagnosed Non-Valvular Atrial Fibrillation Treated with Warfarin or NOAC. A Cohort Study. Thromb Haemost. 2015 Dec 22;115(1):31-9. doi: 10.1160/TH15-04-

Mechanism of Stroke in AF

LAA: 91% of intracardiac thrombi



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

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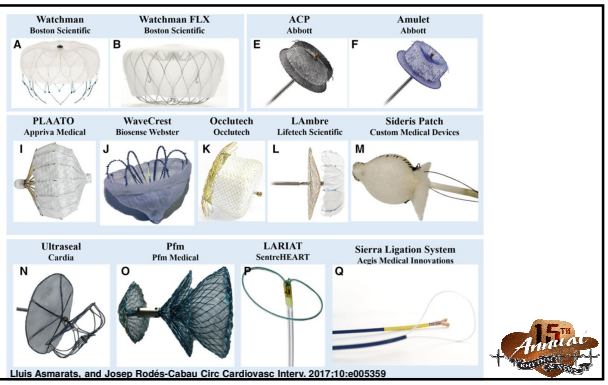
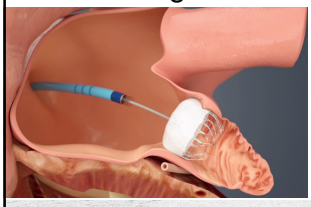


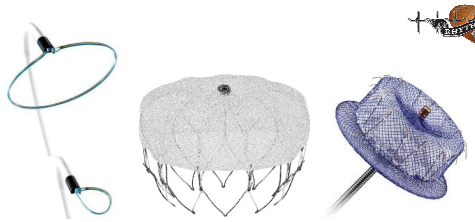
Luis Asmarats, and Josep Rodés-Cabau Circ Cardiovasc Interv. 2017;10:e005359

Two Basic Approaches for Percutaneous LAA Closure

"Plug"

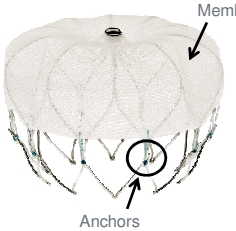


External Suture

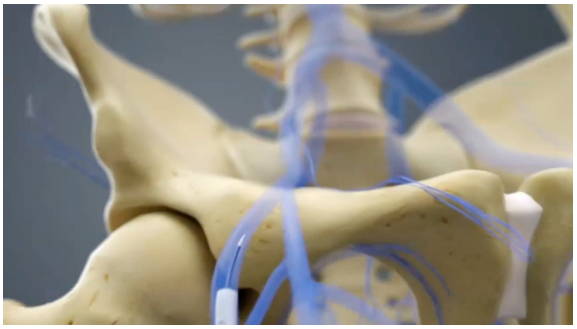


	Lariat	Watchman	Amulet
FDA Approval	Initial 510(k) approval in Feb 2009 for soft tissue approximation and/or ligation. Lariat XT – 510(k) approval May 5, 2016	March 13, 2015	IDE Trial Currently Enrolling (CE Mark: Jan 18, 2013)

Watchman LAA Closure Device



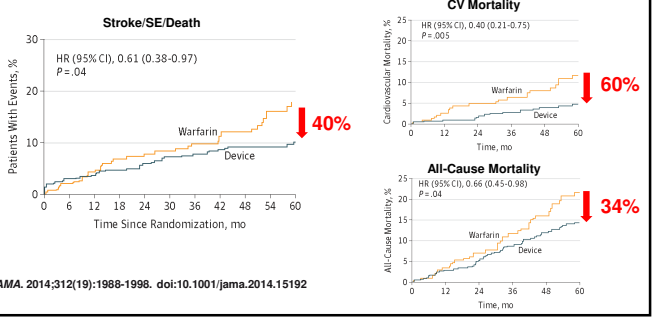
- Available sizes: 21, 24, 27, 30, 33 mm diameter
- Self-expanding Nitinol frame
- 10 active fixation anchors - designed to engage tissue for stability
- 160 micron membrane PET cap designed to block emboli and promote healing



