Reducing Thromboembolic Risk in Atrial Fibrillation :

"The Watchman Experience"

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ORLANDO HEALTH HEART INSTITUTE CARDIOLOGY
October 7, 2017


08 19 2015


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Reducing Thromboembolic Risk in Atrial Fibrillation

- Case Study
- Epidemiology
- Risk Assessment
- Oral Anticoagulation
- Non Pharmacologic Strategies

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  Watchman – the Left Atrial Appendage Occluder

Reducing Thromboembolic Risk in Atrial Fibrillation

Case :

- 80 yo female with h/o asymptomatic permanent atrial fibrillation – CHA2DS2VAsc- 4 (age,gender,HTN). Therapeutic trials with warfarin and one target specific oral anticoagulant led to multiple hospitalizations secondary to GI bleed. Work up did not identify a correctable source. HASBLED -3
- Exam – notable for irregular heart rate in the 70-80 ‘s
- Meds - Warfarin

Reducing Thromboembolic Risk in Atrial Fibrillation

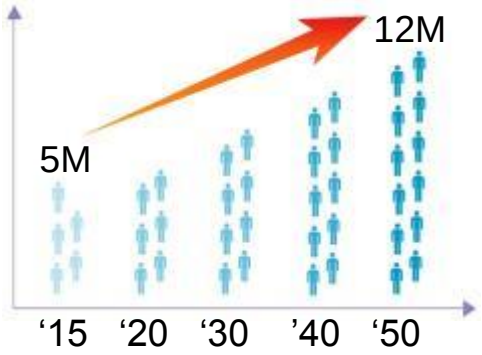
Case :

Dillema : What Would You Do Next ?

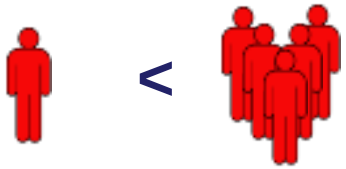
A. Discontinue warfarin and start ASA
B. Discontinue warfarin and start clopidogrel
C. Try another target specific oral anti-coagulant
D. Consult your nearest friendly neigborhood electrophysiologist or structural heart disease specialist for a Left atrial appendage occluder ie The Watchman

AF is a Growing Problem Associated with Greater Morbidity and Mortality

AF = most common cardiac arrhythmia, and growing



AF increases risk of stroke



~5 M
people with AF in U.S., expected to more than double by 2050[1]

5x
greater risk of stroke with AF[2]

- 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

1. Go AS, et al. Heart Disease and Stroke Statistics—2013 Update: A Report From the American Heart Association. Circulation. 2013; 127: e6-e245.
2. Holmes DR, Atrial Fibrillation and Stroke Management: Present and Future, Seminars in Neurology 2010;30:528–536.

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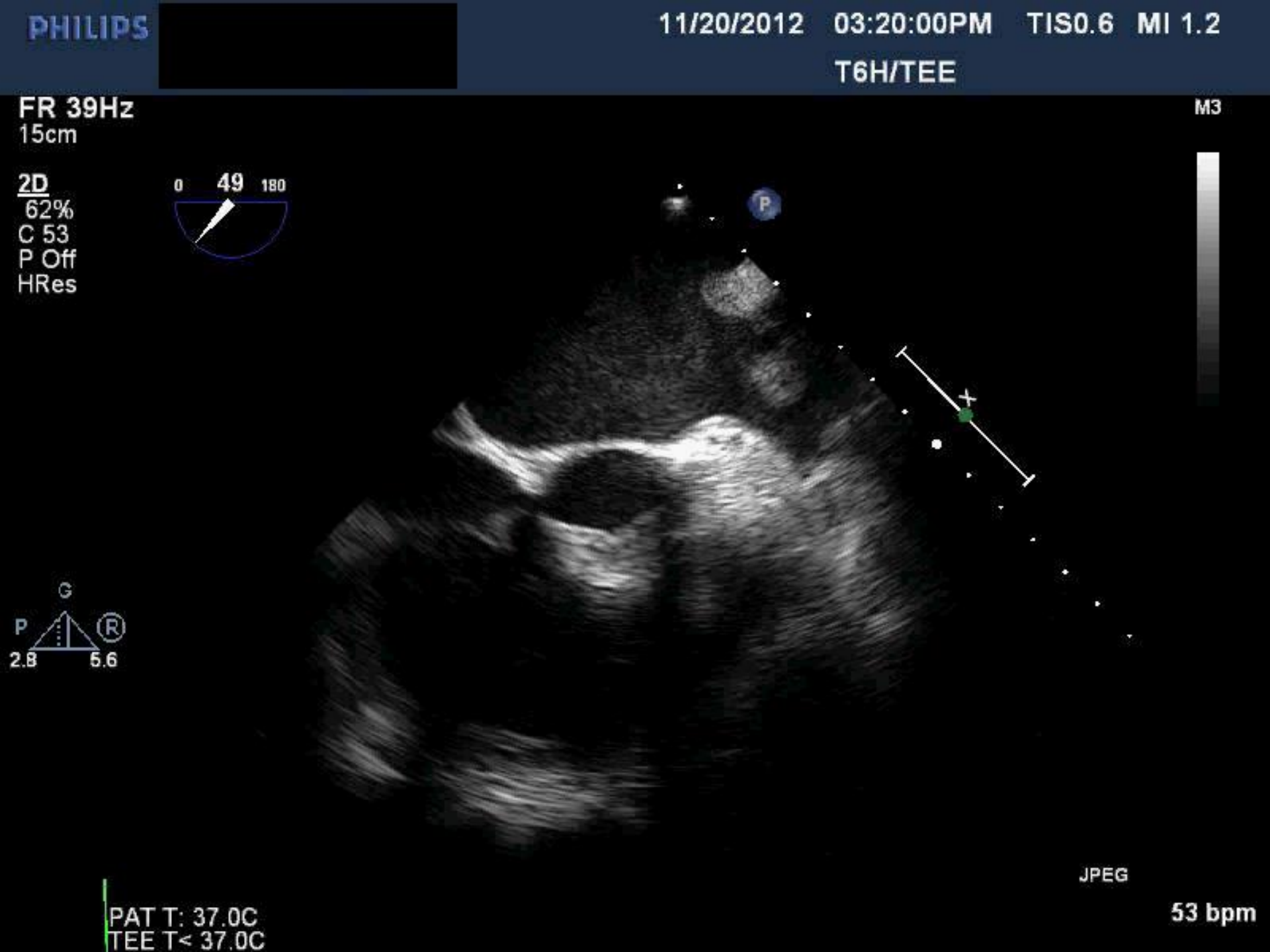
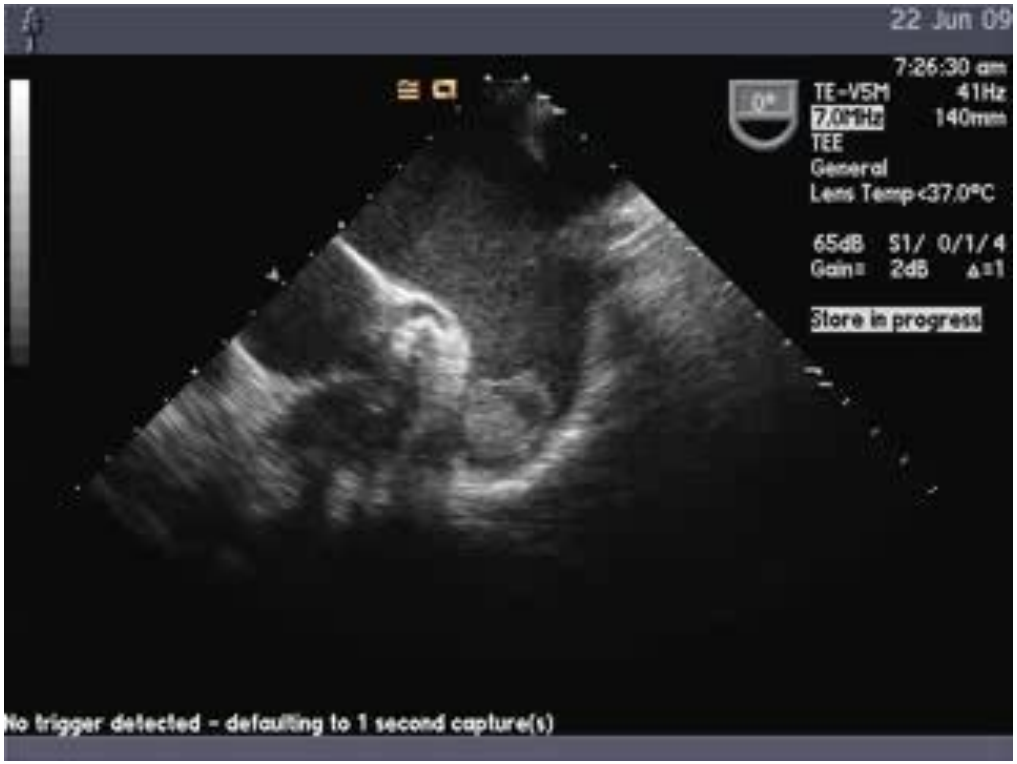

PHILIPS
11/20/2012 03:20:00PM TIS0.6 MI 1.2
T6H/TEE
FR 39Hz
15cm
M3
2D
62%
C 53
P Off
HRes
0 49 180
P
G
P
R
2.8
5.6
JPEG
53 bpm
PAT T: 37.0C
TEE T< 37.0C

Connection Between Non-Valvular AF-Related Stroke and the Left Atrial Appendage

AF Creates Environment for Thrombus Formation in Left Atrium

- Stasis-related LA thrombus is a predictor of TIA[1] and ischemic stroke[2].
- In non-valvular AF, >90% of stroke-causing clots that come from the left atrium are formed in the LAA[3].



1. Stoddard et al. Am Heart J. (2003)
2. Goldman et al. J Am Soc Echocardiogr (1999)
3 Blackshear JL. Odell JA. *Annals of Thoracic Surg* (1996)

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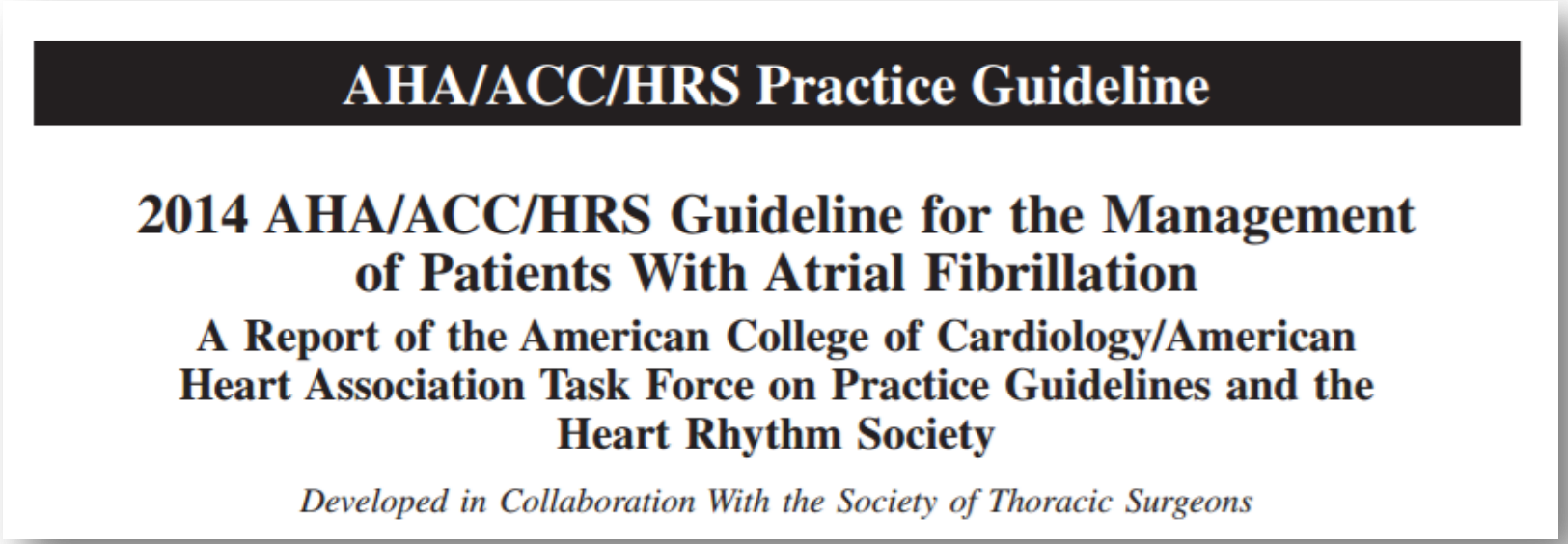
2014 ACC/AHA/HRS Treatment Guidelines Recommend OAC for Stroke Risk



