Update on Atrial Fibrillation Clinical Trials

Sreedhar Billakanty MD FHRS
Ohio ACC-Spring Summit
March 28th, 2018

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Disclosures

- Honorarium
  - Bristol-Myers Squibb (Apixaban)
  - Janssen (Rivaroxaban)

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Objectives

- A.Fib and Heart Failure clinical trials (CASTLE AF, PABA CHF)
- Watchman device approval (alternative to anticoagulation, PROTECT AF and PREVAIL)
- Persistent A.Fib ablation trials (Converge and AMAZE trials)

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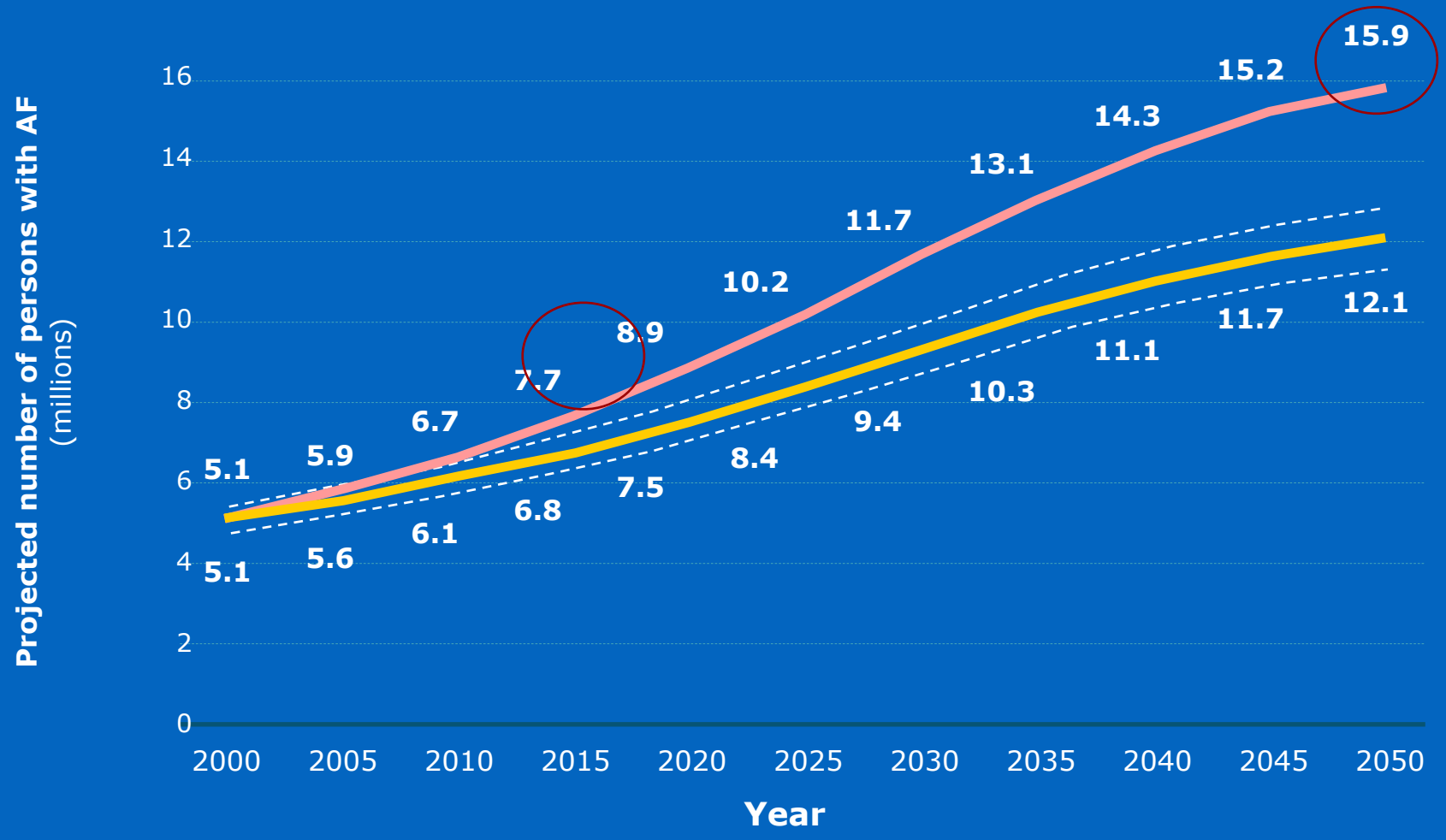
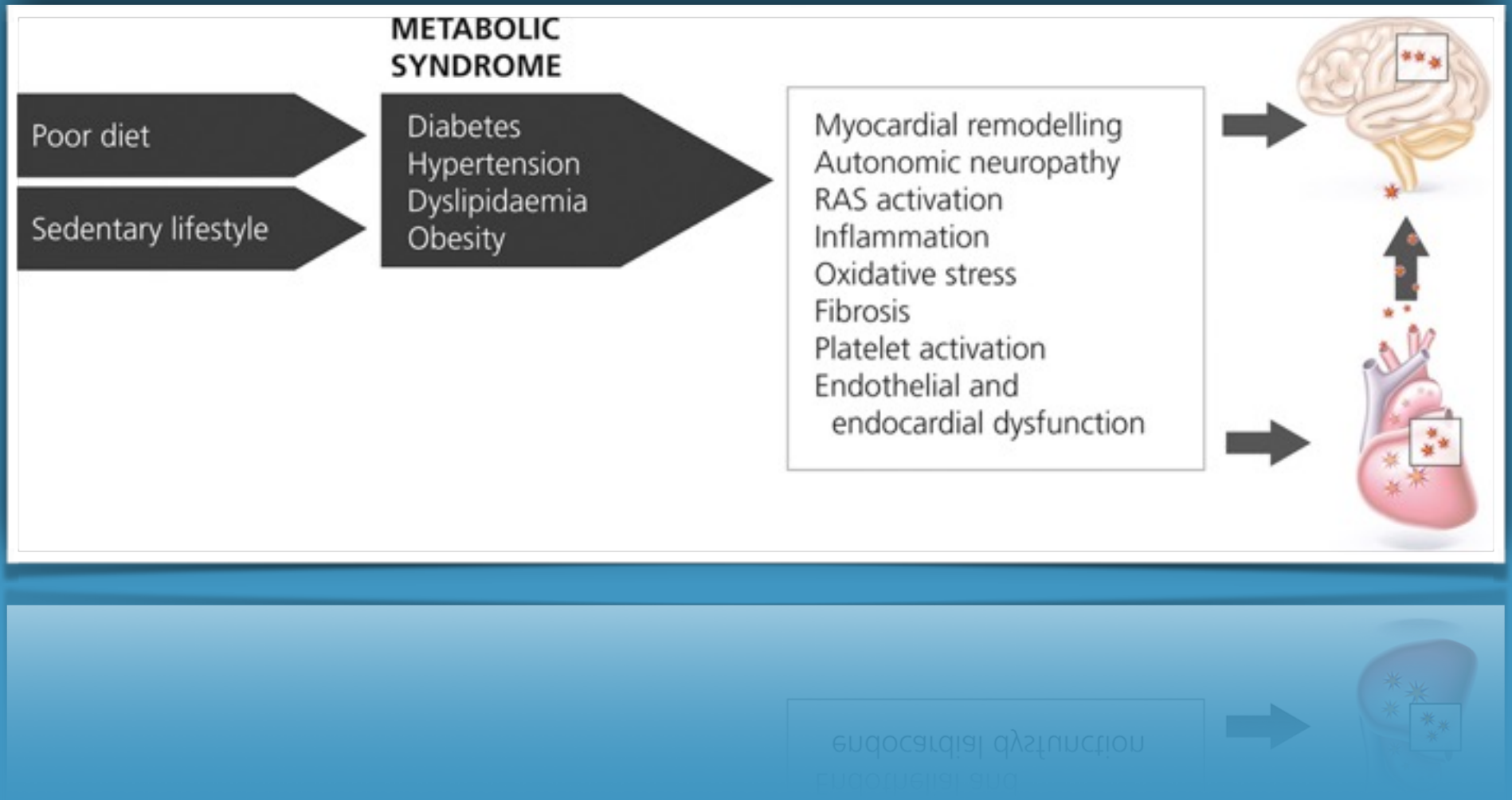
A.fib Prevalence

Olmsted County study



Miyasaka Y, et al. *Circulation* (2006) 114: 119

Metabolic syndrome-Conundrum



Heart Rhythm 2015 12, 2332-2343DOI: (10.1016/j.hrthm.2015.06.038)

Classification

- **Paroxysmal AF**
  - Self-terminating or with intervention < 7 days
- **Persistent AF**
  - Sustained >7 days
- **Long-standing persistent AF**
  - Continuous ≥1 year
- **Permanent AF**
  - Cease further attempts to restore and/or maintain sinus rhythm by patient (and physician)
- **NonValvular AF**
  - absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair

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The Consequences of AF

Thromboembolism
- Stroke: 4.5× ↑risk
- Microemboli: ↓cognitive function

Hospitalizations
- Most common arrhythmia requiring hospitalization
- 2-3× ↑risk for hospitalization

- ↓*Quality of life*
- Palpitations, dyspnea, fatigue, ↓exercise tolerance

Impaired hemodynamics
- Loss of atrial kick
- Irregular ventricular contractions
- Heart failure
- Tachycardia-induced cardiomyopathy

- Health care burden
- Estimated US cost burden: 15.7 billion

Van Gelder IC et al. *Europace*. 2006;8:943-9; Narayan SM et al. *Lancet.* 1997;350:943-50.
Wattigney WA et al. *Circulation*. 2003;108:711-6. Wyse DG et al. *Circulation*. 2004;109:3089-95.

