Left Atrial Appendage Closure: Has It Found It's Rhythm?

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Disclosures:

- Phillips/Volcano: consultant, speaker, trainer
- Boston Scientific: Medical advisory board, speaker, educational grants, trainer, investigator
- Medtronic Corporation: speaker, educational grants, investigator
- Shockwave Medical: Medical Advisory Board
- Ostialcorp: Medical Advisory Board; stock holder
- Asia Pacific Medical Technologies: Stock Holder
- Endoshape, Inc.: Stock Holder
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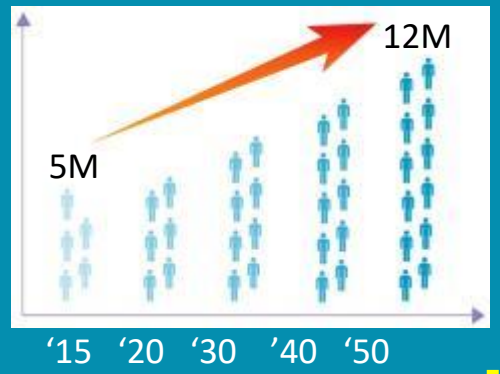
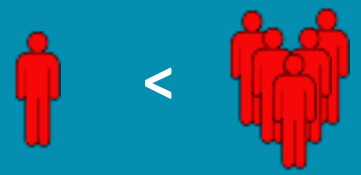
AF is a Growing Problem Associated with Greater Morbidity and Mortality

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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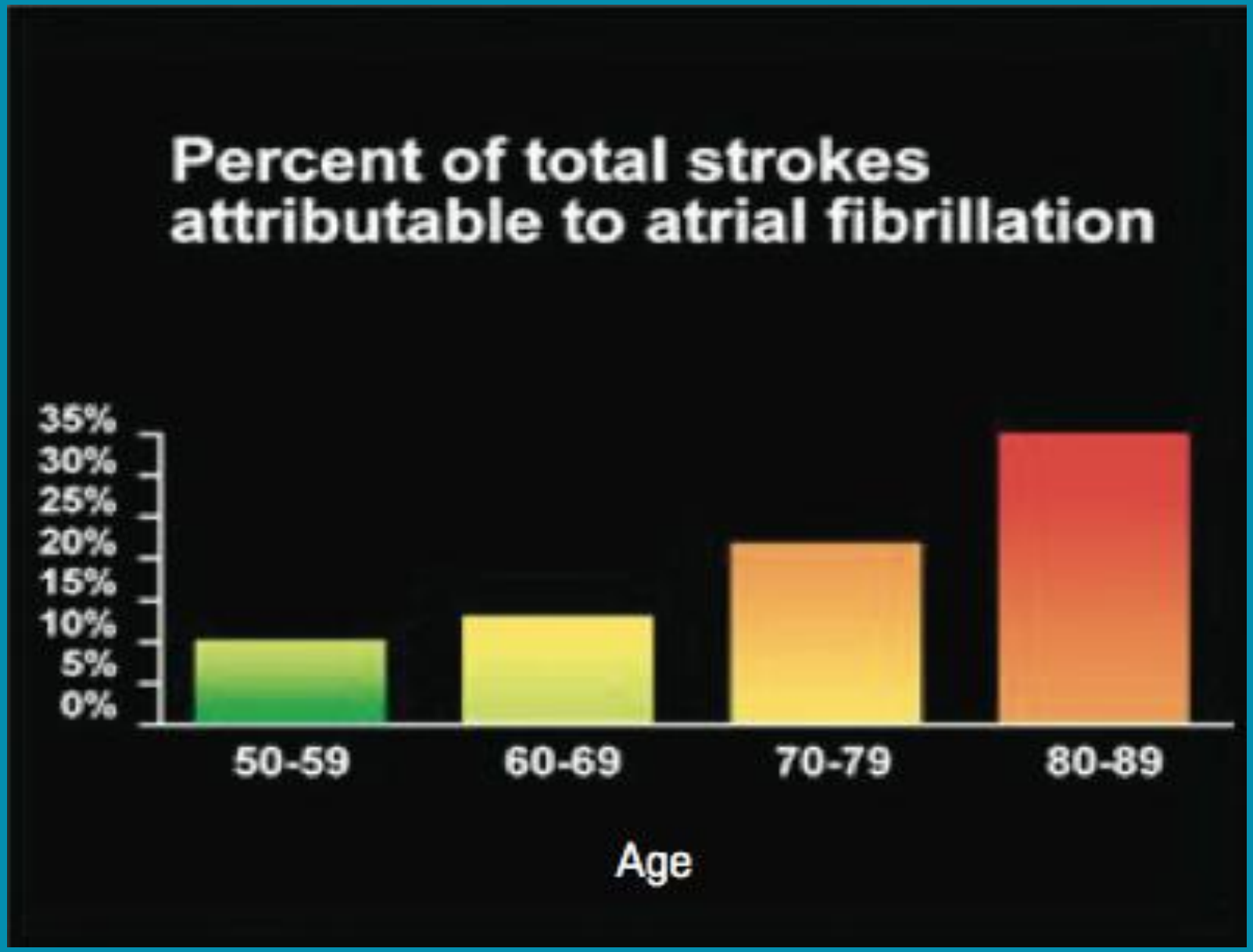
Stroke Risk by Age