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**

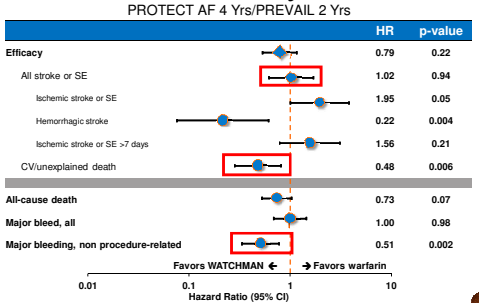
PROTECT-AF



JAMA. 2014;312(19):1988-1998. doi:10.1001/jama.2014.15192

Meta-Analysis

PROTECT AF 4 Yrs/PREVAIL 2 Yrs



JDR Holmes, SK Doshi, et al. JACC 2015; 65(24): 2614-2623. Combined data set of all PROTECT AF and PREVAIL WATCHMAN patients versus chronic warfarin patients

WATCHMAN Therapy

Indications for Use

FDA Approval: March 13, 2015

The WATCHMAN Device is indicated to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who:

- Are at increased risk for stroke and systemic embolism based on $CHADS_2$ or CHA_2DS_2-VASc scores and are recommended for anticoagulation therapy;
- Are deemed by their physicians to be suitable for warfarin
- Have an appropriate rationale to seek a non-pharmacologic alternative to warfarin, taking into account the safety and effectiveness of the device compared to warfarin.

The Food and Drug Administration

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WATCHMAN Therapy

National Coverage Determination Effective Feb. 8, 2016

CMS will cover percutaneous LAAC implants when specific criteria are met:

Documented in medical record

- Eligible patients must have a $CHADS_2$ score ≥ 2 or a CHA_2DS_2-VASc score ≥ 3
- Patients must be suitable for short-term warfarin, but deemed unable to take long-term oral anticoagulation
- Documented evidence of a formal shared decision interaction between the patient and an independent non-interventional physician using an OAC evidence-based decision tool
- *LAA Registry*: Patients must be enrolled in a prospective national registry

CMS CENTERS FOR MEDICARE & MEDICAID SERVICES

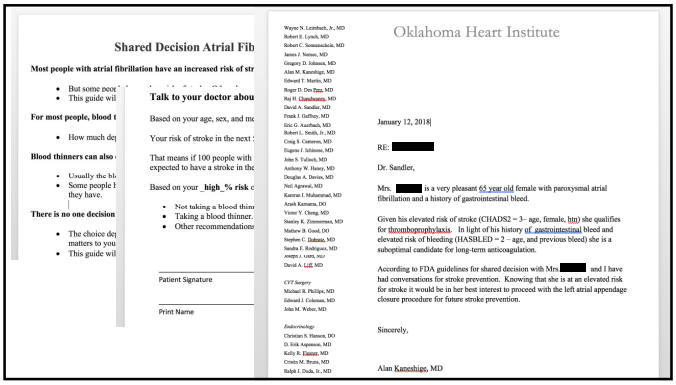
Shared Decision Making Tools

ACP — https://www.acponline.org/patients_families/products/brochures/afib_booklet.pdf

NICE — https://www.nice.org.uk/guidance/cg180/resources/patient-decision-aid-243734797

CardioSmart — http://www.acc.org/tools-and-practice-support/quality-programs/anticoagulation-initiative/anticoagulation-shared-decision-making-tool

15th Annual — OKLAHOMA HEART RESEARCH AND EDUCATION FOUNDATION PRESENTS


Shared Decision Atrial Fib

Most people with atrial fibrillation have an increased risk of str

- But some peop
- This guide wil

Talk to your doctor abou

For most people, blood t

- How much de

Blood thinners can also

- Usually the bl
- Some people h they have.

There is no one decision

- The choice de matters to you
- This guide wil

Based on your age, sex, and m

Your risk of stroke in the next

That means if 100 people with expected to have a stroke in the

Based on your _high_% risk

- Not taking a blood thin
- Taking a blood thinner.
- Other recommendations

Patient Signature

Print Name

Oklahoma Heart Institute

January 12, 2018

RE: [redacted]

Dr. Sandler,

Mrs. [redacted] is a very pleasant 65 year old female with paroxysmal atrial fibrillation and a history of gastrointestinal bleed.

Given his elevated risk of stroke (CHADS2 = 3– age, female, htn) she qualifies for thromboprophylaxis. In light of his history of gastrointestinal bleed and elevated risk of bleeding (HASBLED = 2 – age, and previous bleed) she is a suboptimal candidate for long-term anticoagulation.

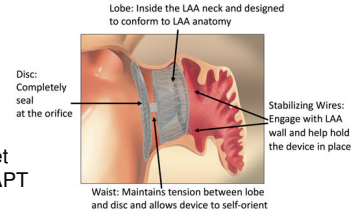
According to FDA guidelines for shared decision with Mrs. [redacted] and I have had conversations for stroke prevention. Knowing that she is at an elevated risk for stroke it would be in her best interest to proceed with the left atrial appendage closure procedure for future stroke prevention.