AHA/ACC/HRS Practice Guideline

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

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society

Developed in Collaboration With the Society of Thoracic Surgeons

CHA_2DS_2 VASc Score	Recommendation
0	No anticoagulant
1	Aspirin (81-325 mg daily) or warfarin (INR 2-3)
≥2	**Oral anticoagulants are recommended** (warfarin (INR 2-3), dabigatran, rivaroxaban or apixaban

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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

Stroke Risks Compound Over Time

CHA_2DS_2-VASc* Score	Annual % Stroke Risk
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7

HAS-BLED** Score	Annual % Bleed Risk	10-Year Bleeding Risk (%)***
0	0.9	8.6
1	3.4	29.2
2	4.1	34.2
3	5.8	45.0
4	8.9	60.6
5	9.1	61.5

* 2014 AHA / ACC / HRS Guidelines
** Lip. JACC (2011)
*** Assumes constant risk despite increasing age and bleeding risk is independent from bleeding risk in previous years

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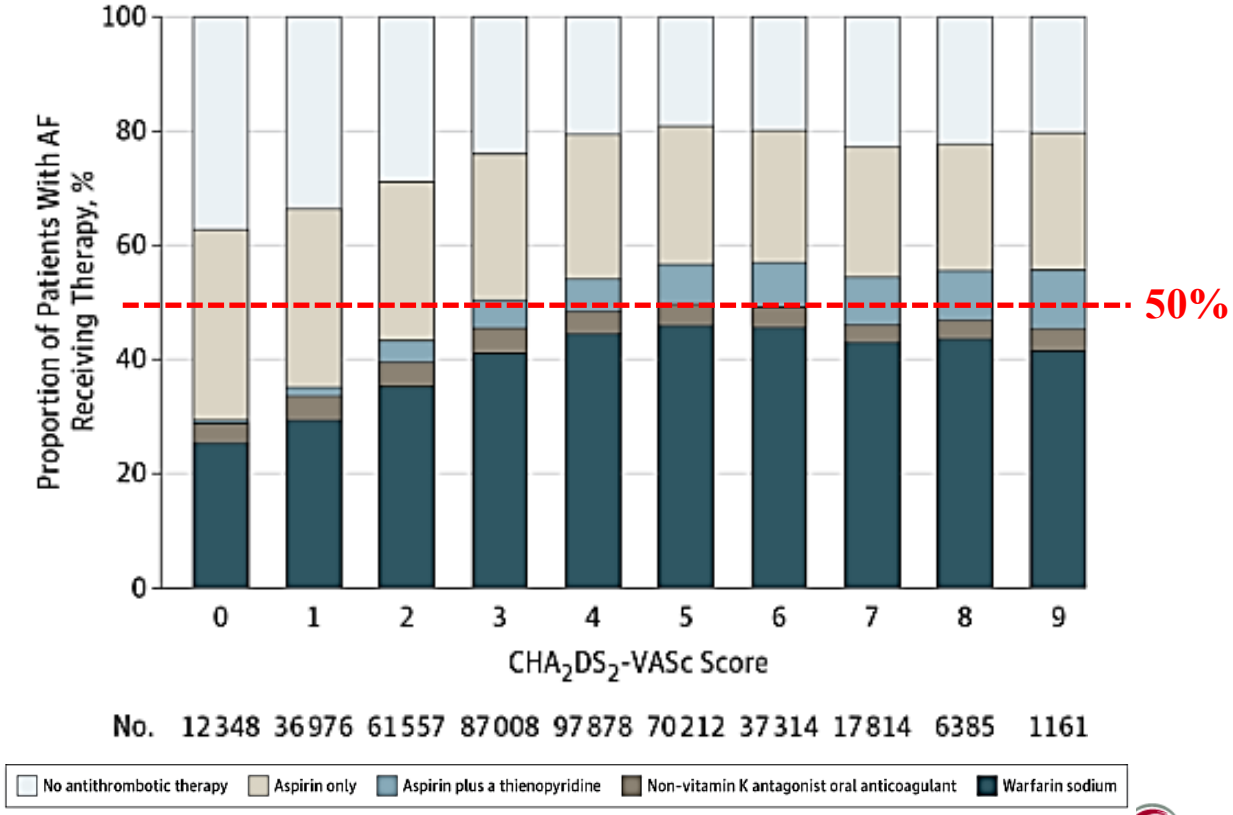
Oral Anticoagulation is Standard of Care, but Not Prescribed for All

NCDR Pinnacle Registry: >400,000 Outpatients w AF

<50% of Patients with AF at Highest Risk of Stroke were Prescribed an OAC



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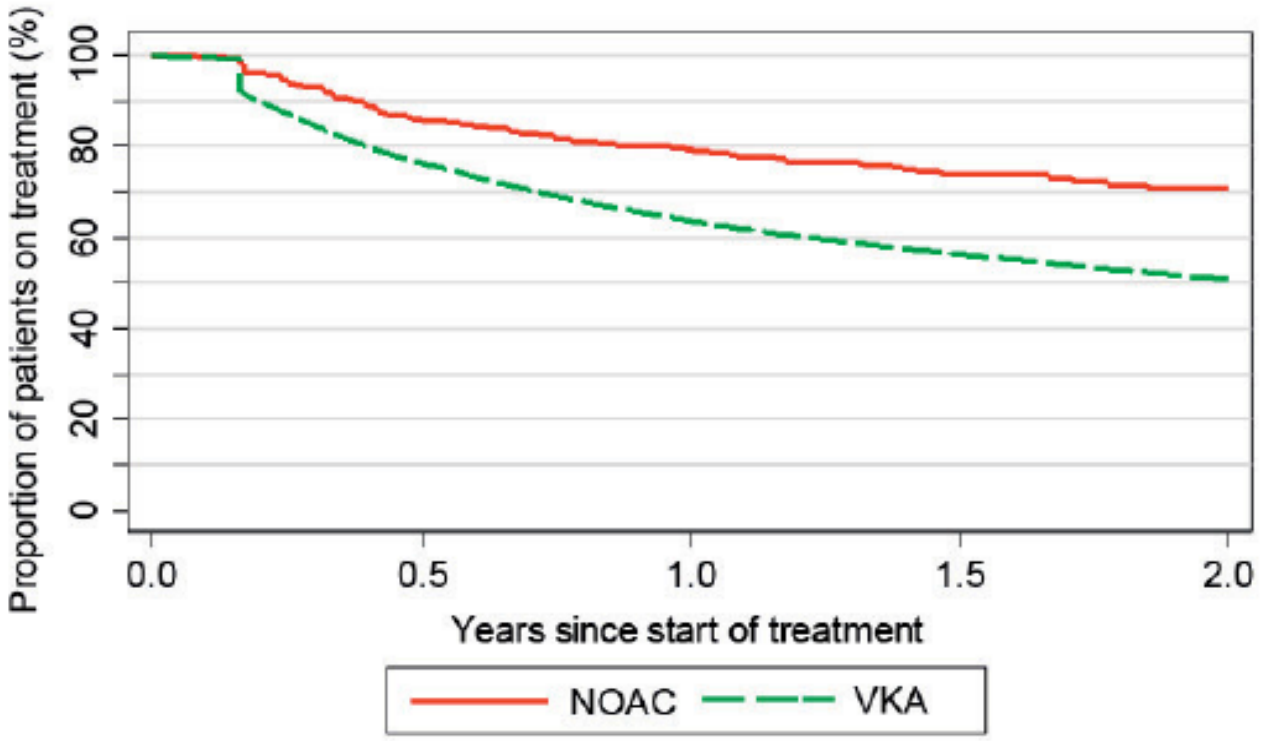
1. Hsu, J et al. *JAMA Cardiol*. Published online March 16, 2016. doi:10.1001/jamacardio.2015.0374

Despite NOAC Adoption and Ability to Switch NOACs, Adherence to Anticoagulation Remains a Challenge

~30% of NOAC patients stop taking any drug at 2 years



NOAC	914	651	342	139	41
VKA	12307	8453	5762	3915	2506

Source: 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/TH15-04-0350.

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NOAC FDA Approval Studies Demonstrated High Discontinuation Rates at ~2 Years

Treatment	Study Drug Discontinuation Rate	Major Bleeding (rate/year)	Non Major Bleeding (rate/year)
Rivaroxaban[1]	***24%***	*3.6%*	*11.8%*
Apixaban[2]	***25%***	*2.1%*	*18%*
Dabigatran[3] *(150 mg)*	***21%***	*3.3%*	*16.4%*
Edoxaban[4] *(60 mg / 30 mg)*	***33 % / 34%***	*2.8% / 1.6%*	*14.5%*
Warfarin[1-4]	***17 – 28%***	*3.1 – 3.6%*	*16-25%*

[1]Connolly, S. NEJM 2009; 361:1139-1151 – 2 yrs follow-up (Corrected) [2]Patel, M. NEJM 2011; 365:883-891 – 1.9 yrs follow-up, ITT
[3]Granger, C NEJM 2011; 365:981-992 – 1.8 yrs follow-up, [4]Giugliano, R. NEJM 2013; 369(22): 2093-2104 – 2.8 yrs follow-up.

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Evidence of Low Adherence Rates

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Feb 2016

Effect of Adherence to Oral Anticoagulants on Risk of Stroke and Major Bleeding Among Patients With Atrial Fibrillation

Xiaoxi Yao, PhD; Neena S. Abraham, MD, MSCE; G. Caleb Alexander, MD, MS; William Crown, PhD; Victor M. Montori, MD, MSc; Lindsey R. Sangaralingham, MPH; Bernard J. Gersh, MB, ChB, DPhil, FRCP; Nilay D. Shah, PhD; Peter A. Noseworthy, MD

- AHA 65,000 AF pts
- >50% NOAC pts and 60% warfarin pts where non-adherent at 1 year

- Circ 45,000 AF pts
- >50% discontinued OAC by 1 year… 73% by 2.25 years

Circulation

Nov 2016

Treatment and Persistence With Oral Anticoagulants Among Newly Diagnosed Patients With Non-Valvular Atrial Fibrillation in a Commercially Insured and Medicare Advantage Population

Rahul Jain, Jessica Franchino-Elder, An-Chen Fu, Cheng Wang, Stephen Sander, Hiangkiat Tan, Elizabeth Kraft, Vincent Willey

JAMA | Original Investigation

Mar 2017

Association of Preceding Antithrombotic Treatment With Acute Ischemic Stroke Severity and In-Hospital Outcomes Among Patients With Atrial Fibrillation

Ying Xian, MD, PhD; Emily C. O'Brien, PhD; Li Liang, PhD; Haolin Xu, MS; Lee H. Schwamm, MD; Gregg C. Fonarow, MD; Deepak L. Bhatt, MD, MPH; Eric E. Smith, MD, MPH; DaiWai M. Olson, PhD, RN; Lesley Maisch, BA; Deidre Hannah, MSN, RN; Brianna Lindholm, BA; Barbara L. Lytle, MS; Michael J. Pencina, PhD; Adrian F. Hernandez, MD, MHS; Eric D. Peterson, MD, MPH

- JAMA 95,000 post-ischemic stroke pts
- 83.5% were not receiving therapeutic OAC before stroke

Introducing the WATCHMAN™ LAAC Device

A **first-of-its-kind, proven alternative** to long-term warfarin therapy for stroke risk reduction in patients with non-valvular AF

Most studied LAAC therapy, only one proven with long-term data from randomized trials and multi-center registries

A **safe alternative** to long-term warfarin therapy which offers **comparable stroke risk reduction** and enables patients to **stop taking warfarin**