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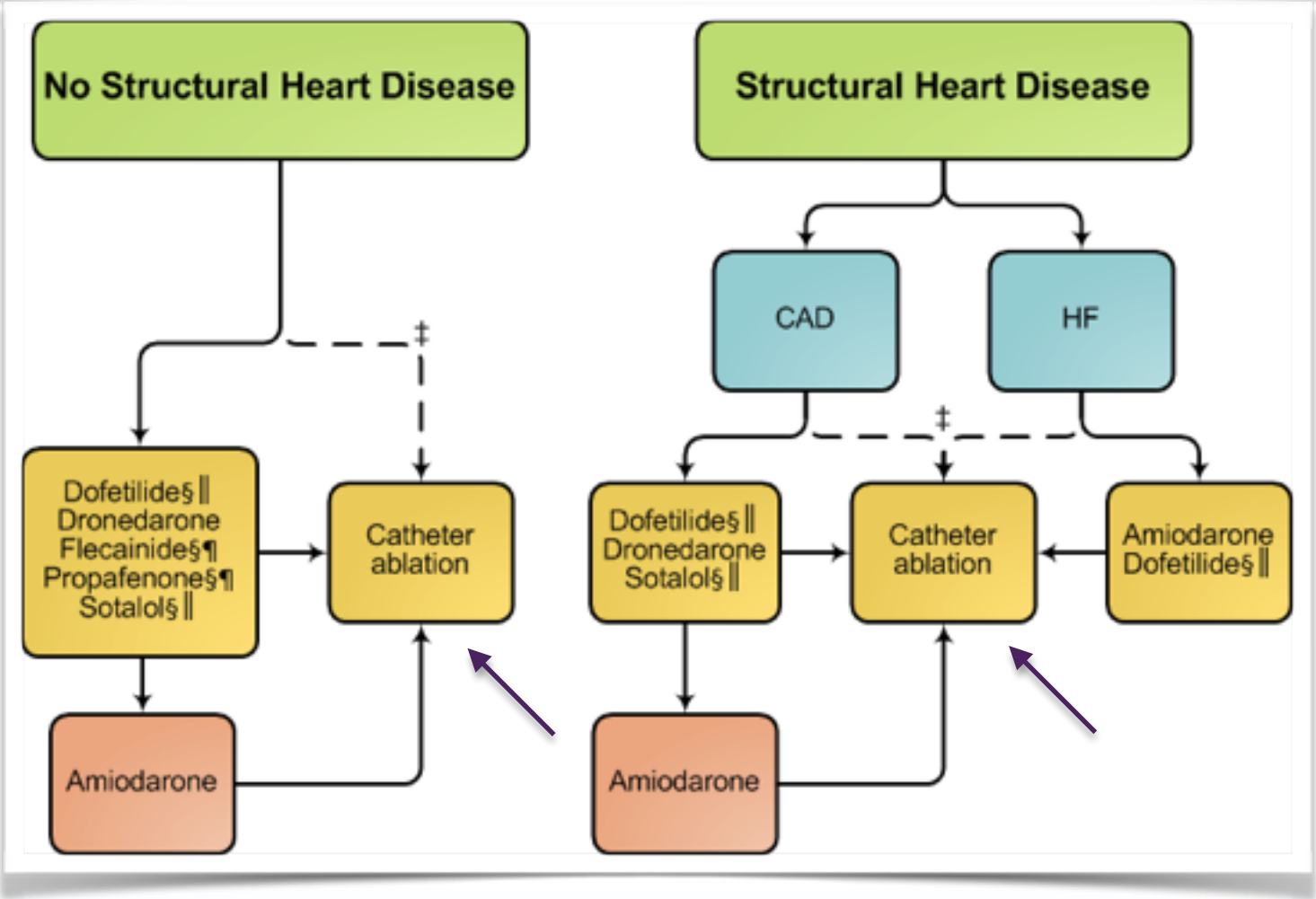
Strategies for Rhythm Control in Patients with Paroxysmal and persistent AF



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A.fib ablation Indications

- Failed / intolerant to AA class Ic / III drug (s)
- Symptomatic paroxysmal A.fib (class IA, “useful”)
- Symptomatic persistent A.fib (class IIA, “reasonable”)
- Symptomatic longstanding persistent (>1 year) (class IIB, may be)

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A.fib ablation Indications

- Symptomatic paroxysmal / persistent AF, can not tolerate or failed AA drug(s)
- Reasonable initial strategy in some patients
- Need to assess procedural risks and outcomes
- Does not obviate the need for anticoagulation

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CASTLE-AF trial

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 1, 2018 VOL. 378 NO. 5

Catheter Ablation for Atrial Fibrillation with Heart Failure

Nassir F. Marrouche, M.D., Johannes Brachmann, M.D., Dietrich Andresen, M.D., Jürgen Siebels, M.D., Lucas Boersma, M.D., Luc Jordaens, M.D., Béla Merkely, M.D., Evgeny Pokushalov, M.D., Prashanthan Sanders, M.D., Jochen Proff, B.S., Heribert Schunkert, M.D., Hildegard Christ, M.D., Jürgen Vogt, M.D., and Dietmar Bänsch, M.D., for the CASTLE-AF Investigators*

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CASTLE AF

- Multicenter, open-label, randomized, controlled trial
- Catheter ablation (N=179)
- Medical therapy (N=184)
- Median follow-up: 37.8 months
- **Primary Outcome**: Death or hospitalization for heart failure

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CASTLE AF

- CHF: NYHA I 11%, NYHA II 58%, NYHA III 29%, NYHA IV 2%
- Ischemic 40%, non-ischemic 60%, LVEF 32.5%
- AF: paroxysmal 30%, persistent 70%, long-standing persistent 28%
- LA diameter 48mm
- Devices: CRT-D 27%, ICD 73%,
- Medications: History of amiodarone use 57%

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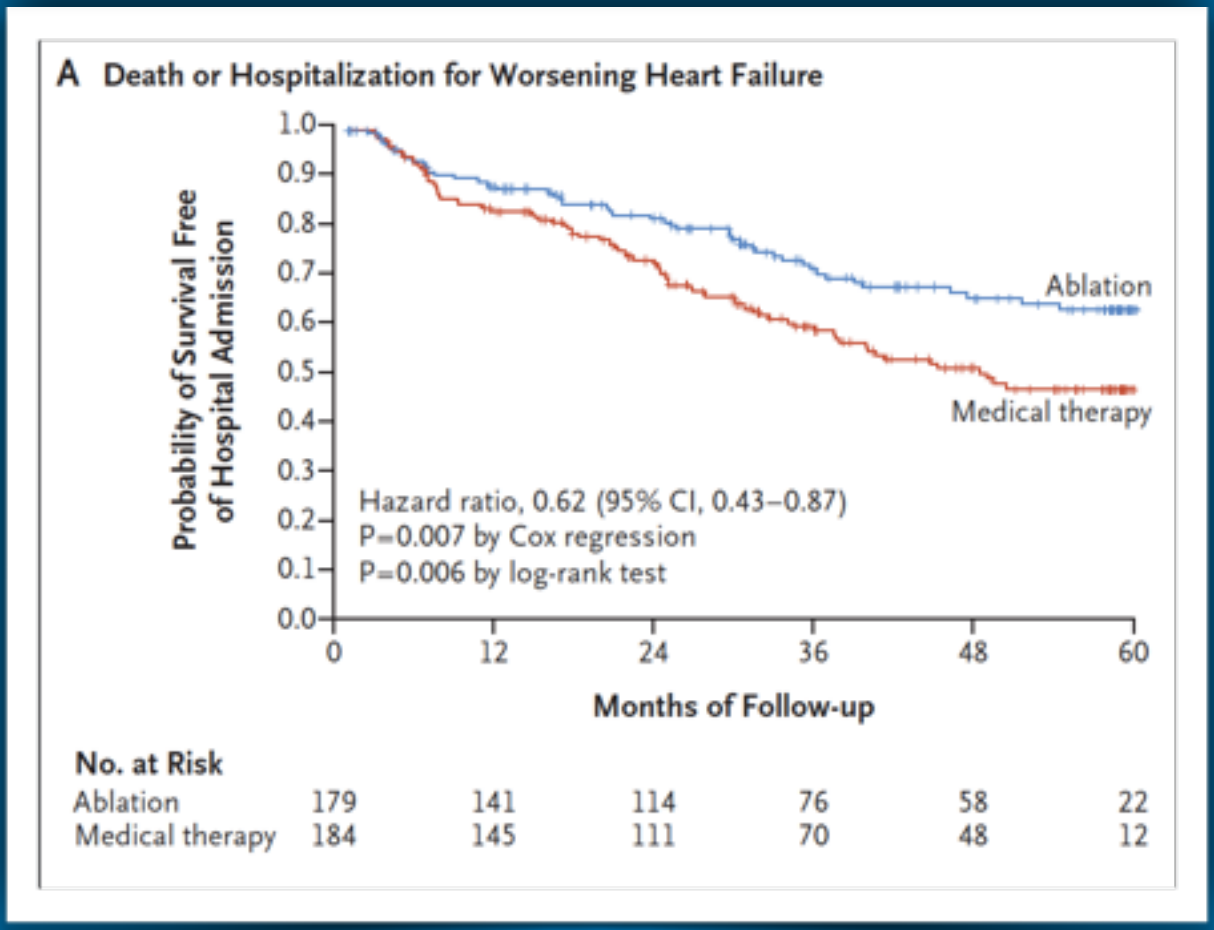
Primary Endpoint