Sincerely,

Alan Kaneshige, MD

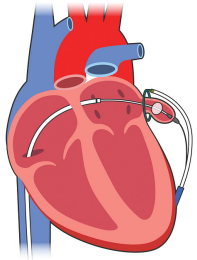
Amulet

- No prospective, randomized data yet.
- Amulet IDE Trial
  - Prospective multicenter randomized US trial
    - N = 1600
    - 1:1 Watchman vs. Amulet
    - Amulet arm may take DAPT



15th Annual — OKLAHOMA HEART RESEARCH AND EDUCATION FOUNDATION PRESENTS

Lariat



- No prospective, randomized data
- No endocardial foreign body
- Possible neurohormonal benefits
- Possible antiarrhythmic benefits
  - aMAZE Trial – enrolling since 9/15
    - PVI vs. PVI with Lariat LAA ligation for persistent AF
    - N = 600 pts

15th Annual

Which of the following patients is NOT a candidate for Watchman LAA Closure?

A. 65 yo woman with persistent AF, HTN, prior TIA, and recurrent GI bleeding on apixaban (Eliquis).

B. 80 yo man with permanent AF, HTN, DM, CHF, and frequent falls on chronic warfarin.

C. 50 yo police officer with parox AF, HTN, DM on rivaroxaban (Xarelto) concerned about his occupational bleeding risk.

D. 65 yo woman with permanent AF, HTN, DM, prior CVA, and recurrent, spontaneous intracranial hemorrhage - deemed not to be a candidate for any anticoagulation (absolute contraindication per neurosurgery).

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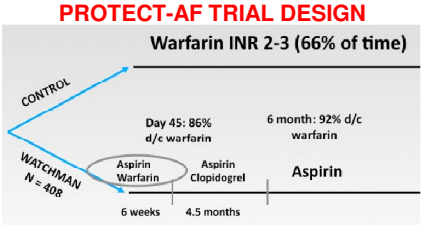
What do you mean, "Watchman patients must be suitable for warfarin?!?!?"

"…suitable for warfain..."

PROTECT-AF TRIAL DESIGN



TEE criteria for warfarin discontinuation: complete closure LAA or residual peri-device flow (jet < 5 mm)

Lancet 2009 Aug 15;374(9689):534-42

ASAP Registry

- Patients had a history of hemorrhagic & bleeding tendencies or a hypersensitivity to warfarin
- 150 patients received Watchman at 4 European Centers
- Post procedure antiplatelet regimen (Clopidogrel through 6 months, Aspirin indefinitely)

Reasons for warfarin ineligibility	
History of hemorrhagic/bleeding tendencies	140 (93.0%)
Blood dyscrasia	11 (7.3%)
Unsupervised senitility/high fall risk	6 (4.0%)
Other	8 (5.3%)
CHA2DS2 VASc	4.4
CHADS2 (avg)	2.8

Reddy et al. JACC 2013; 61(25): 551–6

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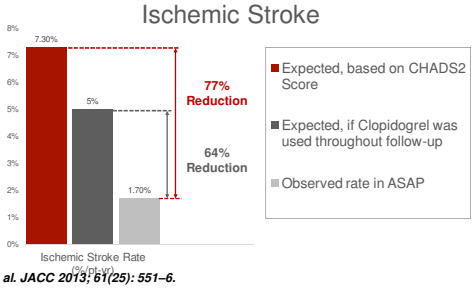
ASAP Registry

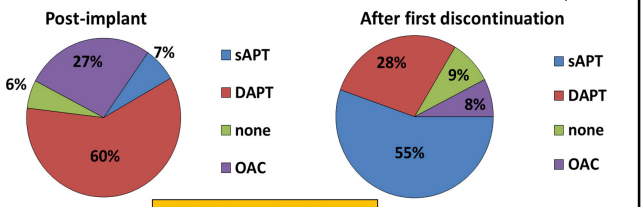
Efficacy Outcome vs. Expected

Ischemic Stroke



Reddy et al. JACC 2013; 61(25): 551–6.