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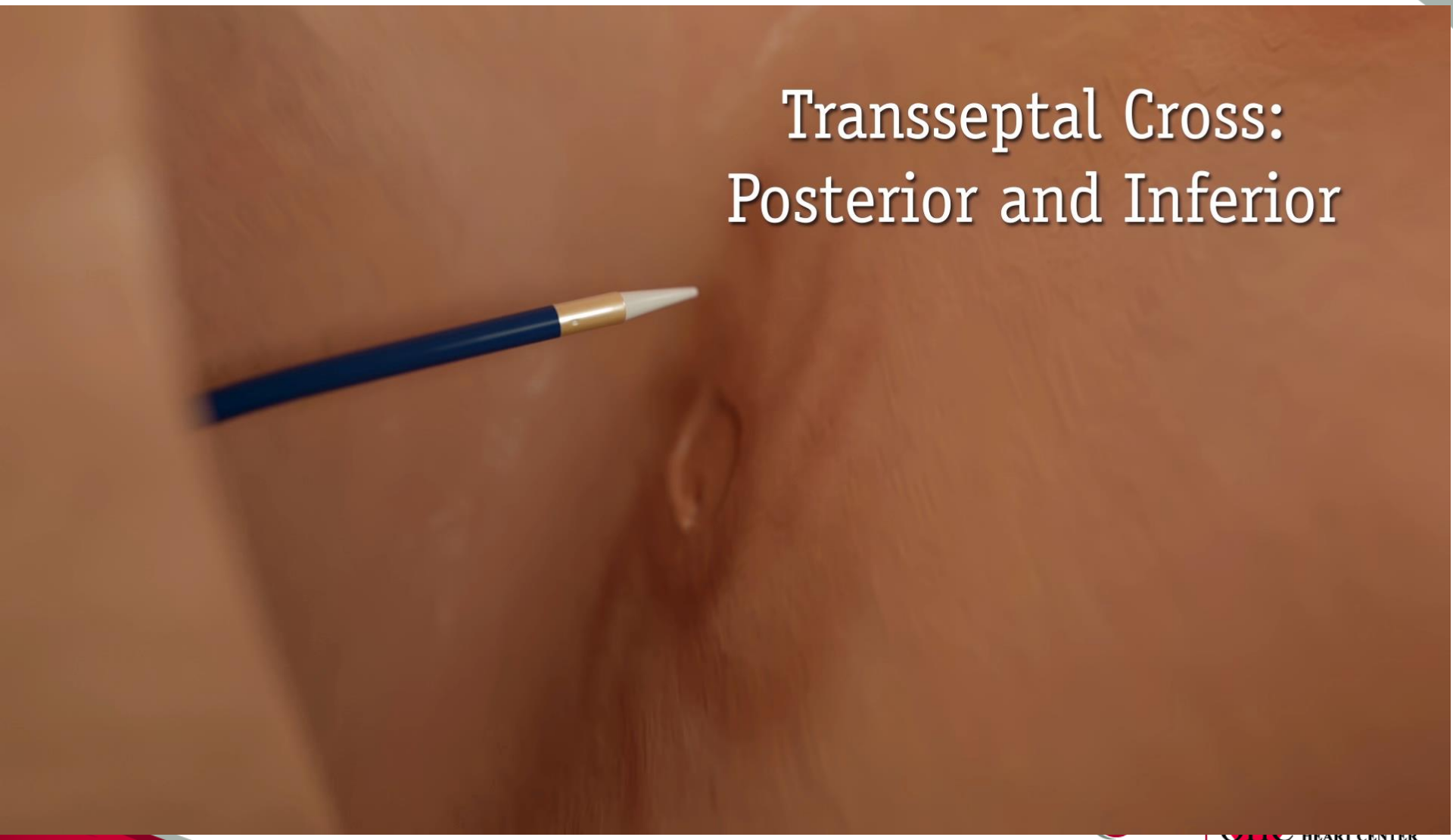
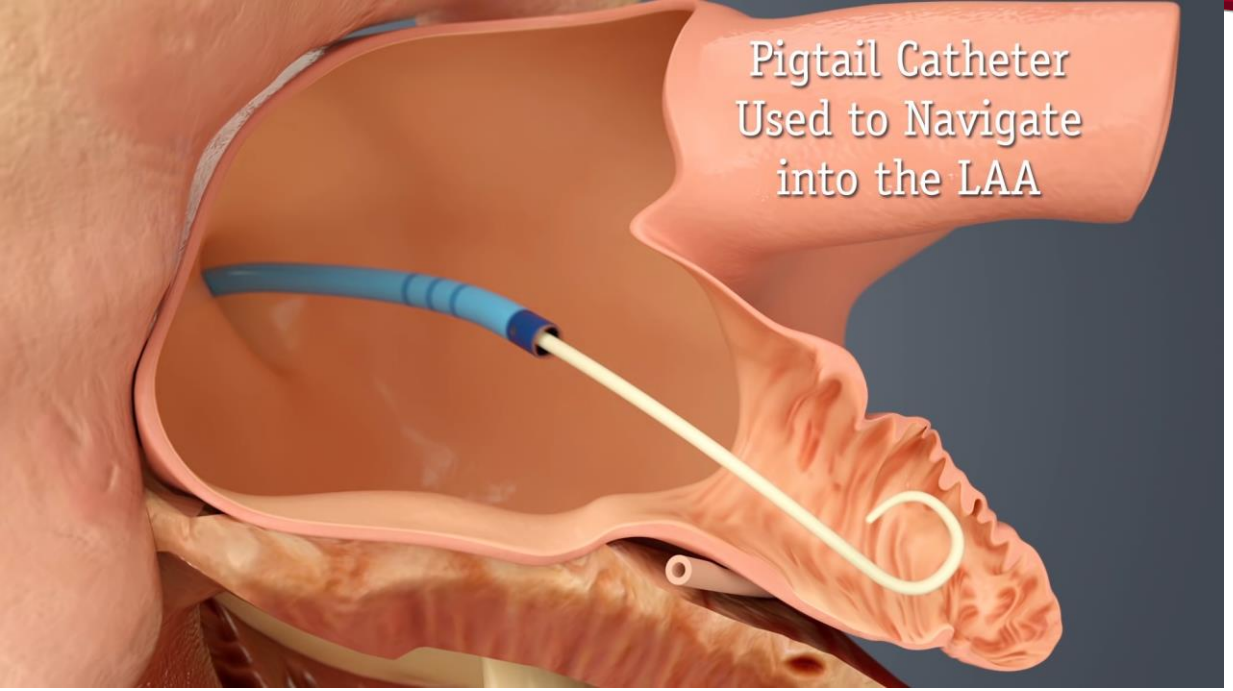
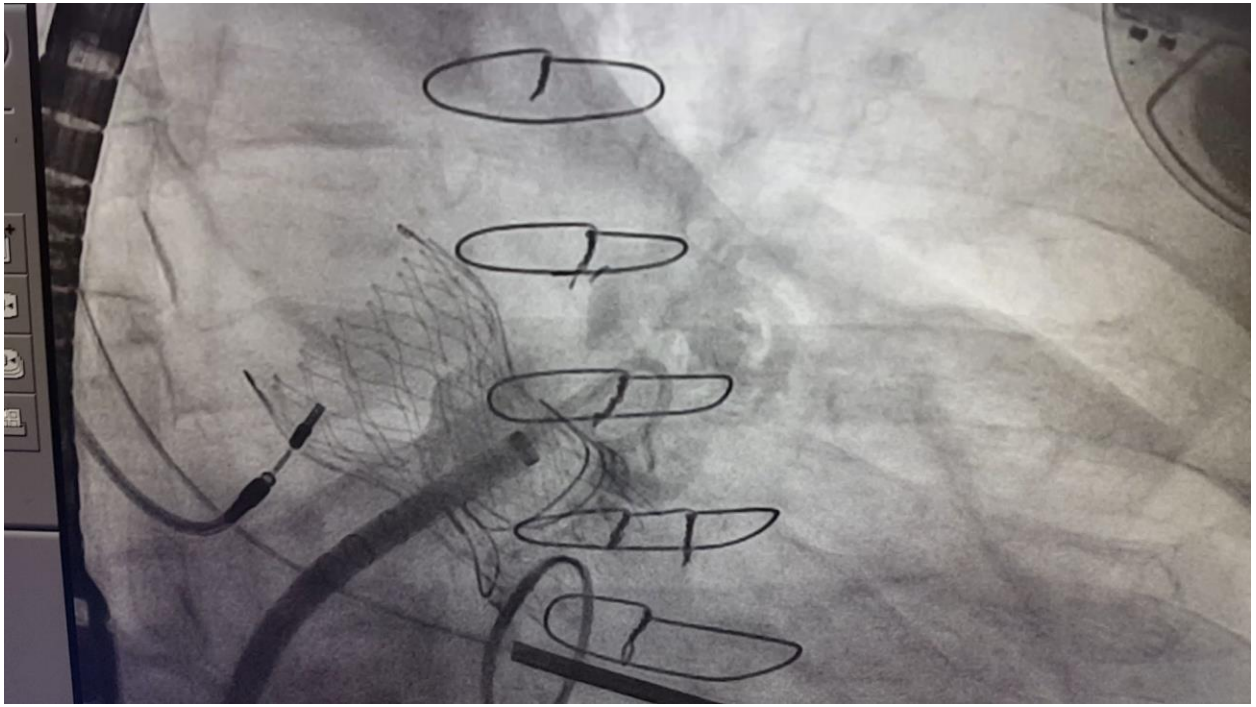
1. Reddy, V et al. JAMA 2014; Vol. 312, No. 19.
2. Reddy, V et al. Watchman I. First Report of the 5-Year PRO


Transseptal Cross:
Posterior and Inferior


Pigtail Catheter
Used to Navigate
into the LAA



Patient Selection Considerations
WATCHMAN™ IFU and CMS Coverage

Patient Selection Considerations

FDA Indication

- 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; and
  - 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

CMS Coverage

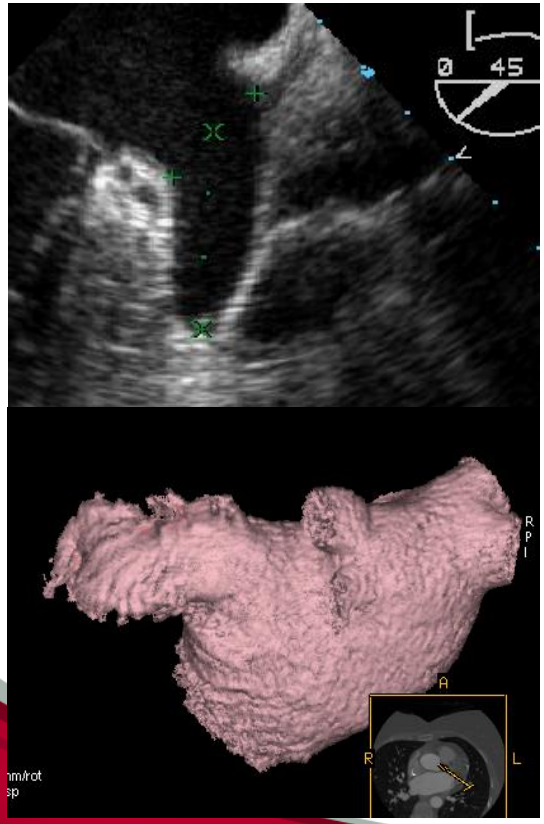
- CHADS2 score ≥2 or a CHA2DS2-VASc score ≥3
- Patients must be suitable for short-term warfarin, but deemed unable to take long-term oral anticoagulation
- Documented evidence of a formal shared decision interaction between the patient and an independent, non-interventional physician

LAA Anatomy / Assessment

Morphology

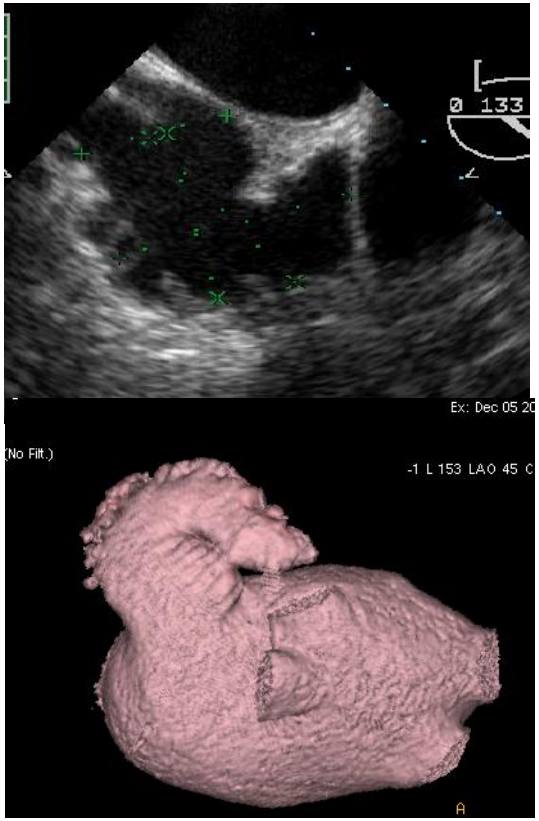
Wind Sock:

An anatomy in which one dominant lobe of sufficient length is the primary structure



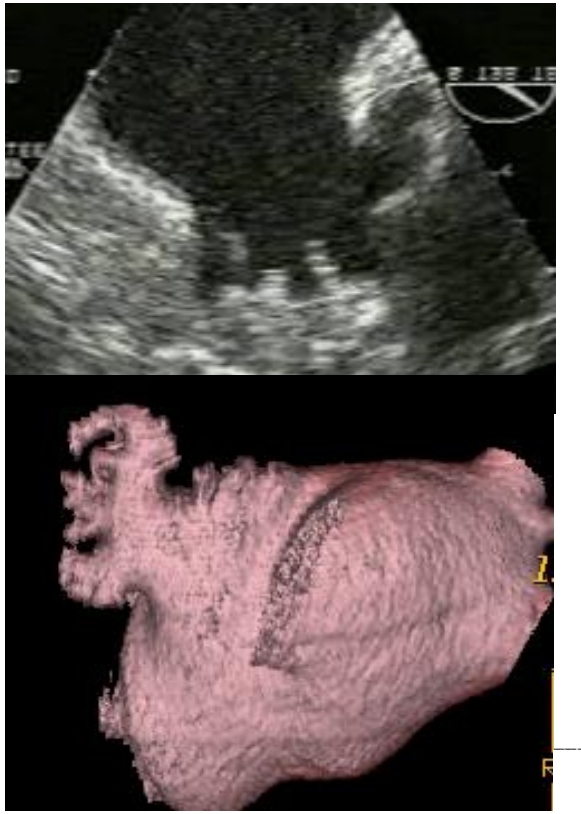
Chicken Wing:

An anatomy whose main feature is a sharp bend in the dominant lobe of the LAA at some distance from the perceived LAA ostium

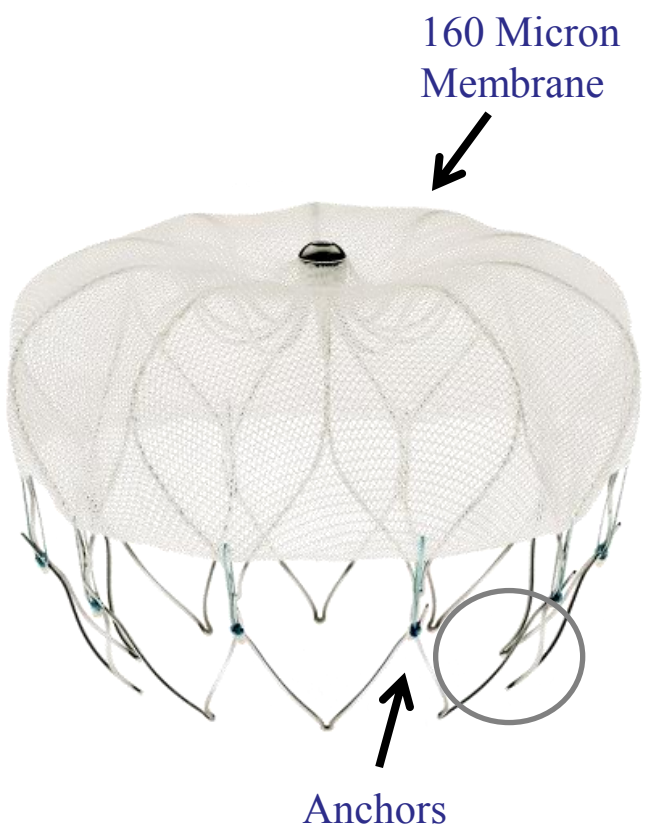


Broccoli:

An anatomy whose main feature is an LAA that has limited overall length with more complex internal characteristics



WATCHMAN™ LAAC Closure Device



Minimally Invasive, Local Solution
- Available sizes: 21, 24, 27, 30, 33 mm diameter

Intra-LAA design
- Avoids contact with left atrial wall to help prevent complications

Nitinol Frame
- Conforms to unique anatomy of the LAA to reduce embolization risk
- 10 active fixation anchors - designed to engage tissue for stability

Proximal Face
- Minimizes surface area facing the left atrium to reduce post-implant thrombus formation
- 160 micron membrane PET cap designed to block emboli and promote healing

Warfarin Cessation
- 92% after 45 days, >99% after 12 months[1]
- 95% implant success rate[1]

1. Holmes, DR et al. JACC 2014; Vol. 64, No. 1

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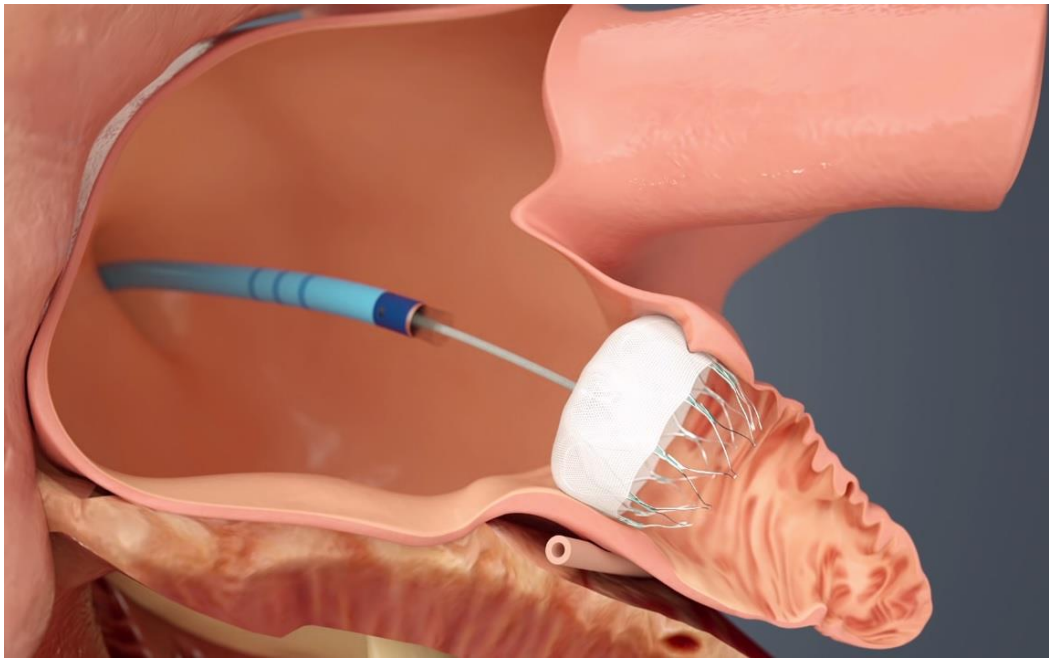
WATCHMAN™ Left Atrial Appendage Closure (LAAC) Device Procedure

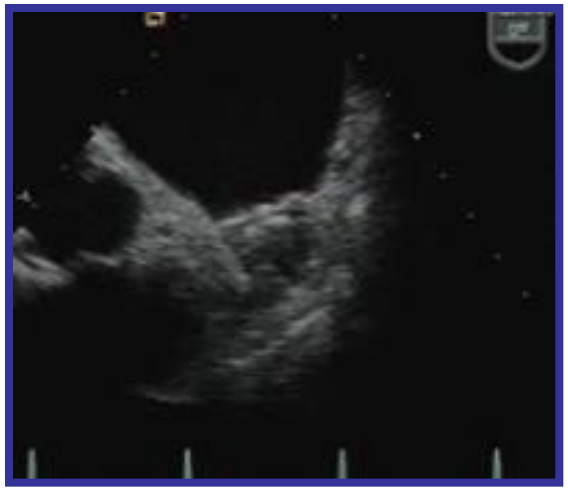
- One-time implant that does not need to be replaced
- Performed in a cardiac cath lab/EP suite, does not need hybrid OR
- Performed by a Heart Team
  - IC/EP or IC&EP, TEE, General Anesthesia, Surgical Back- up, WATCHMAN Clinical Specialist
- Transfemoral Access: Catheter advanced to the LAA via the femoral vein
  (Does not require open heart surgery)
- General anesthesia*
- 1 hour procedure*
- 1-2 day hospital stay*

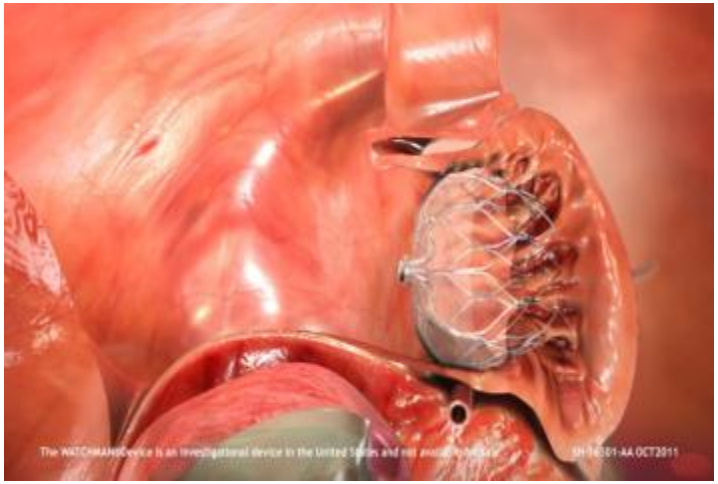


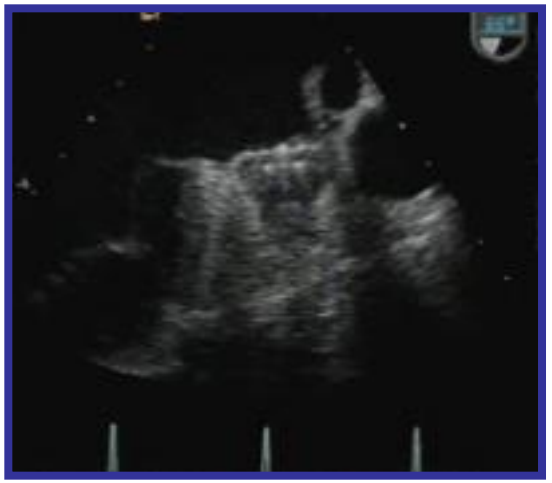
* Typical to patient treatment in U.S. clinical trials

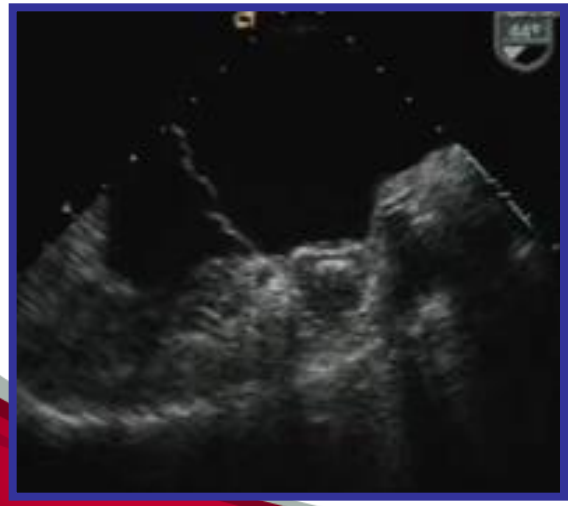
Device Release Criteria – Position

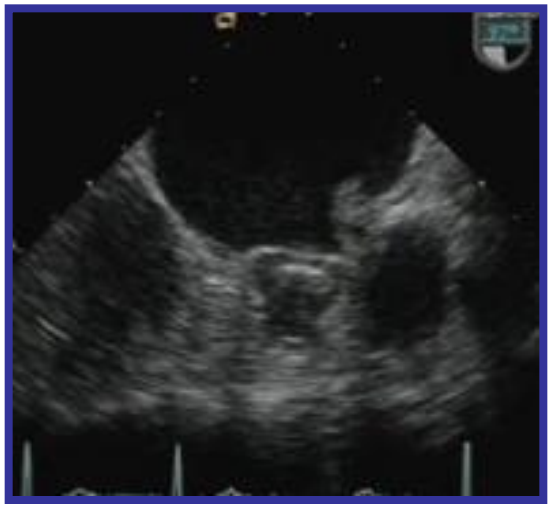
Device should be at or just distal to the LAA ostium

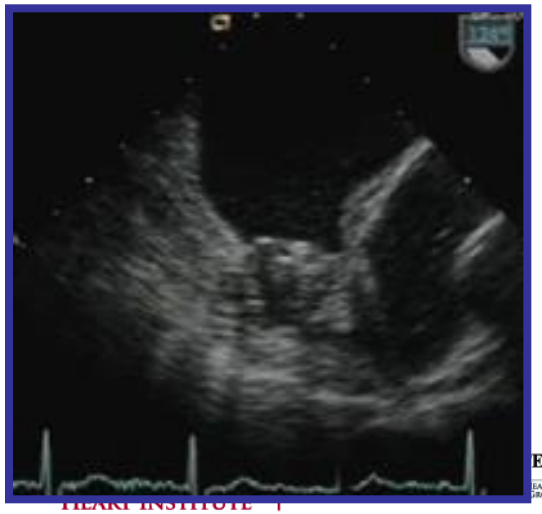




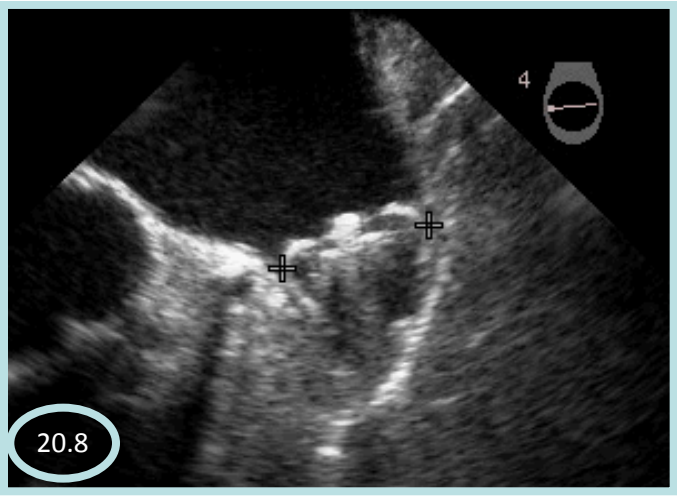


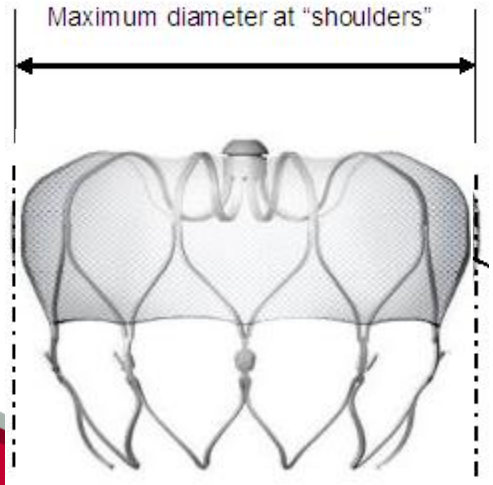






Device Release Criteria - Size





"threaded insert" must be visible when measuring on echo to ensure device was measured at widest cross-section in all angles