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A-fib Related Strokes are More Debilitating

Stroke

#1 cause of **adult disability** worldwide[1]

AF-related Stroke

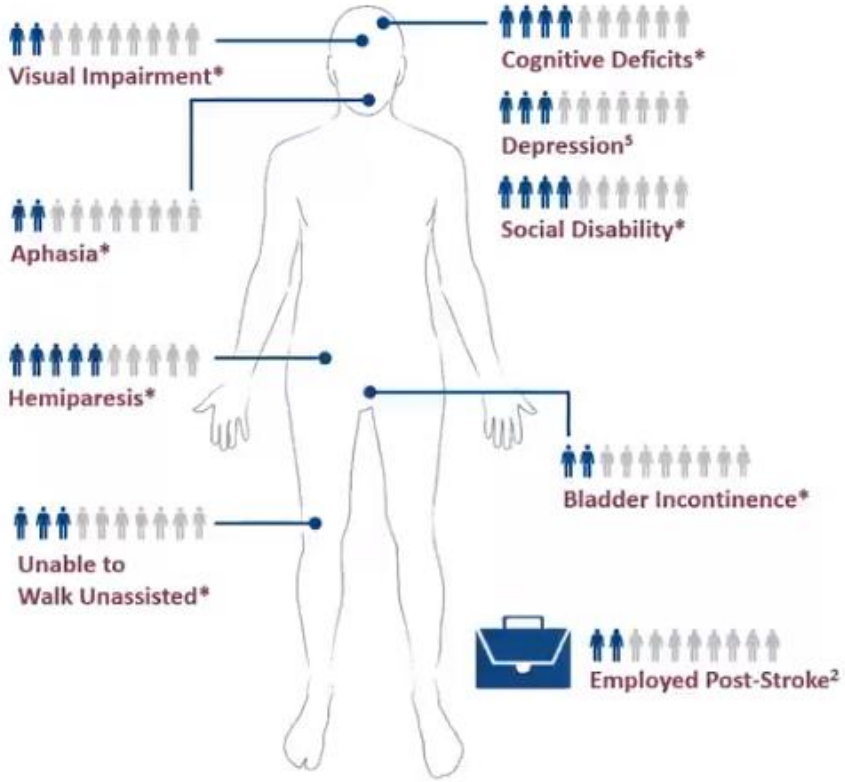
1.5X higher **disability**[3**]

2X higher **mortality**[3**]

70% result in **death or permanent disability**[6]

*at 6 months post-stroke[4]

**compared with stroke patients without AF



[1]Chee and Tan. Med J Malaysia 69.3 (2014): 119-23. [2]Sreedharan et al. Journ of the neurological sciences 332.1 (2013): 97-101. [3]Lamassa et al. Stroke 32.2 (2001): 392-398. [4]Kelly-Hayes et al. Journ of Stroke and Cerebrovascular Diseases 12.3 (2003): 119-126. [5]Loo and Gan. International Journ of Stroke 7.2 (2012): 165-167. [6]Holmes DR, Seminars in Neurology 2010;30:528-536.