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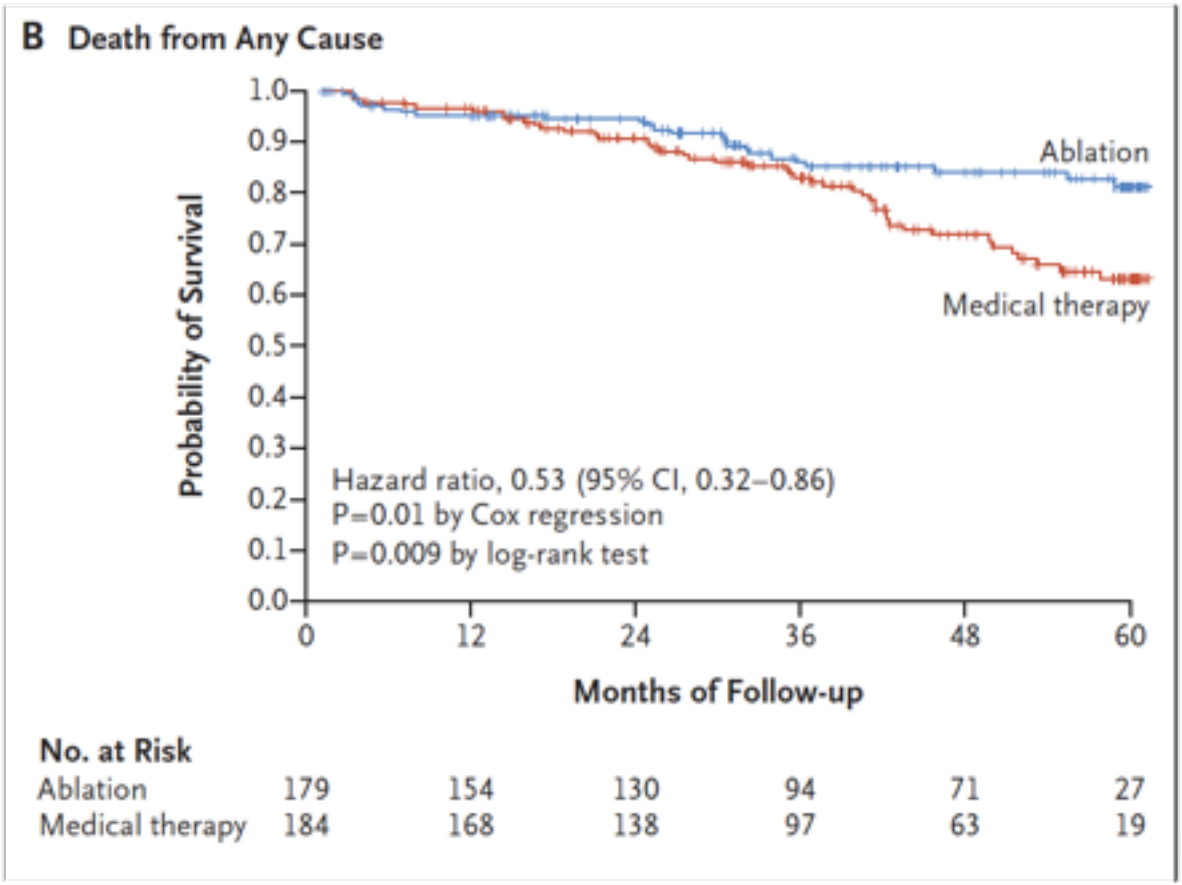
Primary Endpoint



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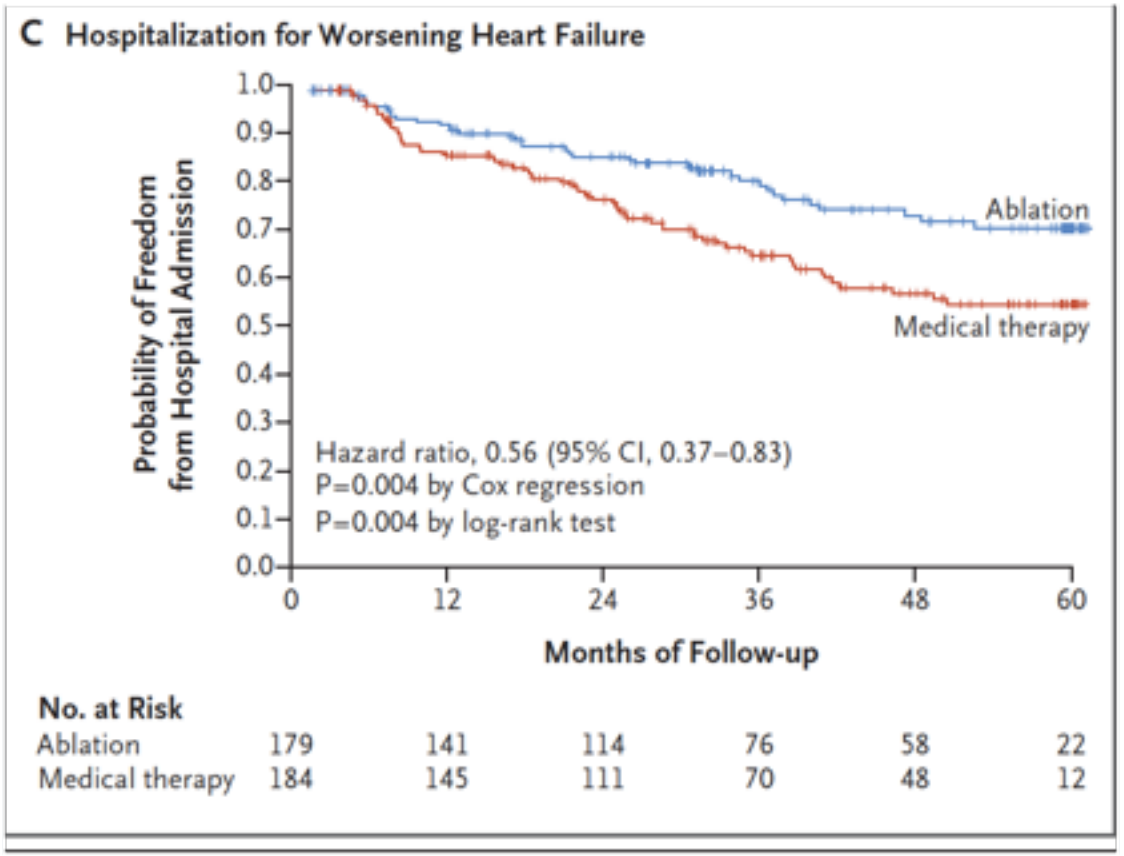
Primary Endpoint



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CASTLE AF

- **Primary Outcomes**
- **Death or hospitalization for heart failure**
- 51 (28.5%) vs. 82 (44.6%); HR 0.62 (95% CI 0.43-0.87); p = 0.007

- **Secondary Outcomes**
- **Death**
- 24 (13.4%) vs. 46 (25.0%); HR 0.53 (95% CI 0.32-0.86) p = 0.01

- **Heart failure hospitalization**
- 37 (20.7%) vs. 66 (35.9%); HR 0.56 (95% CI 0.37-0.83); p = 0.004

- **Cardiovascular death**
- 20 (11.2%) vs. 41 (22.3%); HR 0.49 (95% CI 0.29-0.84); p = 0.009

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PABA-CHF: Study Design

Prospective, randomized, controlled trial

N = 81 with symptomatic, drug-resistant AF; LVEF ≤40%; NYHA Class II or III HF

↓ ↓

Pulmonary-vein isolation (n = 41)

Atrioventricular-node ablation with biventricular pacing (n = 40)

↓ ↓

Primary outcome: Composite of ejection fraction, 6-minute walk distance, and Minnesota Living with Heart Failure score at 6 months

Pulmonary Vein Antrum Isolation versus AV Node Ablation with Bi-Ventricular Pacing
Khan MN et al. *N Engl J Med*. 2008;359:1778-85.