EWOLUTION



OAC drop within 3 mo
DAPT drop within 6 mo

Heart Rhythm 2017 14, 1302-1308DOI: (10.1016/j.hrthm.2017.05.038)

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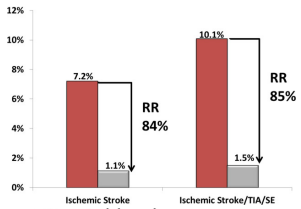
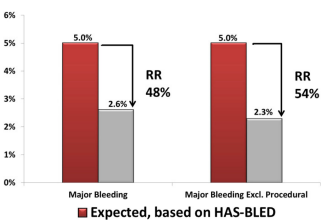
Stroke



Bleeding



Heart Rhythm 2017 14, 1302-1308DOI: (10.1016/j.hrthm.2017.05.038)

ASAP-TOO Trial

- Randomized 2:1 (WATCHMAN:Control) IDE trial in NVAF subjects deemed unsuitable for anticoagulation
- Control group: Single antiplatelet medication or no medication
- Up to 888 subjects
- Primary effectiveness endpoint: Time to first event of ischemic stroke or systemic embolism
- Primary safety endpoint: 7-day combined rate of death, ischemic stroke, systemic embolism and complications requiring major cardiovascular or endovascular intervention.

Adequately powered to address the fundamental question of benefit-risk in patients who would otherwise not be treated with anticoagulation

Which of the following patients is the BEST candidate for Watchman LAA Closure?

A. 65 yo woman with persistent AF, HTN, prior TIA, and recurrent GI bleeding on apixaban (Eliquis).

B. 80 yo man with permanent AF, HTN, DM, CHF, and frequent falls on chronic warfarin who lives in a nursing home.

C. 50 yo man with HTN, DM, and paroxysmal AF tolerating apixaban (Eliquis) well who "wants to come off of his blood thinner."

D. 65 yo woman with permanent AF, HTN, DM, prior CVA, and recurrent, spontaneous intracranial hemmorrhage - deemed not to be a candidate for any anticoagulation (absolute contraindication per neurosurgery).

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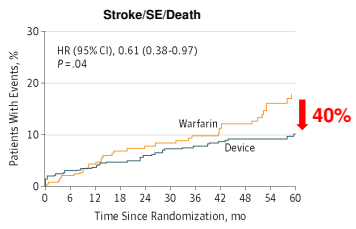
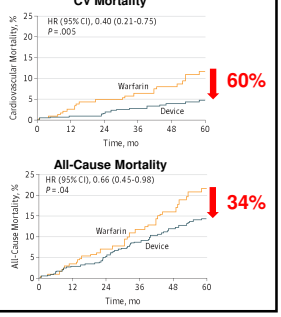
PROTECT-AF

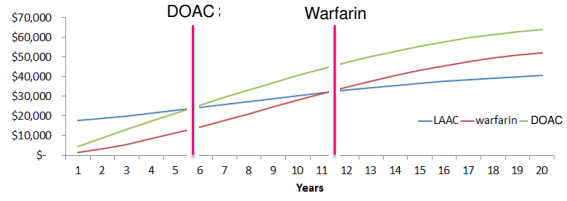




JAMA. 2014;312(19):1988-1998. doi:10.1001/jama.2014.15192

COST EFFECTIVENESS

Total costs through 20 Years with Watchman versus warfarin & DOAC



Reddy VY et al. TCT 2016 Abstract

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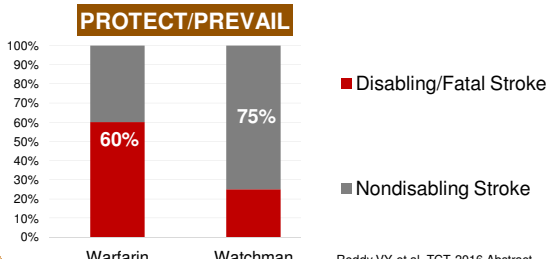
Stroke Disability Rates



Reddy VY et al. TCT 2016 Abstract.

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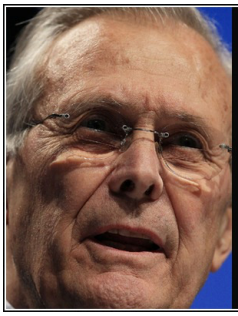
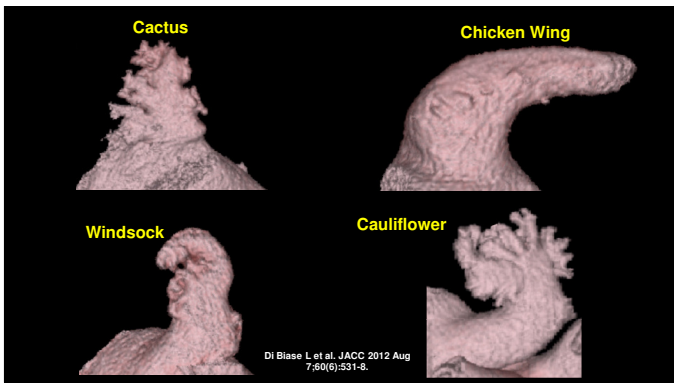


There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don't know.