Device Compression Table

8 – 20% of original device size selected

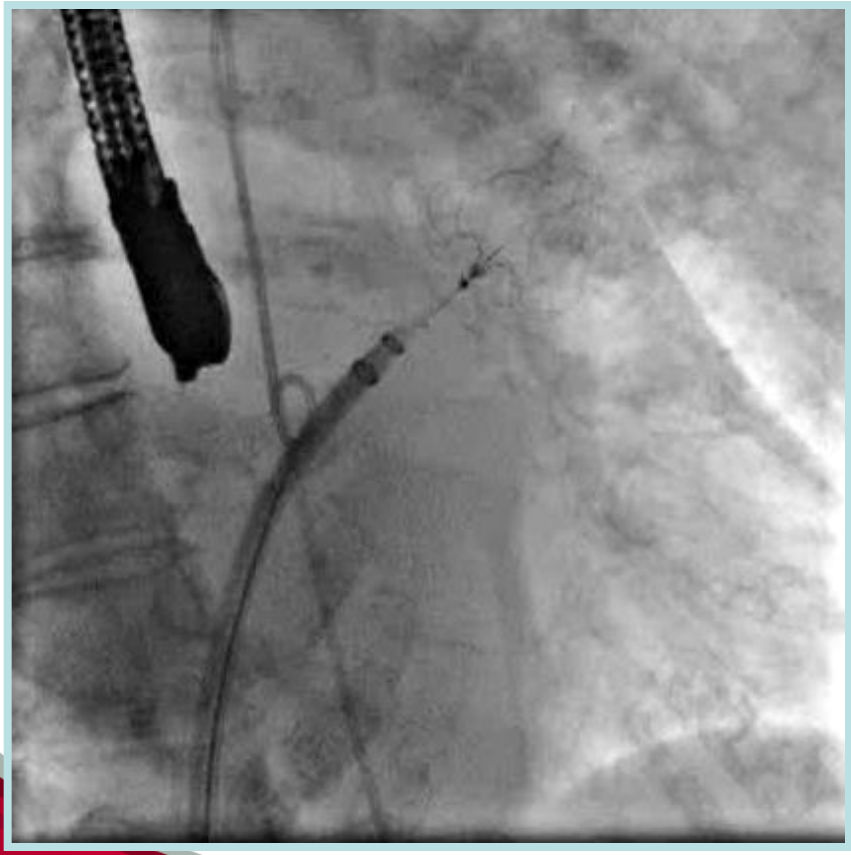
Device Size *(uncompressed diameter)*	**Maximum (20%)** Compression Measured Diameter*	**Minimum (8%)** Compression Measured Diameter*
21	16.8 mm	19.3 mm
24	19.2 mm	22.1 mm
27	21.6 mm	24.8 mm
30	24.0 mm	27.6 mm
33	26.4 mm	30.4 mm

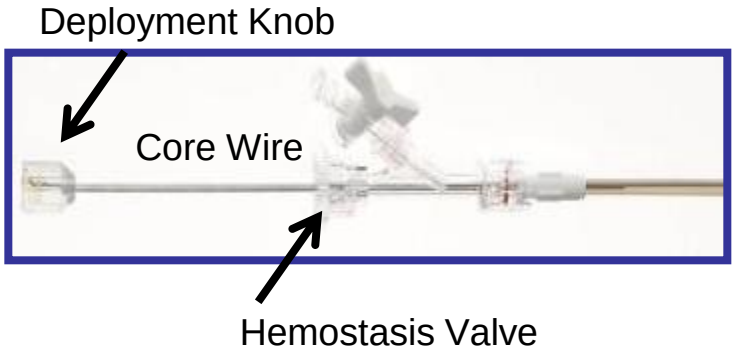
**Measure in-situ device diameter at approximate TEE angles of 0, 45, 90 and 135 degrees to accurately assess device compression*

Device Release Criteria – Anchor

1. To test stability, gently retract deployment knob and let go, observe device returns to original position

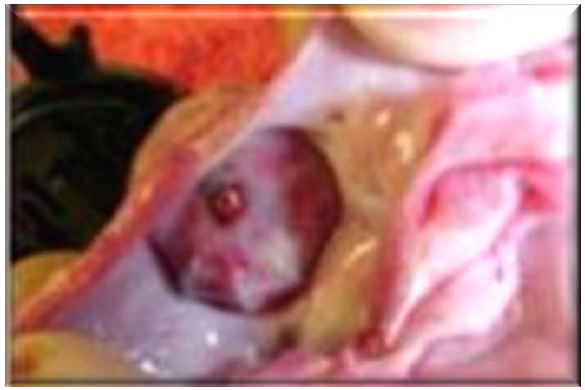
Pass or Fail Test



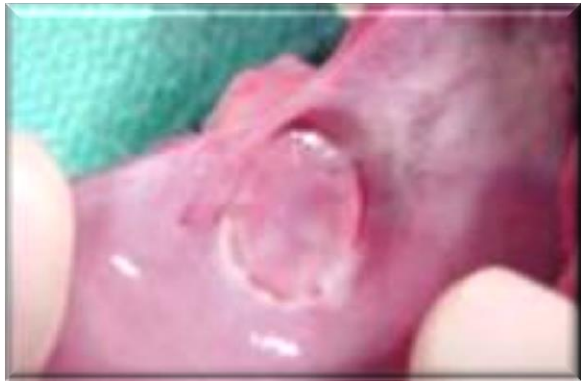


2. If the device moves to where position is no longer acceptable or the compression is no longer sufficient, the device should be recaptured
3. Test stability more than once if device stability is questionable

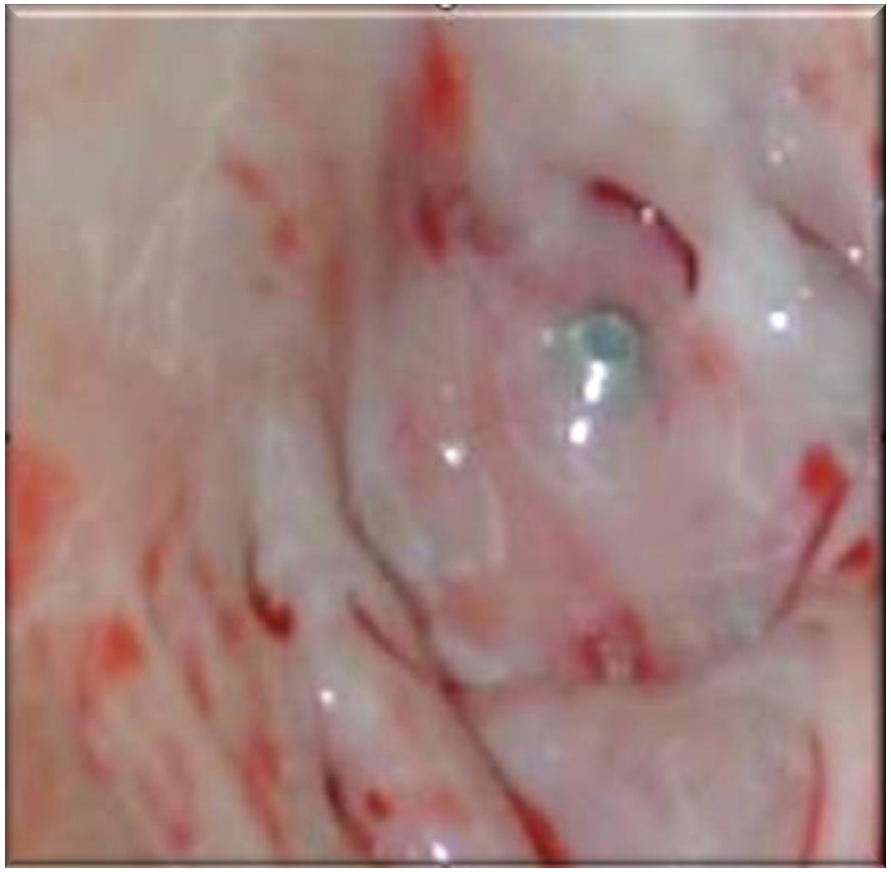
WATCHMAN™ Device Endothelialization



Canine Model – 30 Day



Canine Model – 45 Day



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

Images on file at Boston Scientific Corporation.
Results in animal models may not necessarily be indicative of clinical outcomes.

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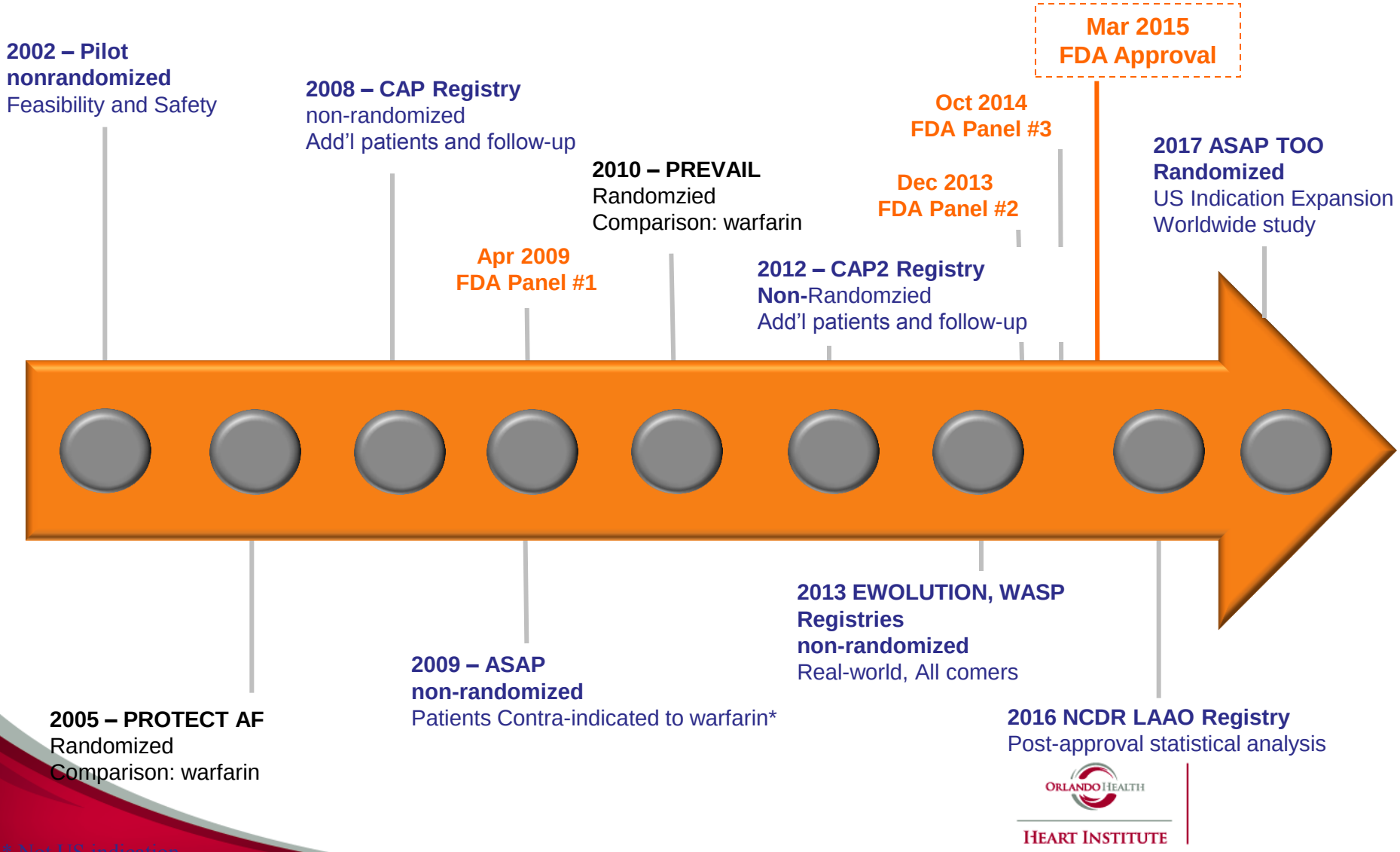
WATCHMAN Clinical Data

Clinical Study Overview

WATCHMAN Clinical Leadership

More than 2,400 patients and nearly 6,000 patient-years of follow-up



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* Not US indication

WATCHMAN™ - Most Studied LAAC Device

Only one proven with long-term data from randomized trials and multi-center registries

Key Trials	N	Highlights
PROTECT AF[1] (2005-2008)	707	Prospective, randomized 2:1, non-inferiority trial of LAA closure vs. warfarin.
CAP[2] (2008-2010)	566	Prospective registry allowing continued access to the WATCHMAN Device and gain further information prior to PMA approval.
PREVAIL[3] (2010-2012)	407	Prospective, randomized 2:1, non-inferiority trial to collect additional information on the WATCHMAN Device.
CAP2 (2012-2014)	579	Prospective registry allowing continued access to the WATCHMAN Device prior to PMA approval.
EWOLUTION (2013-2015)[4*]	1025	Prospective registry allowing all patients receiving a WATCHMAN Device at participating centers in Europe, Middle East and Russia
Total patients	>3,000	~7,000 Patient-Years of Follow-up

* Majority of patients enrolled could not take anticoagulation and therefore *contraindicated* in the US per current labeling.