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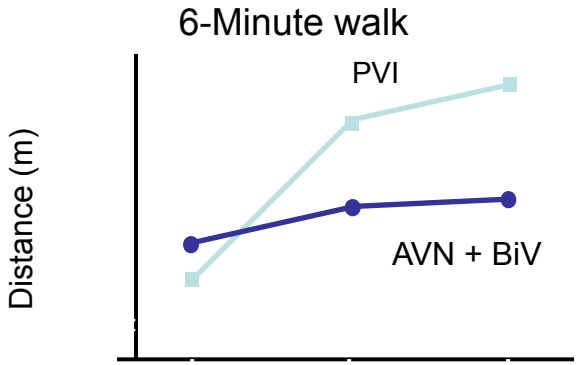
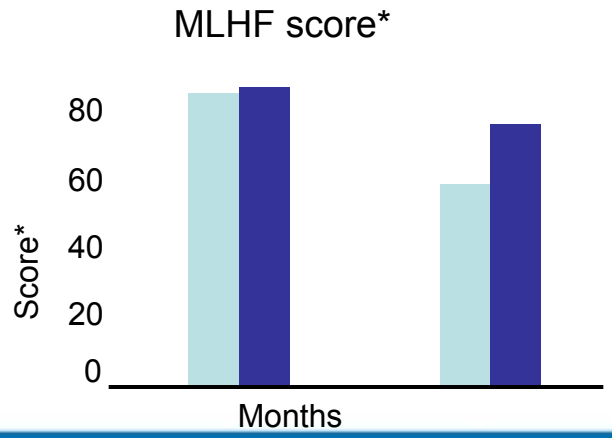
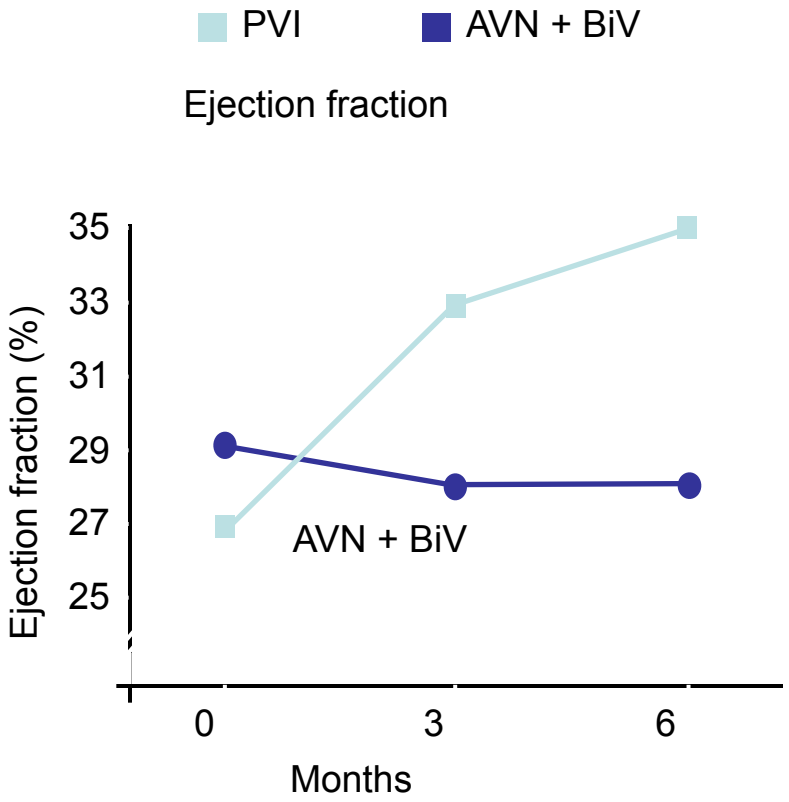
PABA-CHF: Composite Primary Endpoints at 6 Months

Randomized trial of NYHA Class II or III CHF & EF <40% to PVI or AVN + BiV







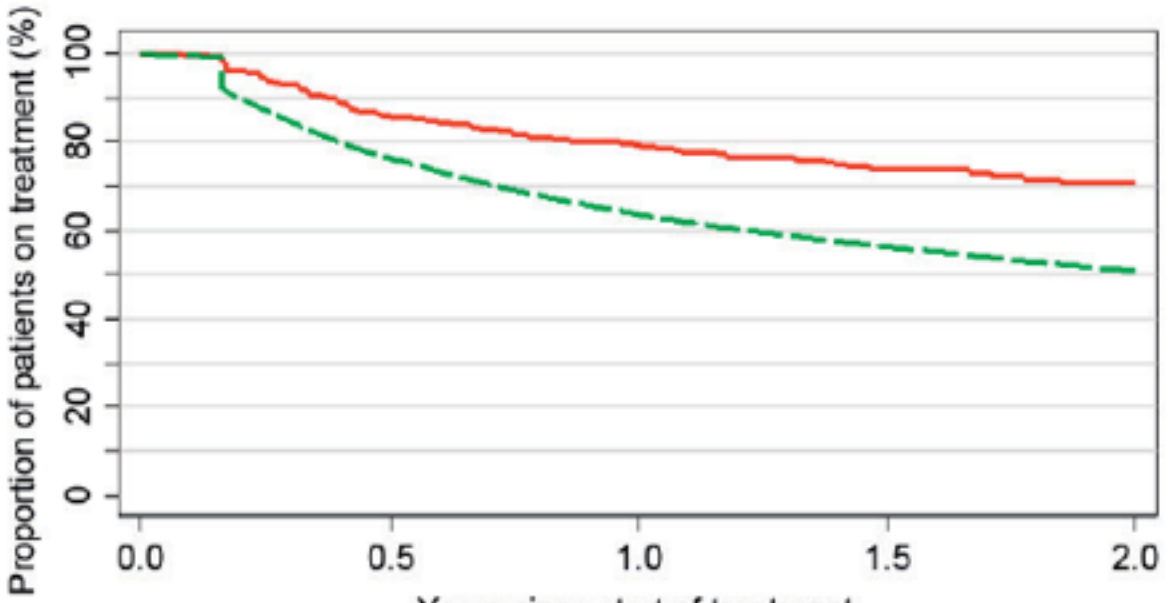
20*↓Score = ↑QoL

Khan MN et al. *N Engl J Med*. 2008;359:1778-85.

WATCHMAN device data

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

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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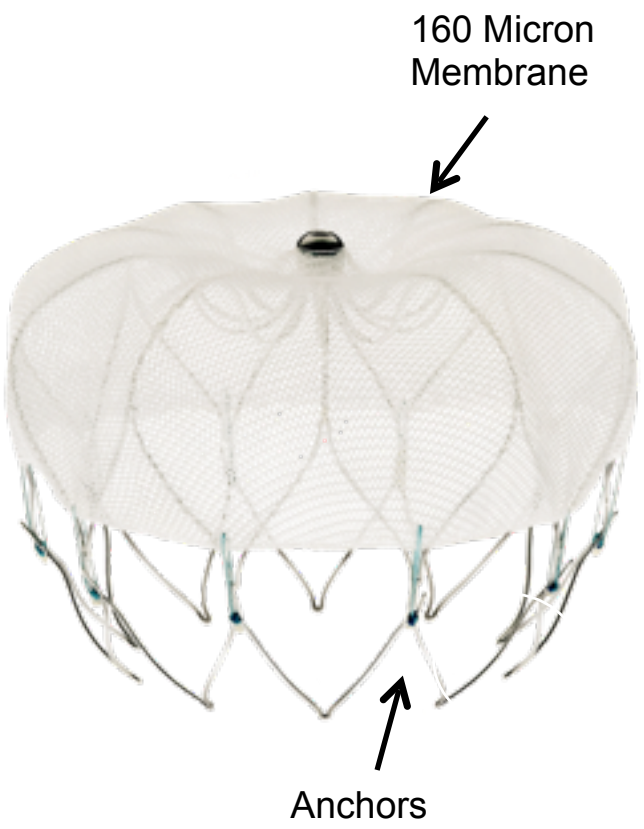
WATCHMAN™ LAAC Closure Device



Nitinol Frame

- Conforms to LAA anatomy 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

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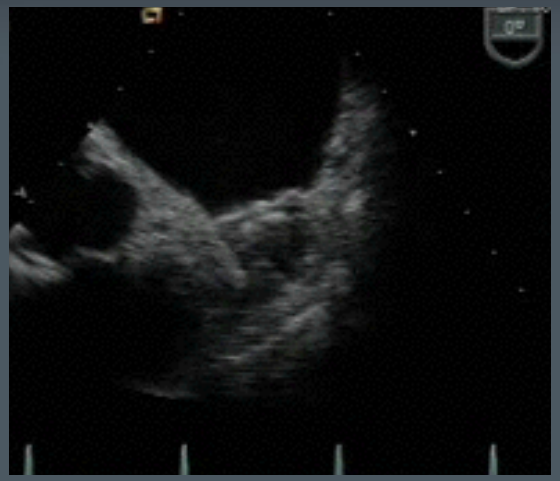
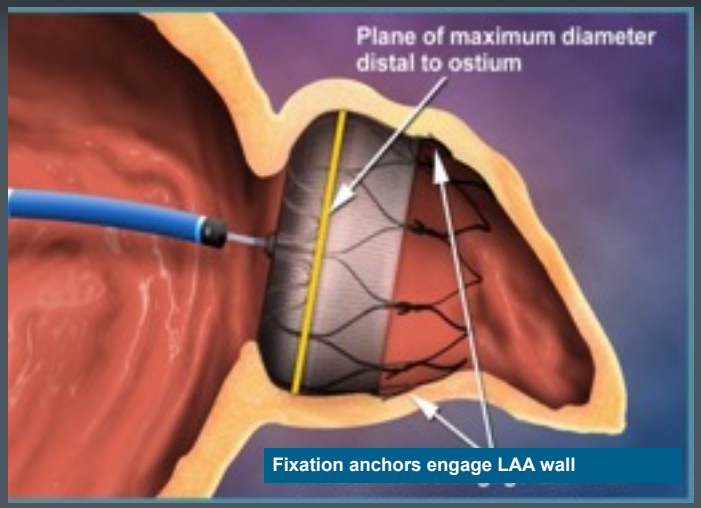
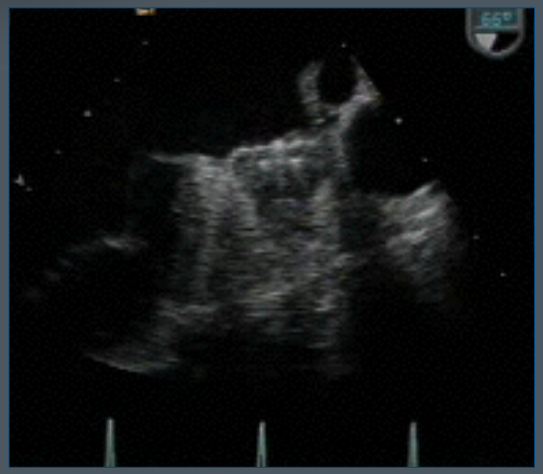
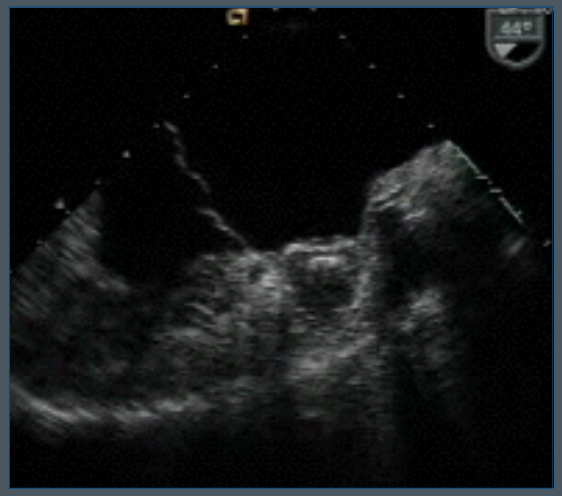
Optimal Device Position