— Donald Rumsfeld —

Knowledge Gaps in LAAC
"The Known Unknowns"

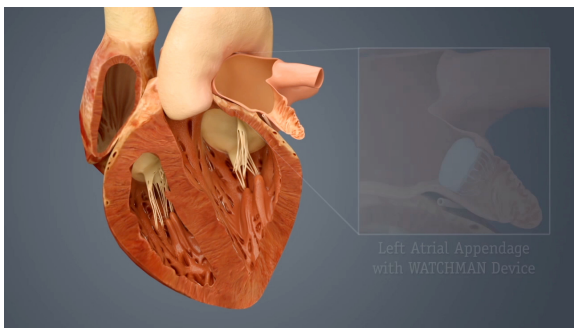
- Only prospective, randomized data for Watchman device.
- Is antiplatelet therapy sufficient?
  - ASAP-TOO
  - AMULET IDE
- No head-to-head comparisons:
  - device vs. DOAC
  - device vs. device
- Safety of cardioversion without anticoagulation post-LAAC?



Summary

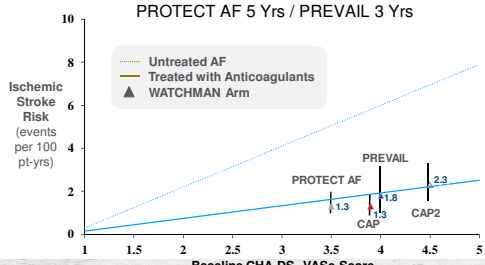
- Percutaneous left atrial appendage closure is here!
- Watchman device – only randomized prospective data
  - But stay tuned…
- Watchman LAAC candidates must be suitable for short-term anticoagulation.
  - Await ASAP-TOO and Amulet IDE studies
- The future looks bright…

Rhythms of the HEARTLAND



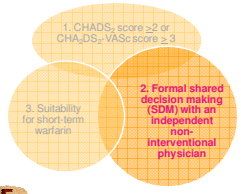
Ischemic Stroke Rate Aligns with Expected Rate Based on Risk Score

PROTECT AF 5 Yrs / PREVAIL 3 Yrs



Friberg. Eur Heart J (2012); NICE UK (2014). WATCHMAN FDA Panel Sponsor Presentation. Oct 2014

NCD Criterion 2: Formal SDM interaction with an independent non-interventional physician using an evidenced-based decision tool on oral anticoagulant (OAC) in patients with NVAF prior to LAAC. This interaction must be documented.



Independent non-interventional physician:
- Physician other than implanter
- CMS references primary care provider, a non-interventional cardiologist, neurologist or those who have experience caring for stroke patients (pg. 77 of decision memo)

OAC evidenced-based decision tool:* (Page 92 of decision memo)
- American College of Physician Foundation: AF Management Guide
- NICE Patient Decision Aid on AF Treatment Options
- ACC Cardiosmart's AF Treatment Options

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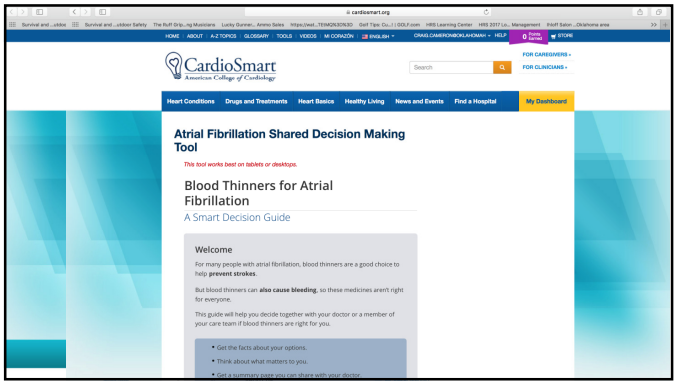