1 Reddy, et al. JAMA. 2014 ;312(19): 1988-1998.
2 Reddy VY et al. Circulation. 2011; 123:417-424.
3 Holmes et al., JACC 2014.;4(1): 1-11.
4Boersma, L. V. A., et al. CCI (2015); 88(3): 460-465.

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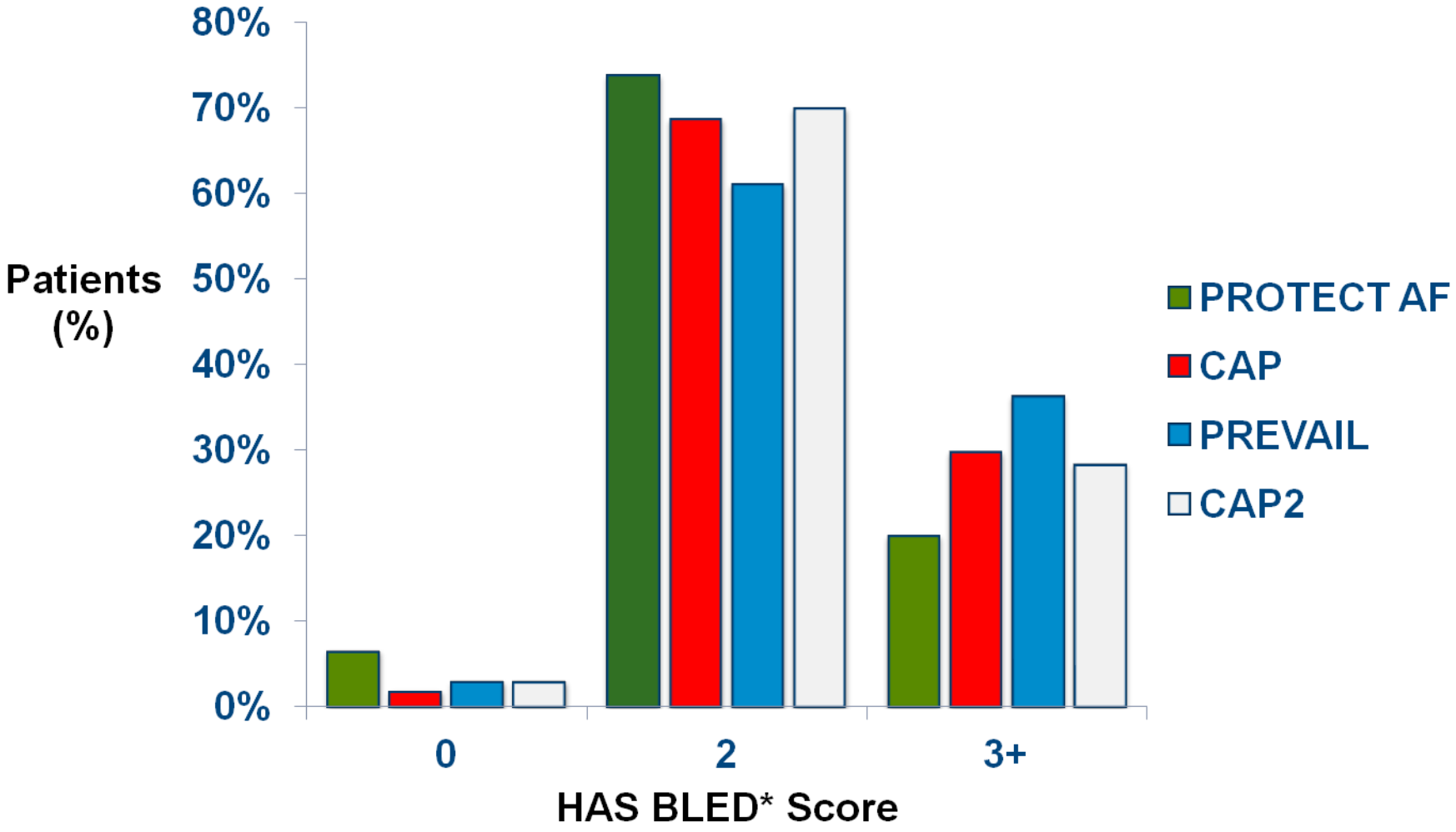
Majority of patients in the trial were at a moderate to high bleeding risk



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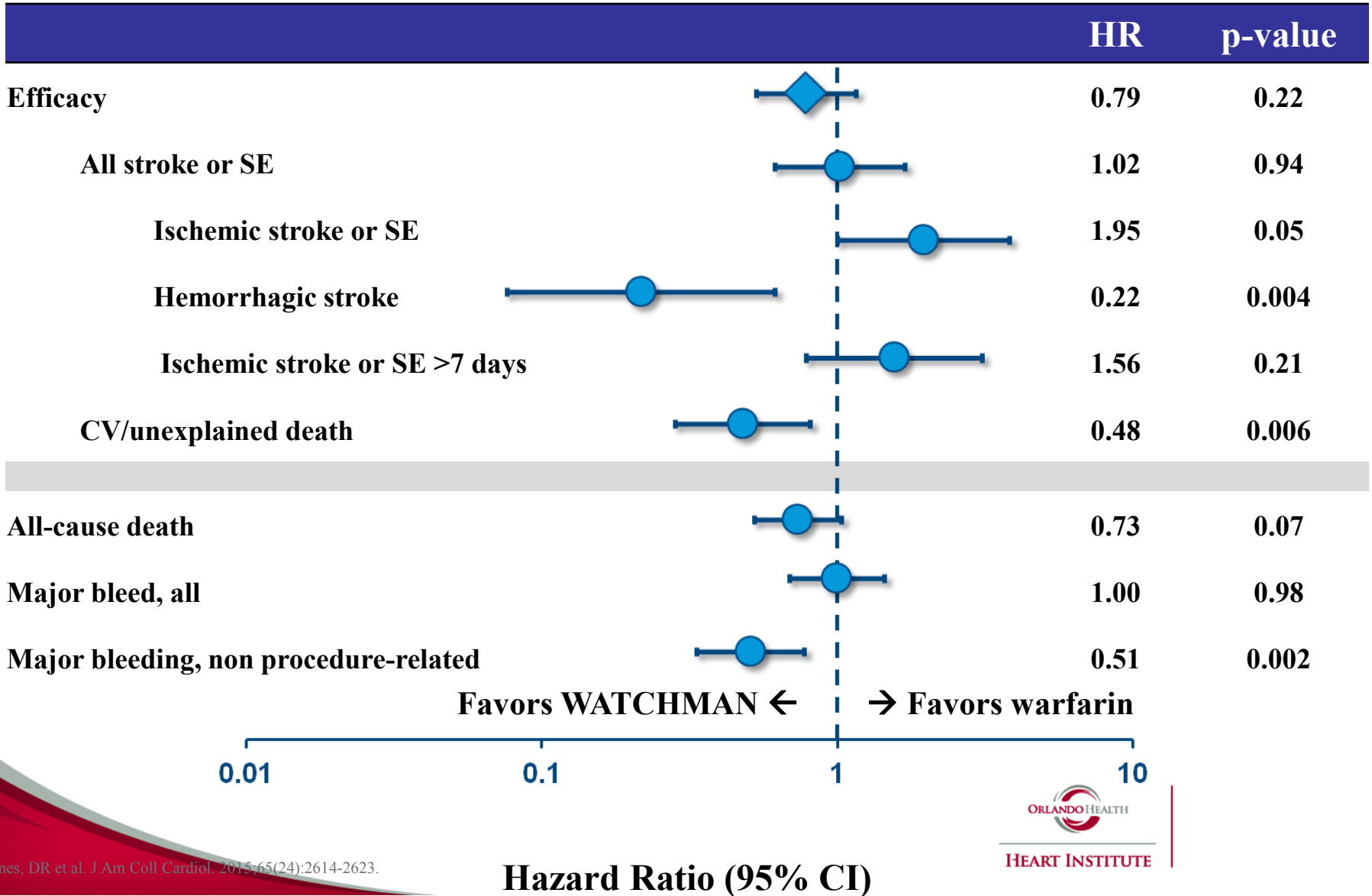
*Estimated

AHA/ACC/HRS Guidelines (2014); Holmes, DR et al. J Am Coll Cardiol. 2015;65(24):2614-2623.

WATCHMAN Clinical Data

Efficacy – Stroke Risk Reduction

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



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Holmes, DR et al. J Am Coll Cardiol. 2015;65(24):2614-2623.

WATCHMAN Disabling Stroke Reduction Superior to Warfarin in PROTECT AF

PROTECT AF	Event Rate (per 100 pt-yrs) WATCHMAN N=463	Event Rate (per 100 pt-yrs) Warfarin N=244	Rate Ratio (95% CrI)	Posterior Probabilities, % Non-Inferiority	Posterior Probabilities, % Superiority
Stroke (all)	**1.5**	**2.2**	**0.68** (0.42, 1.37)	**>99**	**83**
Disabling	**0.5**	**1.2**	**0.37** (0.15, 1.00)	**>99**	**98**
Non-disabling	**1.0**	**1.0**	**1.05** (0.54, 2.80)	**89**	**34**

Disabling stroke defined as Modified Rankin Score 3-6

63% reduction in disabling/fatal strokes with WATCHMAN

Bayesian – Posterior prob for NI must be ≥97.5%; Posterior Prob for Superiority must be >95%
Reddy, et al. JAMA. 2014

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WATCHMAN Clinical Data

Efficacy – Bleeding Reduction

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Bleeding Risks Compound Over Time

CHA_2DS_2-VASc* Score	Annual % Stroke Risk
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7

HAS-BLED** Score	Annual % Bleed Risk	10-Year Bleeding Risk (%)***
0	0.9	8.6
1	3.4	29.2
2	4.1	34.2
3	5.8	45.0
4	8.9	60.6
5	9.1	61.5

* 2014 AHA / ACC / HRS Guidelines
** Lip. JACC (2011)
*** Assumes constant risk despite increasing age and bleeding risk is independent from bleeding risk in previous years