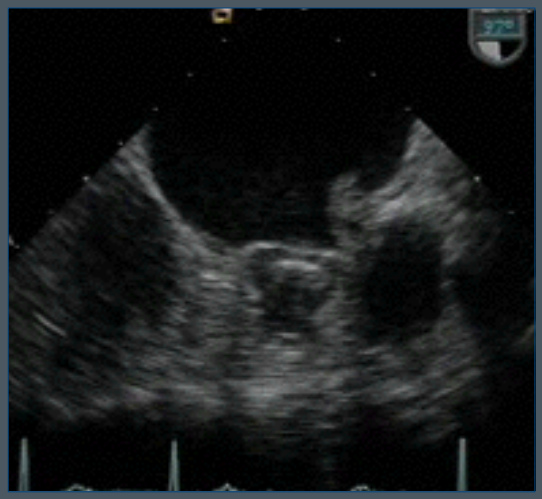
WATCHMAN™
LEFT ATRIAL APPENDAGE
CLOSURE DEVICE

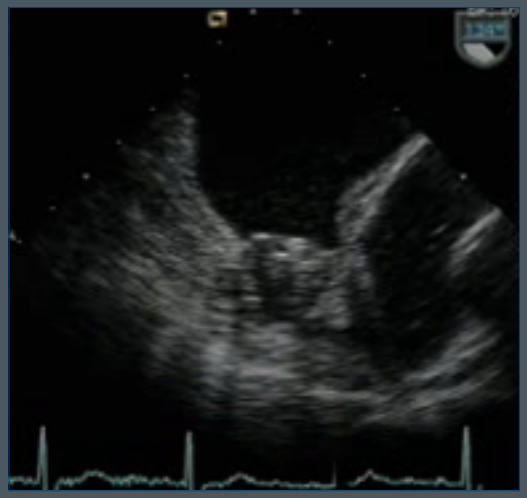












SH-53515-AB MAR2015

WATCHMAN™ - Most Studied LAAC Device

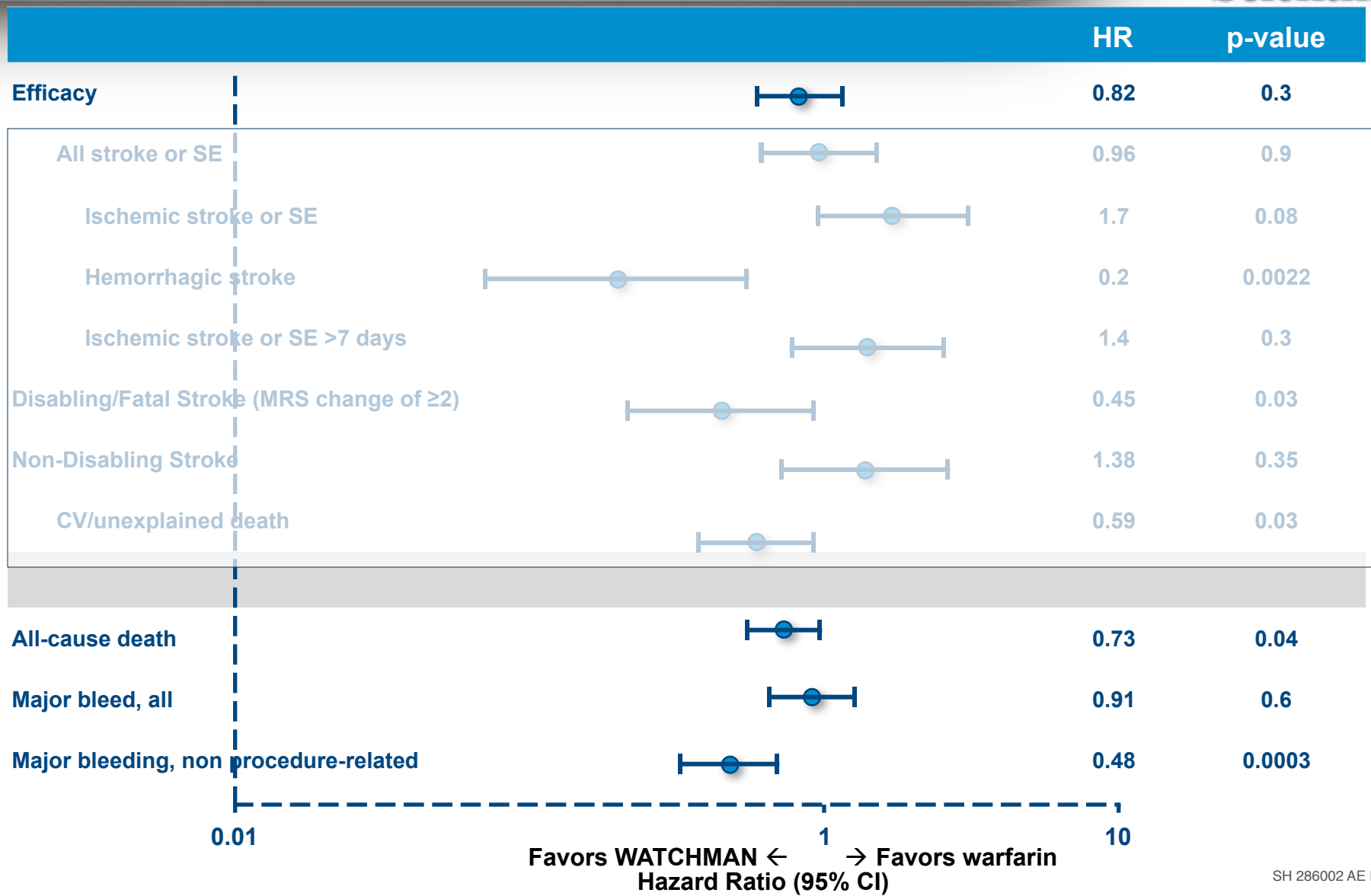
Only one proven with long-term data from randomized trials and multi-center registries

WATCHMAN™
LEFT ATRIAL APPENDAGE
CLOSURE DEVICE

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	~9,000 Patient-Years of Follow-up

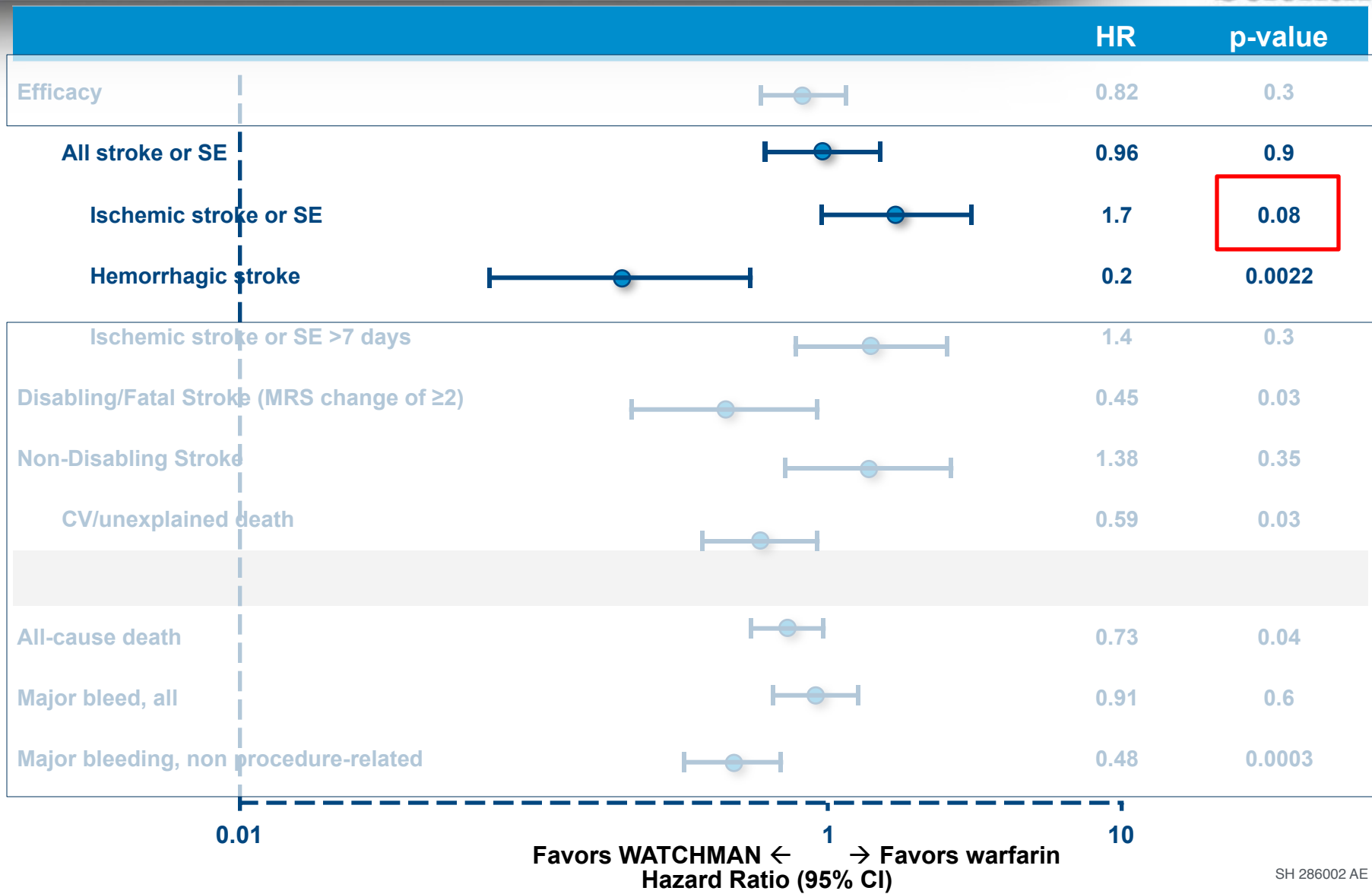
1 Reddy, et al. JAMA. 2014 ;312(19): 1988-1998.
2 Reddy VY et al. Circulation. 2011; 123:417-424.
3 Holmes et al., JACC 2014.;4(1): 1-11.
4Boersma, L. V. A., et al. CCI (2015); 88(3): 460-465.