- Five studies, >2400 patients, nearly 6000 patient-years of follow-up

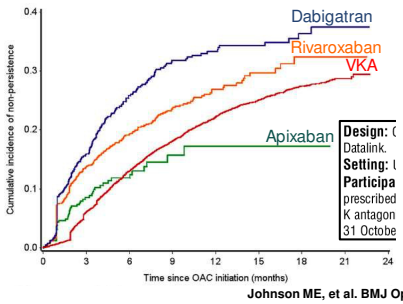
WATCHMAN™ Clinical Leadership

WATCHMAN™ LEFT ATRIAL APPENDAGE CLOSURE DEVICE

- WATCHMAN is a **safe alternative** to long-term warfarin therapy which offers **comparable stroke risk reduction** and enables patients to **stop taking warfarin**[1,2]
  - 95% implant success rate[3]
  - >92% warfarin cessation after 45 days, >99% after 1 year[1]
- WATCHMAN™ therapy demonstrated **comparable stroke risk reduction** and **statistically superior reductions in major non-procedure related bleeding and cardiovascular death** compared to warfarin[2,4]:

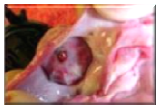
1. Holmes, DR et al. JACC 2014; Vol. 64, No. 1. 2. Holmes, DR et al. JACC 2015; Vol. 65, No. 2. 3. Reddy VY, Holmes DR, et al. JACC 2016; Article in press. 4. Price, M. J., V. Y. Reddy, et al. JACC: CV Interv. 2015; 8(15): 1825-1834

Real-World OAC Discontinuation Rate

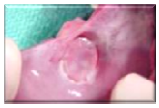


Johnson ME, et al. BMJ Open 2016;6:e011471.

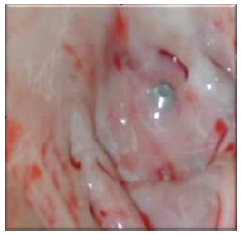
Watchman Device Endothelialization



Canine Model – 30 Day



Canine Model – 45 Day



Human Pathology – 9 Months Post-implant
Non-device related death

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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_2DS_2-VASc	3.5 ± 1.6	3.9 ± 1.5	4.0 ± 1.2	4.5 ± 1.3	<0.0001

Source: FDA Oct 2014 Panel Sponsor Presentation.
This chart is not based on a head-to-head trial and is not intended to support head-to-head comparisons of the separate trials on the therapies under study.

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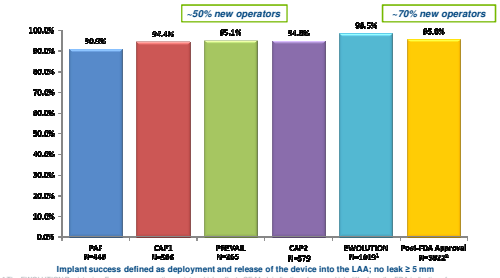
Procedural Success



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

* The EWOLUTION Registry is a European prospective registry which reflects CE Mark indications for use which differ from the FDA indications for use.
1 Boersma L et al. EHJ published online Jan 2016 in press 2 Reddy VY, Holmes DR, et al. JACC 2016; Article in press

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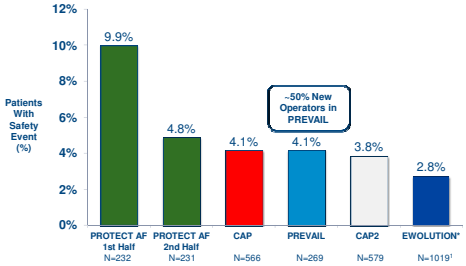
Favorable Procedural Safety Profile:
All Device and/or Procedure-related Serious Adverse Events within 7 Days



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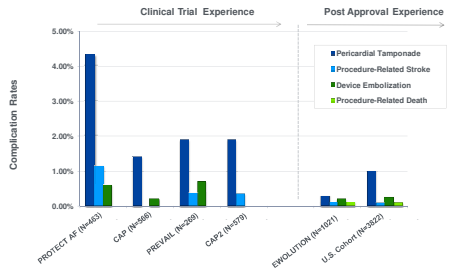
Favorable Procedural Safety Profile:
Major Procedural Complications Across WATCHMAN Studies



* The EWOLUTION Registry is a European prospective registry which reflects CE Mark indications for use which differ from the FDA indications for use.
Source: Reddy VY, Holmes DR, et al. JACC 2016; Article in press

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Favorable Procedural Safety Profile:
Major Procedural Complications Across WATCHMAN Studies