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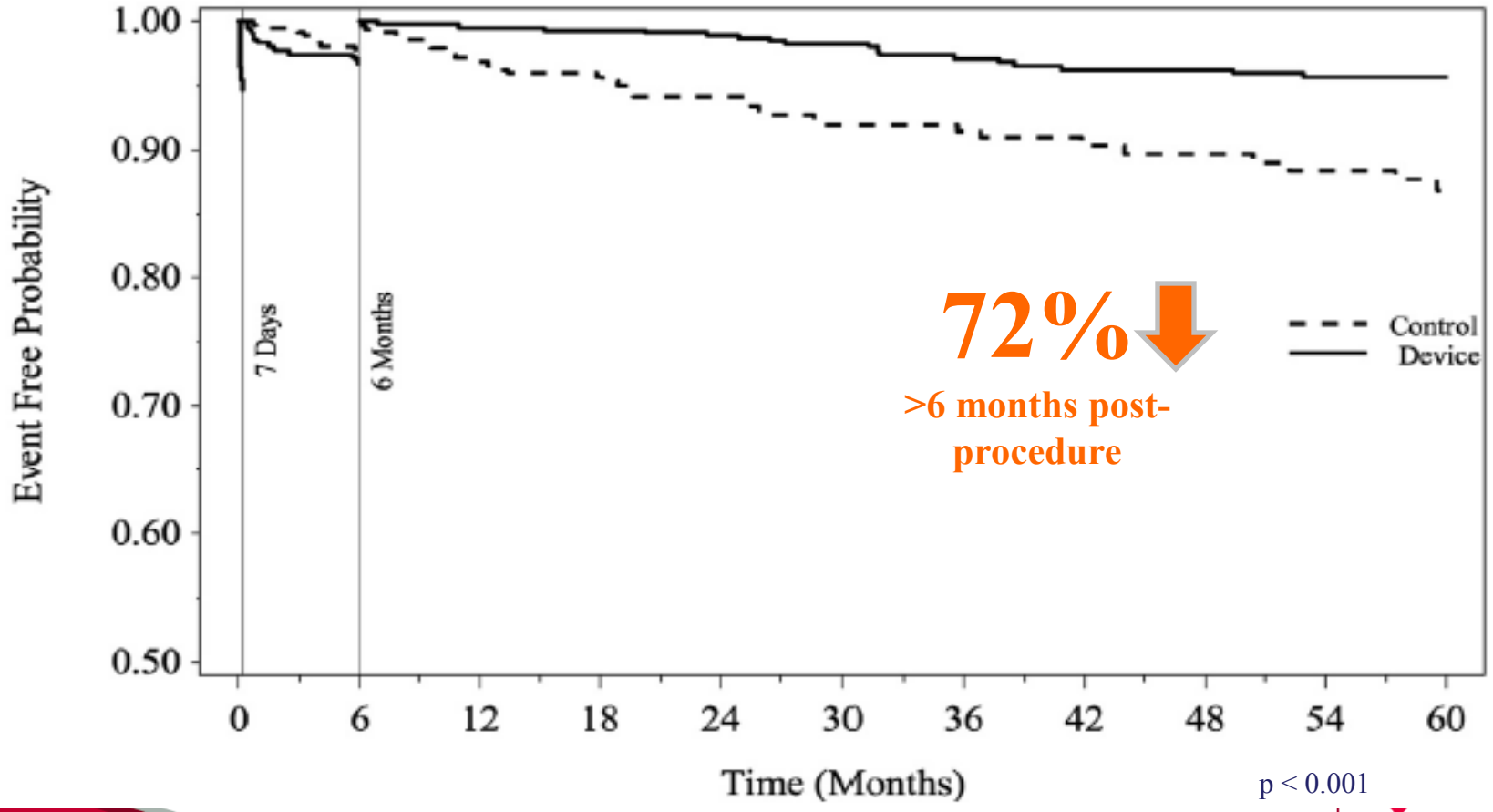
N

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

WATCHMAN Clinical Data

Procedural Success and Safety

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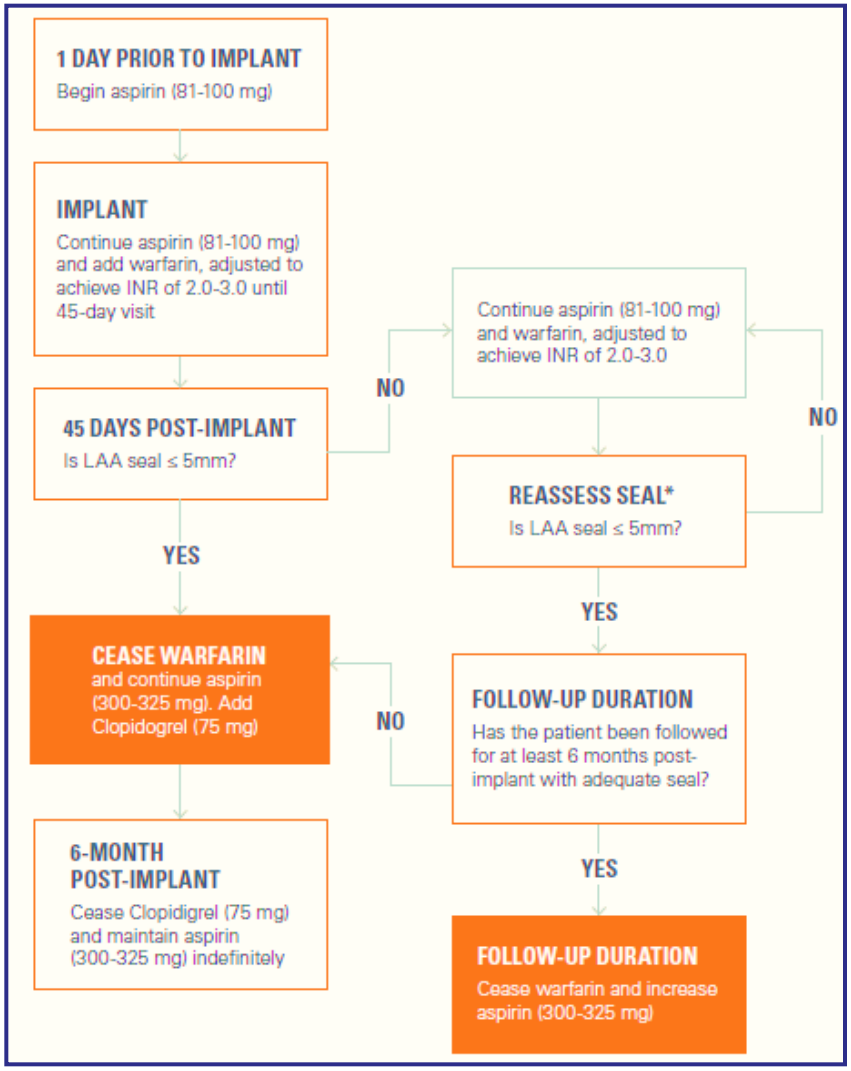
WATCHMAN Implant Procedure



*The performance and timing of TEE to re-evaluate the LAA seal is left to physician discretion. Typical to patient treatment in U.S. clinical trials

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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 suggest head-to-head comparisons of the separate trials or the therapies under study.

WATCHMAN enables patients to discontinue taking long-term OAC

92% of patients were able to discontinue warfarin after 45 days, with 99% able to discontinue after 1 year[3]

Warfarin Cessation with WATCHMAN

Study*	45-day	12-month
PROTECT AF[1]	87%	>93%
CAP[2]	96%	>96%
PREVAIL[3]	92%	>99%

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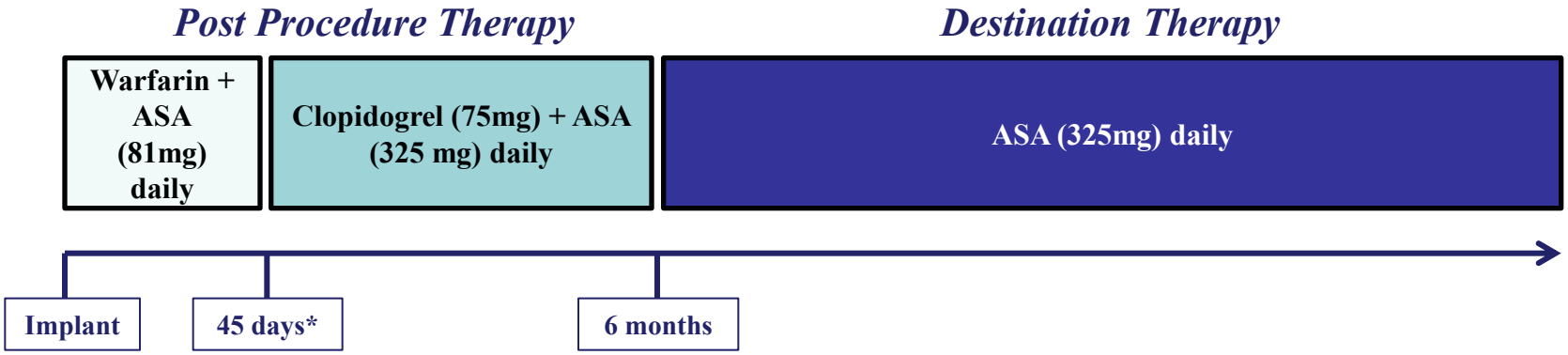
1. Reddy, VY et al. Circulation. 2011;123:417-424. 2 WATCHMAN FDA Panel Sponsor Presentation. Oct 2014.. 3 Holmes, DR et al. *JACC* 2014; 64(1):1-12.

72% Major Bleeding Reduction Long Term Post-Impalnt



*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.

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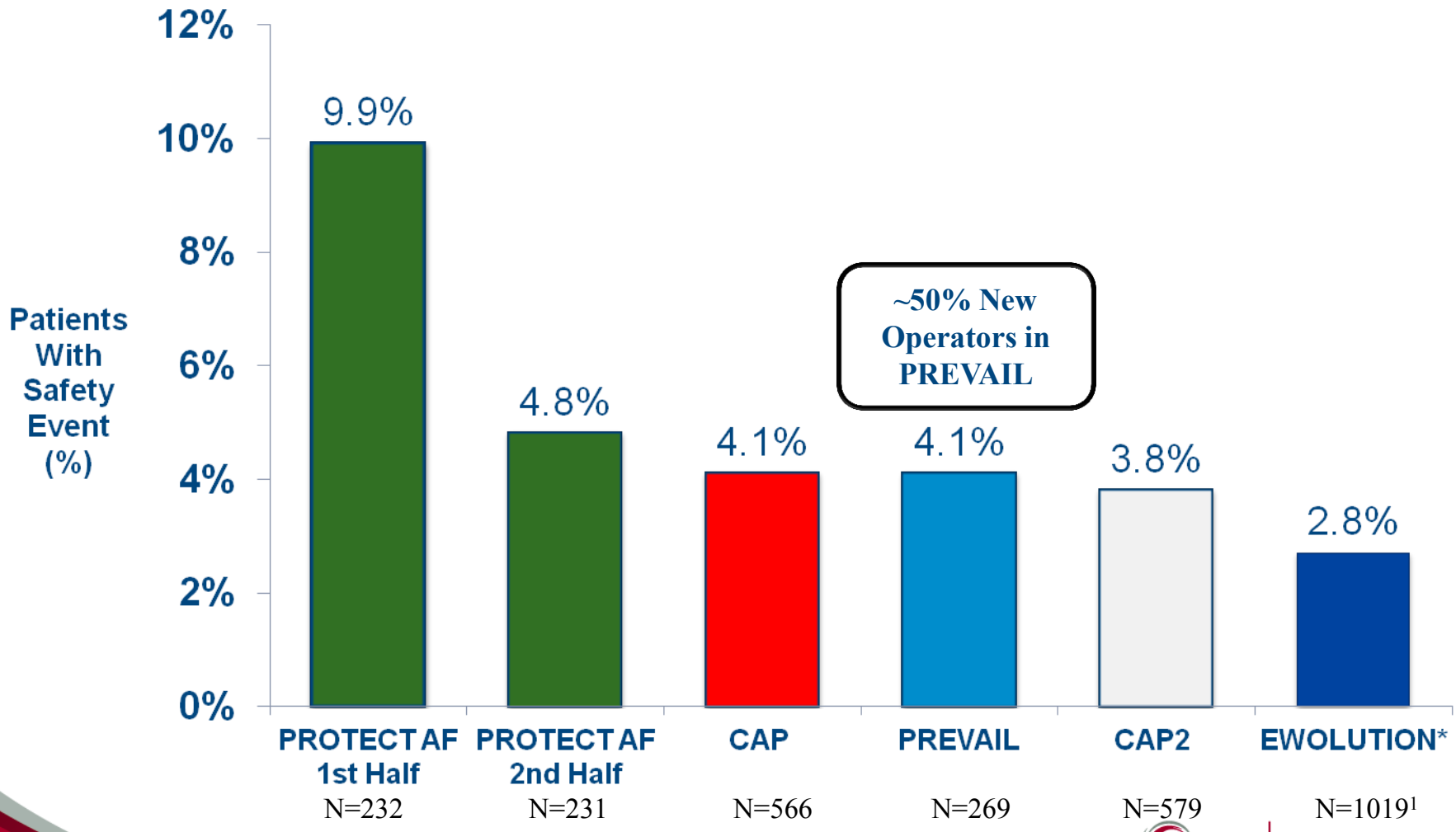
Price, M. J., V. Y. Reddy, et al. JACC: CV Interv 2015; 8(15): 1925-1932

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



* The EWOLUTION Registry is a European prospective registry which reflects CE Mark indications for use which differ from the FDA indications f

1 Boersma, LVA.et al. *EHJ 2016;* 37(31):2465.

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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	29%
Removed surgically	2	2	1	0	1	6	71%
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.

Reddy VY, Holmes DR, et al. JACC 2016; 69(3): 253-261.