Patient Level Meta-Analysis
PROTECT AF, PREVAIL 5 Years



Source: , Reddy VY, Doshi SK, Kar S, et al. 5-Year Outcomes After Left Atrial Appendage Closure: From the PREVAIL and PROTECT AF Trials. J. Am Coll Cardiol. 2017; In Press

Patient Level Meta-Analysis
PROTECT AF, PREVAIL 5 Years



Source: Reddy VY, Doshi SK, Kar S, et al. 5-Year Outcomes After Left Atrial Appendage Closure: From the PREVAIL and PROTECT AF Trials. J Am Coll Cardiol. 2017; In Press

WATCHMAN Enables Patients to Discontinue Long-term OAC

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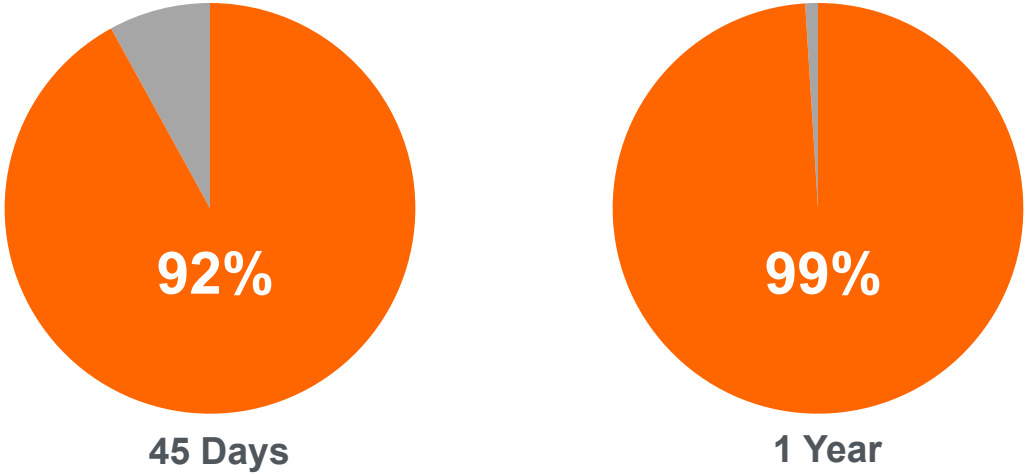
LEFT ATRIAL APPENDAGE
CLOSURE DEVICE

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%

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.

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

WATCHMAN™
LEFT ATRIAL APPENDAGE
CLOSURE DEVICE

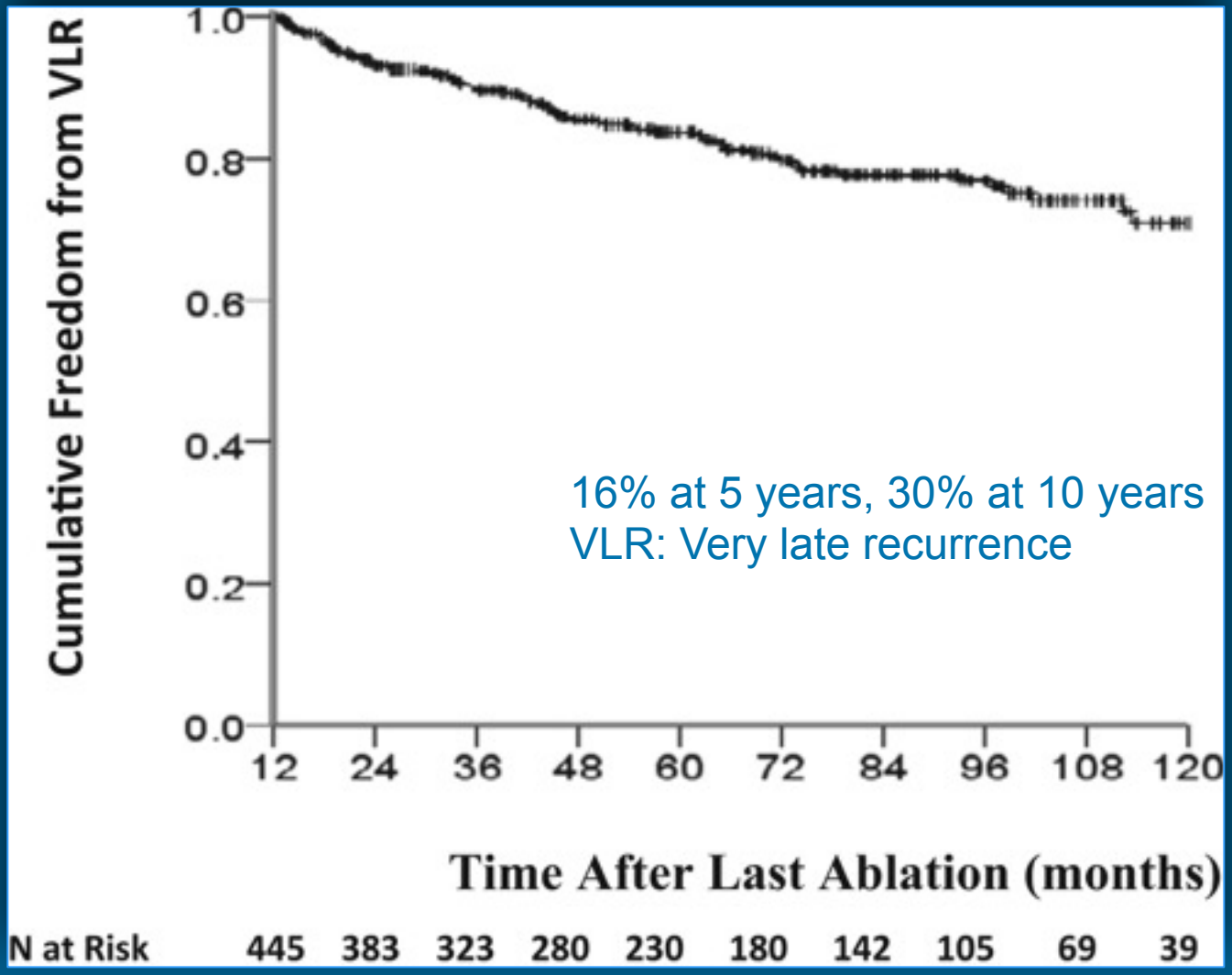
		Results
Safety	WATCHMAN procedure is **safe**	**95%** implant success; **~4%** complication rates[1]
Primary Efficacy	WATCHMAN **comparable** to warfarin	**18%** reduction in events (p=0.27)[2]
Stroke	WATCHMAN **comparable** to warfarin	**55%** reduction in disabling/fatal stroke (p=0.03)*, largely driven by **80%** reduction in hemorrhagic stroke (p=0.003)[2]
Mortality	WATCHMAN **statistically significant** to warfarin	**27%** reduction in all-cause mortality (p=0.04)[2] **41%** reduction in CV/unexplained mortality (p=0.03)[2]
Major Bleeding	WATCHMAN **statistically significant** to warfarin **post-procedure**	**72%** reduction after 6-months (p=0.001)[3]
Warfarin Cessation	WATCHMAN allows the **majority** of patients to **discontinue warfarin**	**92%** of patients discontinue after 45-days; **99%** of patients discontinue after 1 year[4]

1. WATCHMAN FDA Panel Sponsor Presentation. Oct 2014.; 2 Reddy VY et al. JACC. 2017; In Press; 3. Price, M. J., V. Y. Reddy, et al. JACC: CV Interv 2015; 8(15): 1925-1932; 4. Holmes, DR et al. JACC 2014; 64(1): 1-12; 6.