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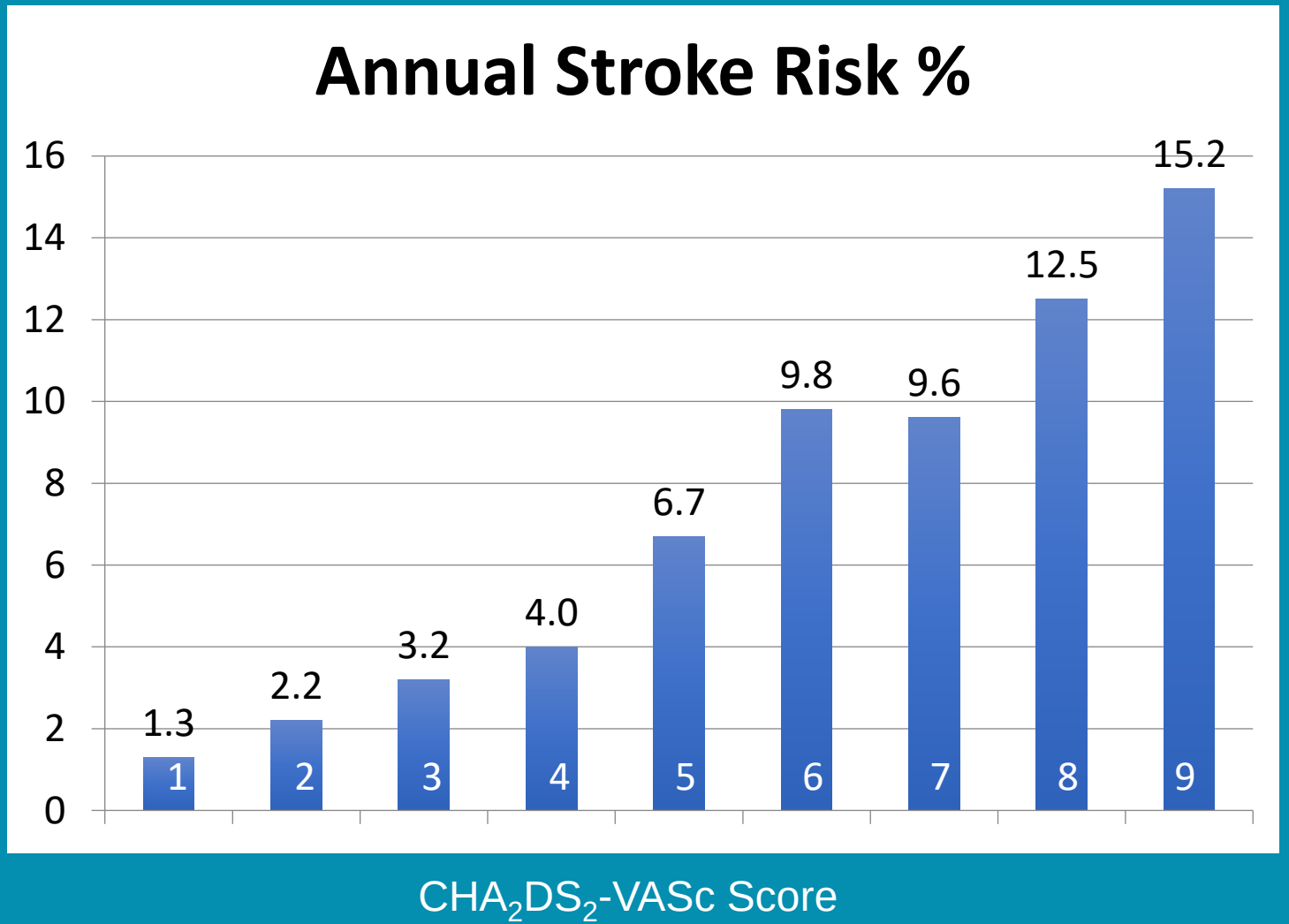
Stoke Risk by CHA_2DS_2-VASc Score