	PROTECT-AF	PREVAIL	CAP	CAP2	EWOLUTION	Post-FDA Approval	Aggregate Data
Pericardial Tamponade	**20 (4.3%)**	**5 (1.9%)**	**8 (1.4%)**	**11 (1.9%)**	**3 (0.29%)**	**39 (1.02%)**	**86 (1.28%)**
Treated with pericardiocentesis	13 (2.8%)	4 (1.5%)	7 (1.2%)	n/a	2 (0.20%)	24 (0.63%)	
Treated surgically	7 (1.5%)	1 (0.4%)	1 (0.2%)	n/a	1 (0.10%)	12 (0.31%)	
Resulted in death	0	0	0	0	0	3 (0.78%)	
Pericardial effusion – no intervention	4 (0.9%)	0	5 (0.9%)	3 (0.5%)	4 (0.39%)	11 (0.29%)	27 (0.40%)
Procedure-related stroke	**5 (1.15%)**	**1 (0.37%)**	**0**	**2 (0.35%)**	**1 (0.10%)**	**3 (0.078%)**	**12 (0.18%)**
Device embolization	**3 (0.6%)**	**2 (0.7%)**	**1 (0.2%)**	**0**	**2 (0.20%)**	**9 (0.24%)**	**17 (0.25%)**
Removed percutaneously	1	0	0	0	1	3	
Removed surgically	2	2	1	0	1	6	
Death							
Procedure-related mortality	0	0	0	0	1 (0.1%)	3 (0.078%)	4 (0.06%)
Additional mortality within 7 days	0	0	0	1 (0.17%)	3 (0.29%)	1 (0.026%)	5 (0.07%)

* The EWOLUTION Registry is a European prospective registry which reflects CE Mark indications for use which differ from the FDA indications for use.
Source: Reddy VY, Holmes DR, et al. JACC 2016; Article in press

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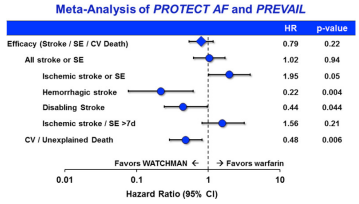
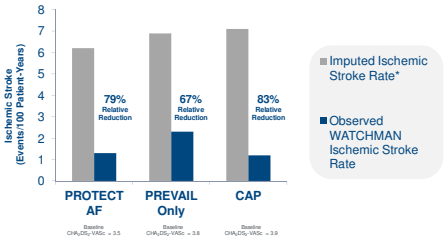
Meta-Analysis of *PROTECT AF* and *PREVAIL*



Heart Rhythm DOI: (10.1016/j.hrthm.2017.10.006)

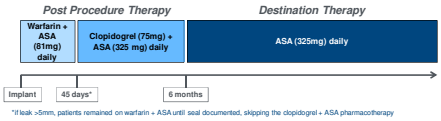
WATCHMAN™ Device Reduces Ischemic Stroke Over No Therapy



* Imputation based on published rate with adjustment for CHA_2DS_2-VASc score (3.0); Olesen JB. Thromb Haemost (2011)

FDA Oct 2014 Panel Sponsor Presentation. Holmes D, et al. TCT 2014 (abstract)

Observed Rates of Major Bleeding Over Time According to Treatment Group



*If leak >5mm, patients remained on warfarin + ASA until seal documented, skipping the clopidogrel + ASA pharmacotherapy

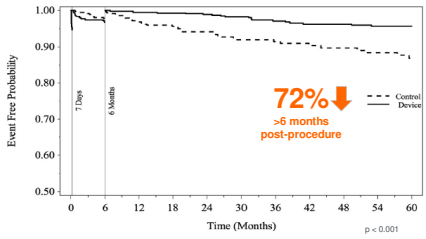
	LAAC (n=732)		Long-term warfarin (n=382)		Rate Ratio	P value
	Bleeding Rate (n events / N at risk)	Event Rate per 100 pt-yrs (n events / N at risk)	Bleeding Rate (n events/N at risk)	Event Rate per 100 pt-yrs (n events / N at risk)		
Overall	10.8 (79/732)	3.5 (79/2268)	11.3 (43/382)	3.6 (43/1187)	0.96	0.84
Post Procedure	5.9 (40/682)	1.8 (40/2255)	11.3 (43/381)	3.6 (43/1180)	0.49	0.001
Destination	3.2 (19/601)	1.0 (19/1958	9.7 (35/360)	3.5 (35/1004)	0.28	<0.001

Overall period defined as after randomization to the end of follow-up; post-procedural period as >7 days after randomization to the end of follow-up; destination therapy period as beyond 180 days post-randomization, when patients assigned to LAA closure were eligible to receive aspirin alone.