Very long-term outcome after initially successful catheter ablation of atrial fibrillation

Heart Rhythm
Volume 11, Issue 5, Pages 771-776 (May 2014)

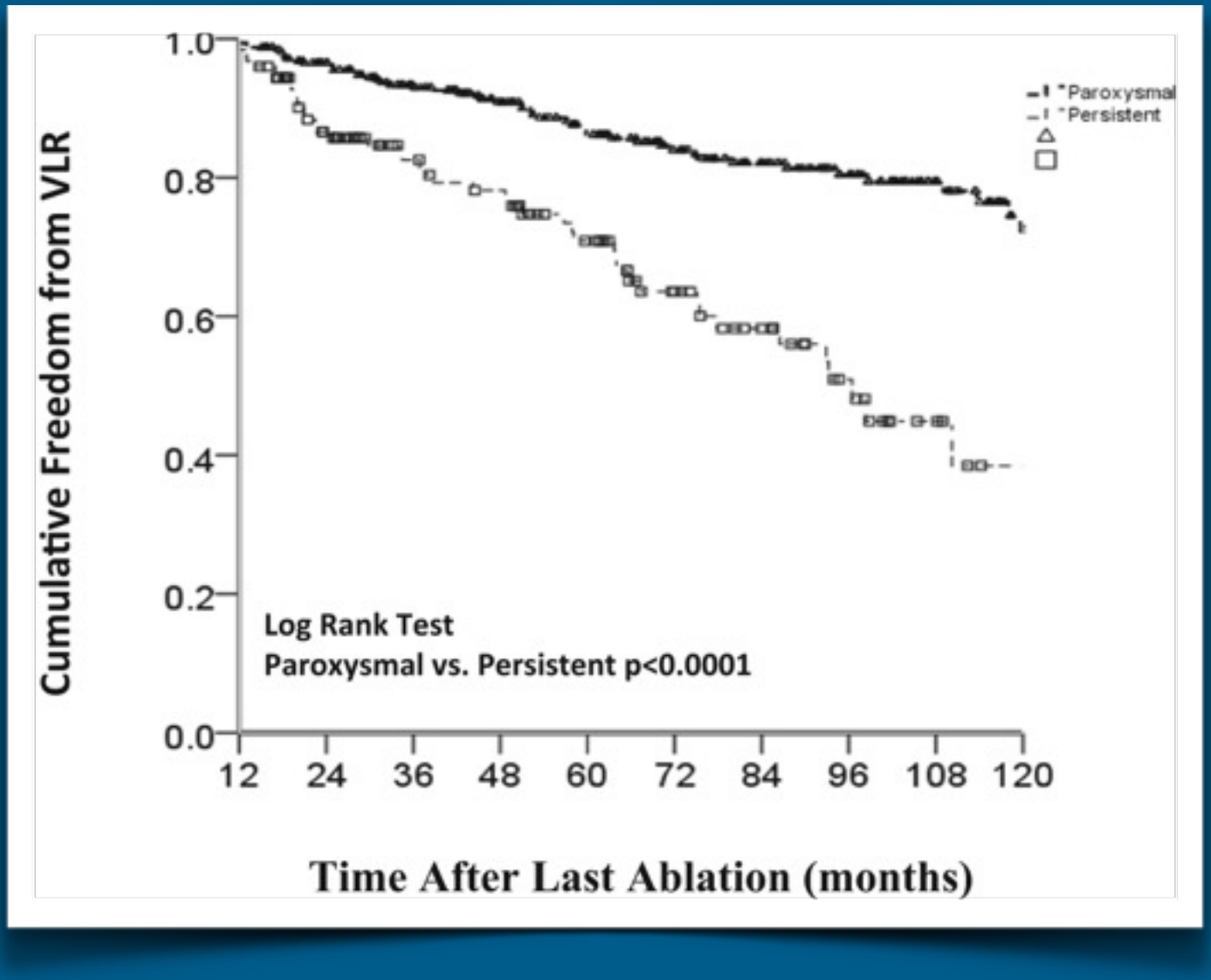
445 patients, 66+/- 34 months f/up



16% at 5 years, 30% at 10 years
VLR: Very late recurrence

Heart Rhythm 2014 11, 771-776DOI: (10.1016/j.hrthm.2014.02.003)

445 patients, 66+/- 34 months f/up



Heart Rhythm 2014 11, 771-776DOI: (10.1016/j.hrthm.2014.02.003)

AtriCure

AtriCure Randomized Pivotal Study
VAL-1200

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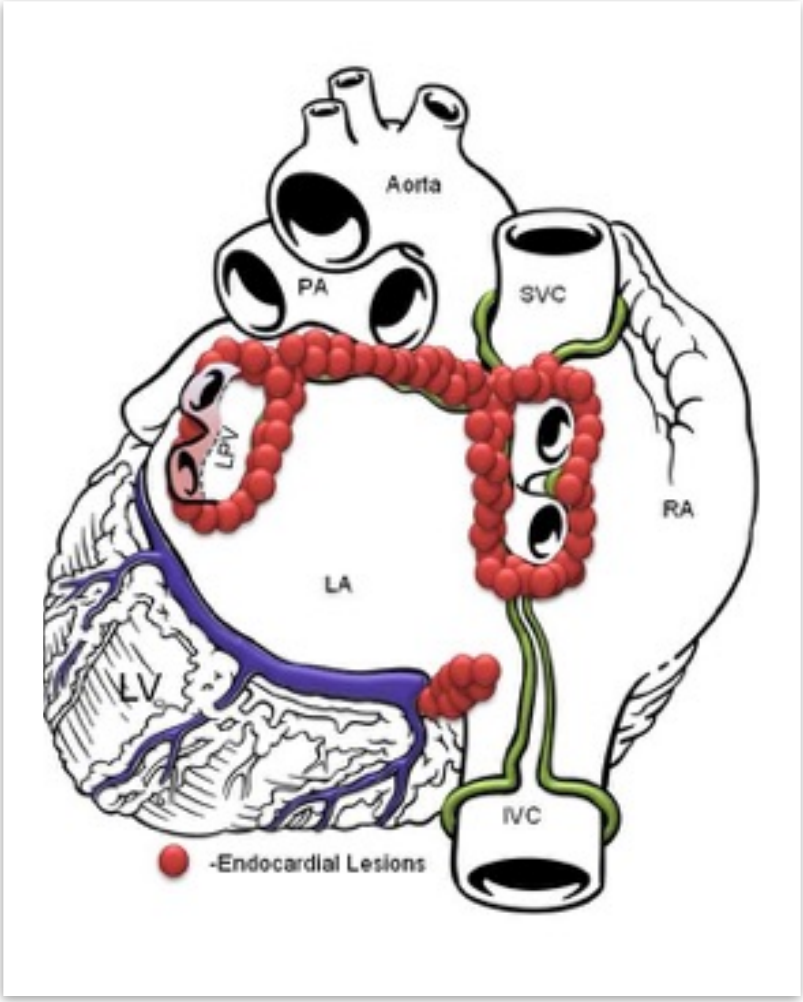
Control Arm
Standalone Endocardial Ablation Procedure



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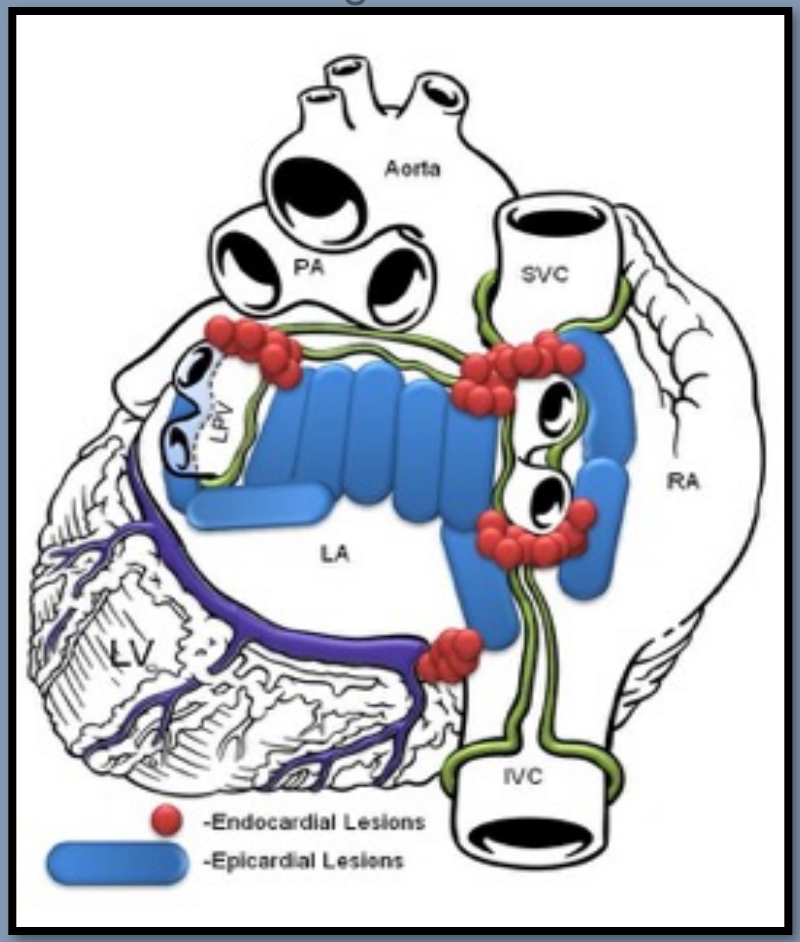
AtriCure

Study Procedure
Convergent Procedure

- Treatment Arm
- Convergent Procedure



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Study Design

- Randomized 2:1 (convergent procedure versus standard ablation) multi-center, prospective, open label pivotal study
- 27 US Sites, 3 OUS sites
- 153 patients
- Initial Post procedure follow-up: 12 months
  - 3 month Blanking Period
- Long-term follow-up 18 months with annual phone follow-up for 5 years