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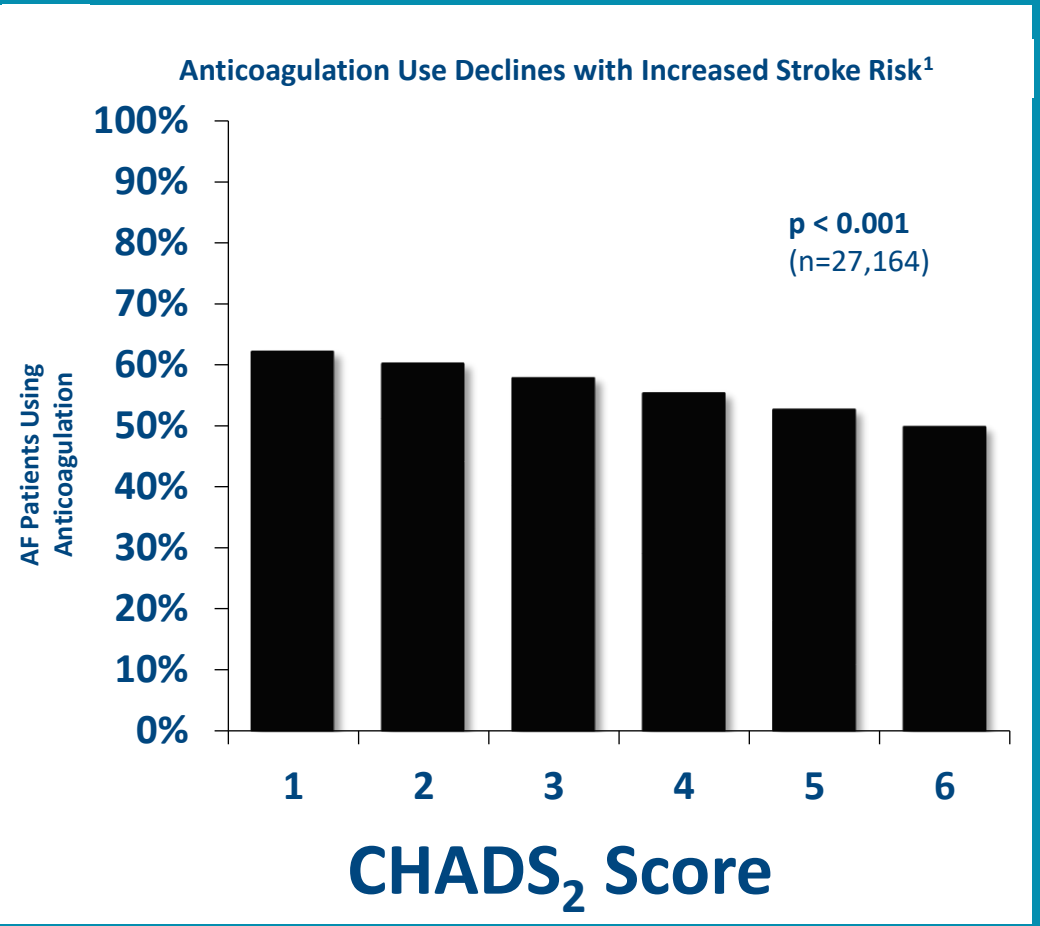
Oral Anticoagulation is Standard of Care, but Not Ideal for All