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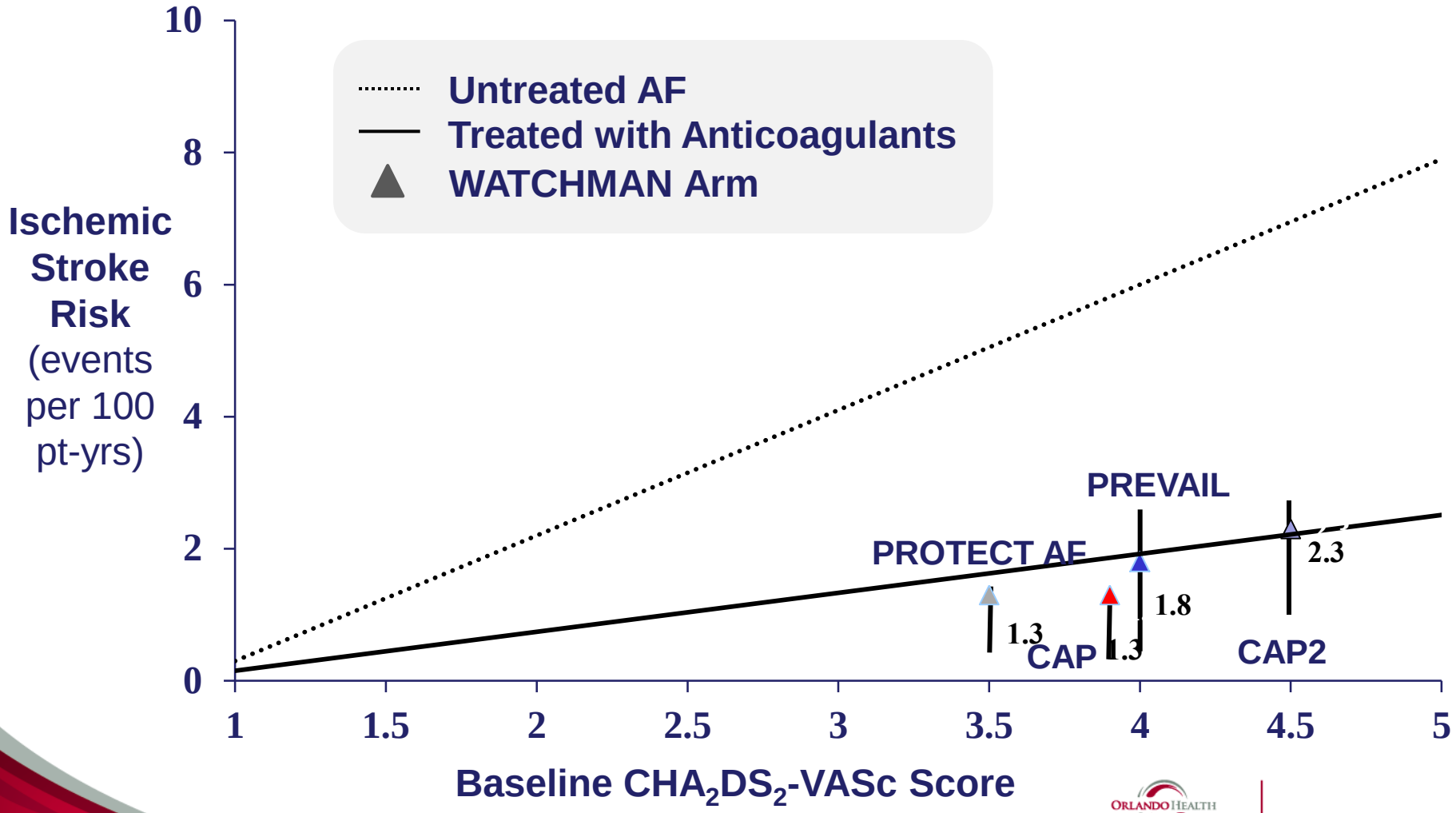
Ischemic Stroke Rate Aligns with Expected Rate Based on Risk Score
PROTECT AF 5 Yrs / PREVAIL 3 Yrs



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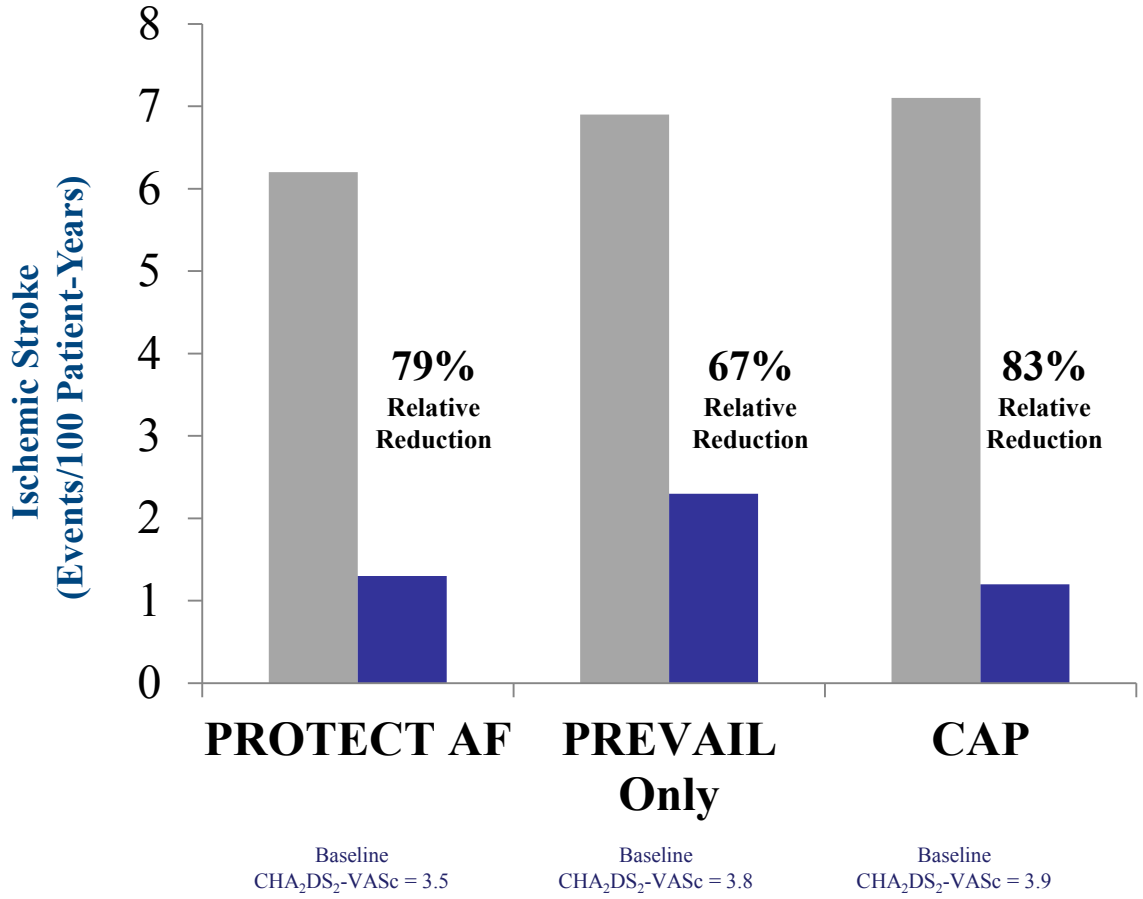
Friberg. Eur Heart J (2012); NICE UK (2014). WATCHMAN FDA Panel Sponsor Presentation. Oct 2014

WATCHMAN™ Device Reduces Ischemic Stroke Over No Therapy



- Imputed Ischemic Stroke Rate*
- Observed WATCHMAN Ischemic Stroke Rate

* 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. Hanzel G, et al. TCT 2014 (abstract)

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WATCHMAN™ Clinical Leadership

- The WATCHMAN™ LAAC Device is the **most studied LAAC device** and the **only one proven with long-term data** from randomized trials or multi-center registries
  - Five studies, >2400 patients, nearly 6000 patient-years of follow-up

- 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]:
  - 52% reduction in cardiovascular death (p= 0.006)[2]
    - Largely driven by 78% reduction in hemorrhagic stroke[2]
  - 72% reduction in major non-procedure related bleeding >6 months post-procedure (p<0.001)[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.
2. 4. Price, M. J., V. Y. Reddy, et al. JACC: CV Interv 2015; 8(15): 1925-1932

WATCHMAN Clinical Data

Future Patient Populations

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* Data presented is in patients primarily contraindicated for LAAC with WATCHMAN in the United States.

ASAP-TOO (NCT02928497): Overview

Study Objective	Evaluate LAA Closure with WATCHMAN in NVAF patients deemed not suitable for oral anti-coagulation therapy
Study Design	Prospective, multi-center Randomized 2:1 (Watchman vs Control) Considering Group Sequential Design
Primary Endpoint	<u>Effectiveness Endpoint</u> Time to first occurrence of ischemic stroke or systemic embolism <u>Safety Endpoint</u> 7-day rate of all-cause death, ischemic stroke, systemic embolism, or device- or procedure- related events requiring open cardiac surgery or major endovascular intervention
Patient Population	888
Number of Sites	100 global sites
Follow-up*	• 45 Day with TEE • 6,18 month phone visit • 12 month with TEE • Bi-annually for years 2-5

- Brain imaging required at baseline if prior stroke or TIA

Holmes et al. AHJ 2017; *in press*

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ASAP-TOO
Device Group Medication Therapy

Visit Interval	Aspirin	Clopidogrel*
Discharge through 3-month visit	Yes, suggested dose: 75-100mg	Yes Suggested dose: 75mg
3-month visit through 12-month visit	Yes, suggested dose: 75-100mg	No, unless other indication
Following the 12-month visit	No, unless other indication	No, unless other indication

****Patients are allowed to be on dual antiplatelet therapy (outside of the protocol required 3-months period) if indicated due to a condition**

Holmes et al. AHJ 2017; In Press

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WATCHMAN™ Therapy Candidates

What type of LAAC candidates are you referring today?

Contra-indicated
(Cannot take any OAC)

Bleeder
(Previous bleed but on OAC)

Future Bleeder
(No prior bleeds but high-risk / include fall risk)

Non-Compliant
(tolerant but not taking OAC)

Lifestyle
(Patient prefers device over OAC)

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ACC, HRS, SCAI Consensus Memo to CMS

Contraindications to Long-Term Warfarin Therapy

WATCHMAN is Not Just for Those at Risk of Bleeding

The CMS NCD for LAAC (20.34) indicates that patients must have *"A suitability for short-term warfarin but deemed unable to take long-term oral anticoagulation…."*

Although not part of the NCD, the professional societies (HRS/ACC/SCAI) recommended the list below to CMS during the public comment period, to describe the population they view as contraindicated to long-term anticoagulation.

Appendix A

Contraindications to Anticoagulation

1. History of intracranial bleeding (intracerebral or subdural) where benefits of LAAC outweigh risks
2. History of spontaneous bleeding other than intracranial (e.g. retroperitoneal bleeding)
3. Documented poor compliance with anticoagulant therapy
4. Inability or significant difficulty with maintaining patients in therapeutic anticoagulation range
5. Intolerance of warfarin and NOACs
6. High risk of recurrent falls
7. Cognitive impairment
8. Severe renal failure
9. Occupation related high bleeding risk
10. Need for prolonged dual antiplatelet therapy
11. Increased bleeding risk not reflected by the HAS-BLED score (e.g. thrombocytopenia, cancer, or risk of tumor associated bleeding in case of systemic anticoagulation)
12. Other situations for which anticoagulation is inappropriate

Source: ACC, HRS, SCAI LAAC NCD consensus memo to CMS

WATCHMAN is the most studied LAAC Device with Long-term Clinical Data

Results		
Safety	WATCHMAN procedure is **safe**	**95%** implant success; **~4%** complication rates[1]
Primary Efficacy	WATCHMAN **comparable** to warfarin	21% reduction in events (p=0.22)[3]
All-Stroke	WATCHMAN **comparable** to warfarin	**63%** reduction in disabling strokes (Ps=>99%)[2]; **78%** reduction in hemorrhagic strokes (p=0.004)[3]
CV / Unexp death	WATCHMAN **superior** to warfarin	**52%** reduction in events (p=0.006)[3]
Major Bleeding	WATCHMAN **comparable** to warfarin; **superior** to warfarin **post-procedure**	**52%** reduction post-procedure (p=0.002); **72%** reduction after 6-months (p=0.001)[4]
Warfarin	WATCHMAN allows the **majority** of patients to **discontinue warfarin**	**92%** of patients discontinue after 45-days; **99%** of patients discontinue after 1 year[5]

1. WATCHMAN FDA Panel Sponsor Presentation. Oct 2014.; 2 Reddy, et al. JAMA. 2014 ;312(19): 1988-1998.
3 Holmes, DR et al. JACC. 2015;65(24):2614-2623.; 4 Price, M. J., V. Y. Reddy, et al. JACC: CV Interv 2015; 8(15): 1925-1932; 5.Holmes, DR et al. JACC 2014; 64(1): 1-12.

Safe, Effective, Stop Taking Warfarin

Once and Done

The WATCHMAN™ Device is a safe alternative to long-term warfarin therapy, offers comparable stroke risk reduction and enables patients to stop taking warfarin.

SAFE

- 95% implant success rate
- Complication rate similar to ablation therapy

EFFECTIVE

- WATCHMAN reduces the risk of stroke as effectively as warfarin
- 52% reduction in cardiovascular/ unexplained death

PATIENTS CAN STOP TAKING WARFARIN

- 92% were able to stop taking warfarin after 45 days
- 99% were able to stop taking warfarin at 1 year

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