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Study Primary Efficacy Endpoint

Primary Efficacy Endpoint

- Recurrent atrial fibrillation / flutter

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AtriCure

Study Safety Endpoints

Primary Safety Endpoint

- 30 day procedure related adverse events

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AtriCure

amaze

Left Atrial Appendage Ligation with the LARIAT® Suture Delivery System as Adjunctive Therapy to Pulmonary Vein Isolation for Persistent or Longstanding Persistent Atrial Fibrillation

LARIAT Procedure

amaze Protocol Overview

Principal Purpose	Evaluate freedom from AF
Patient Population	Persistent or longstanding persistent AF (< 3 yrs continuous AF) planned for catheter ablation
Investigational Tx	LARIAT LAA ligation followed by PVI catheter ablation (4 weeks)
Control Tx	PVI catheter ablation without LAA ligation

ASAP-TOO (NCT02928497): Overview

WATCHMAN™
LEFT ATRIAL APPENDAGE
CLOSURE DEVICE

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	Effectiveness Endpoint Time to first occurrence of ischemic stroke or systemic embolism Safety Endpoint 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

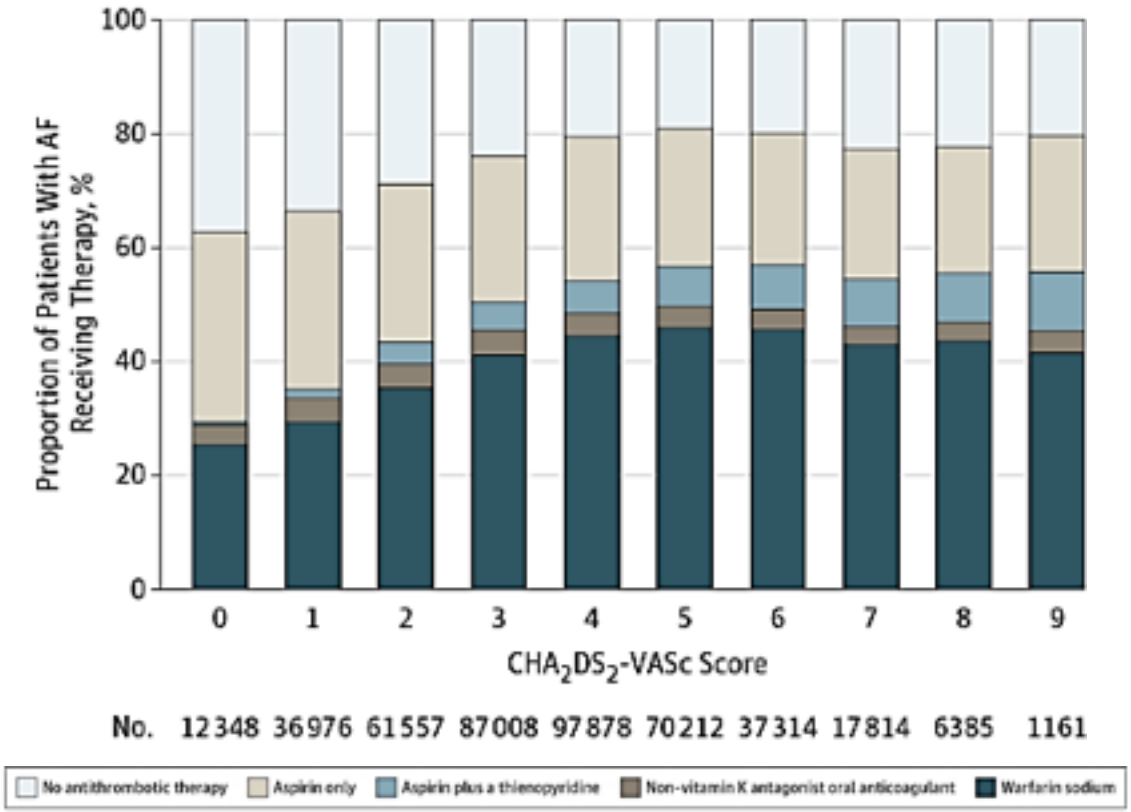
Holmes et al. AHJ 2017; *in press*

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

NCDR Pinnacle Registry

WATCHMAN™
LEFT ATRIAL APPENDAGE
CLOSURE DEVICE

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



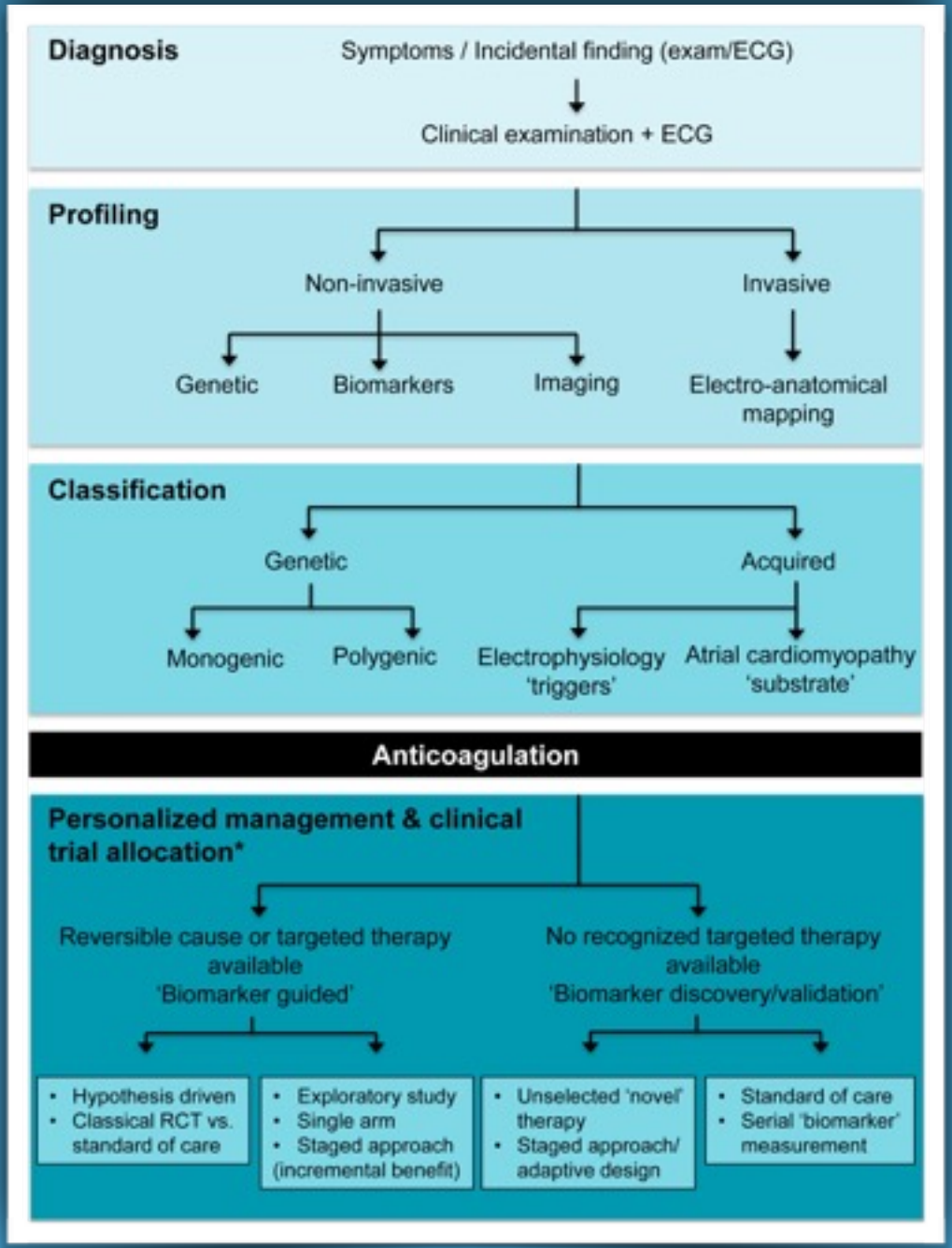
Warfarin

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

Novel Oral Anticoagulants

- Bleeding risk
- Daily or 2x/daily regimen
- High non-adherence rates
- Complicates surgical procedures
- Limited reversal agents
- High cost

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



Heart Rhythm 2017 14, 763-782DOI: (10.1016/j.hrthm.2017.01.032)

Ablation is salvation

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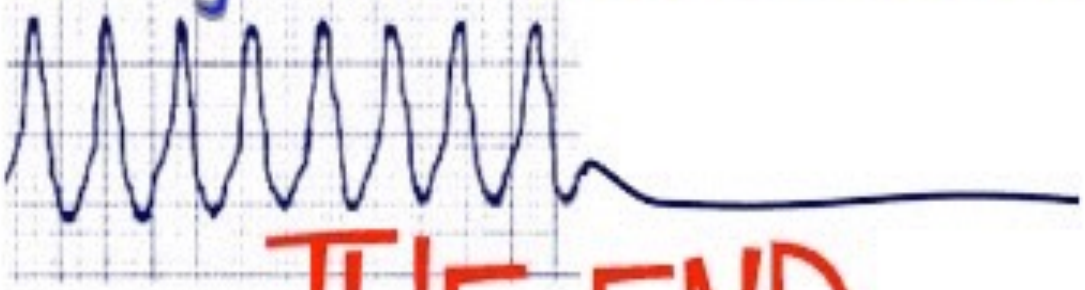
All Arrythmias

Straighten Themselves Out in



THE END