Price, M. J., V. Y. Reddy, et al. JACC: CV Interv. 2015; 8(15): 1925-1932

Bleeding Outcomes after Left Atrial Appendage Closure Compared with Long-term Warfarin

Freedom of Major Bleeding Over 3 Adjunctive Pharmacotherapy Intervals

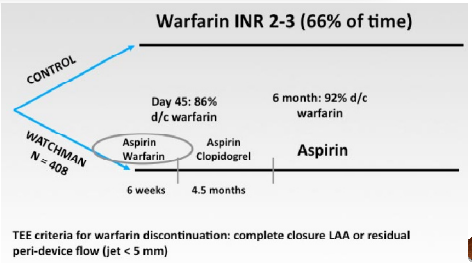


Price, M. J., V. Y. Reddy, et al. JACC: CV Interv. 2015; 8(15): 1925-1932

PROTECT-AF: Methods

N = 800 (707 randomized) NVAF Pts with CHADS2 ≥ 1 and eligible for Warfarin
2:1 Randomization to Watchman or Warfarin

WATCHMAN™ LEFT ATRIAL APPENDAGE CLOSURE DEVICE



TEE criteria for warfarin discontinuation: complete closure LAA or residual peri-device flow (jet < 5 mm)

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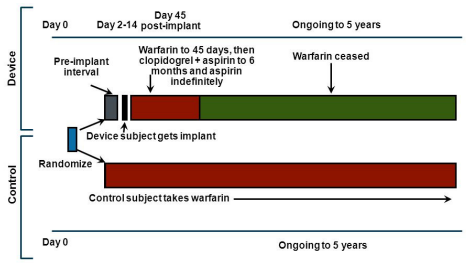
PROTECT AF

Design



Fountain RB, et al. *Am Heart J.* 2006;151:956-961 [6]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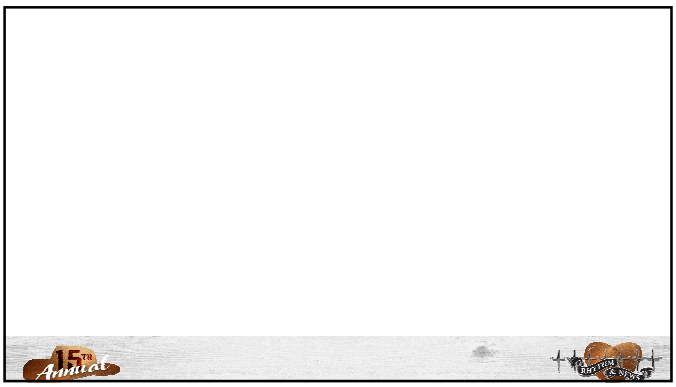
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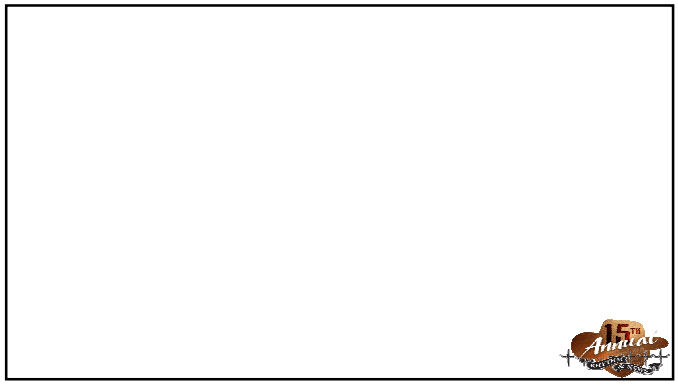
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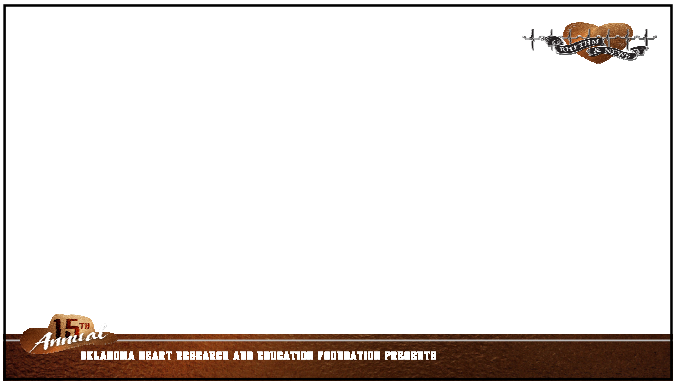
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Rhythms
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