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 regimen
- High non-adherence rates
- Complicates surgical procedures
- Lack of reversal agents
- High cost



1. Piccini, et al.. Pharmacotherapy in Medicare beneficiaries with atrial fibrillation. Heart Rhythm. 2012;9:1403-1408

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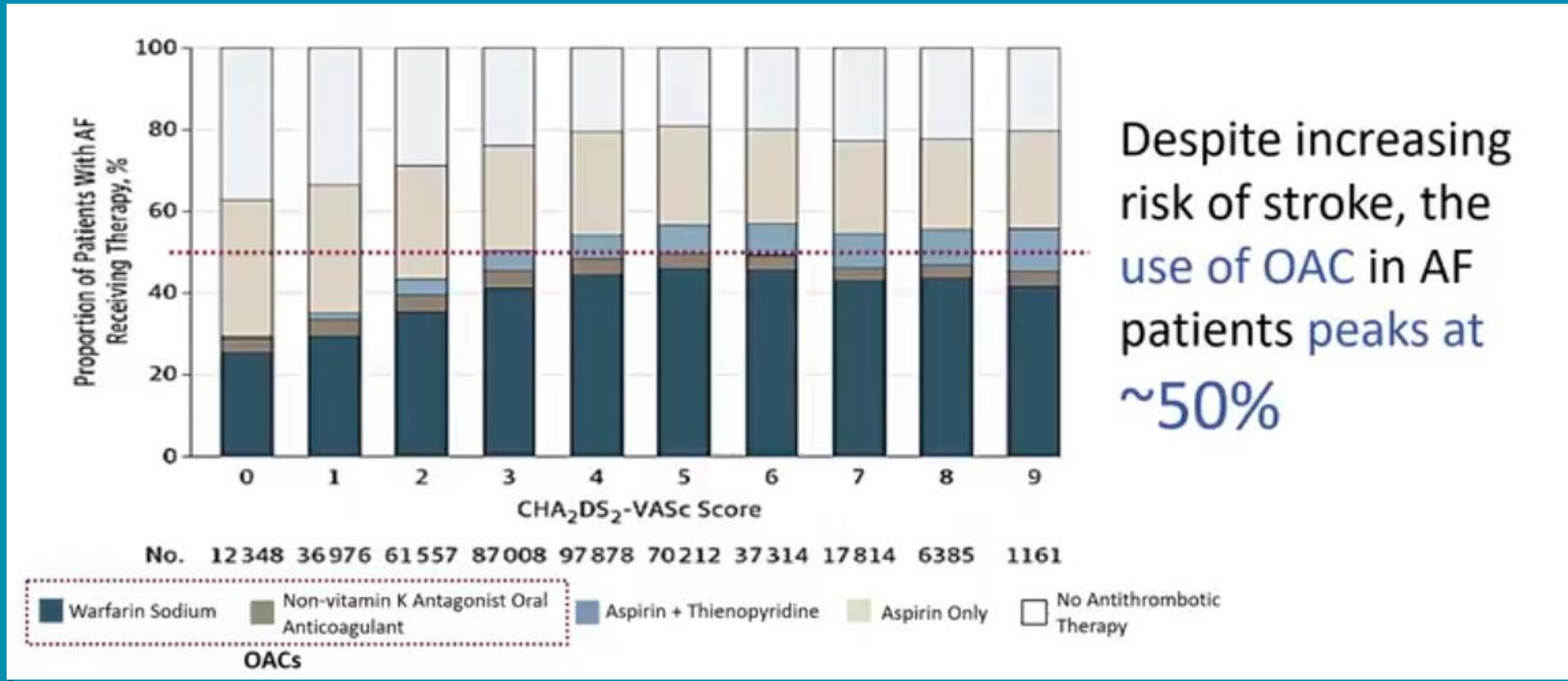
While Oral Anticoagulation is Standard of Care for NVAF, Gaps in Care Remain



Despite increasing risk of stroke, the use of OAC in AF patients peaks at ~50%

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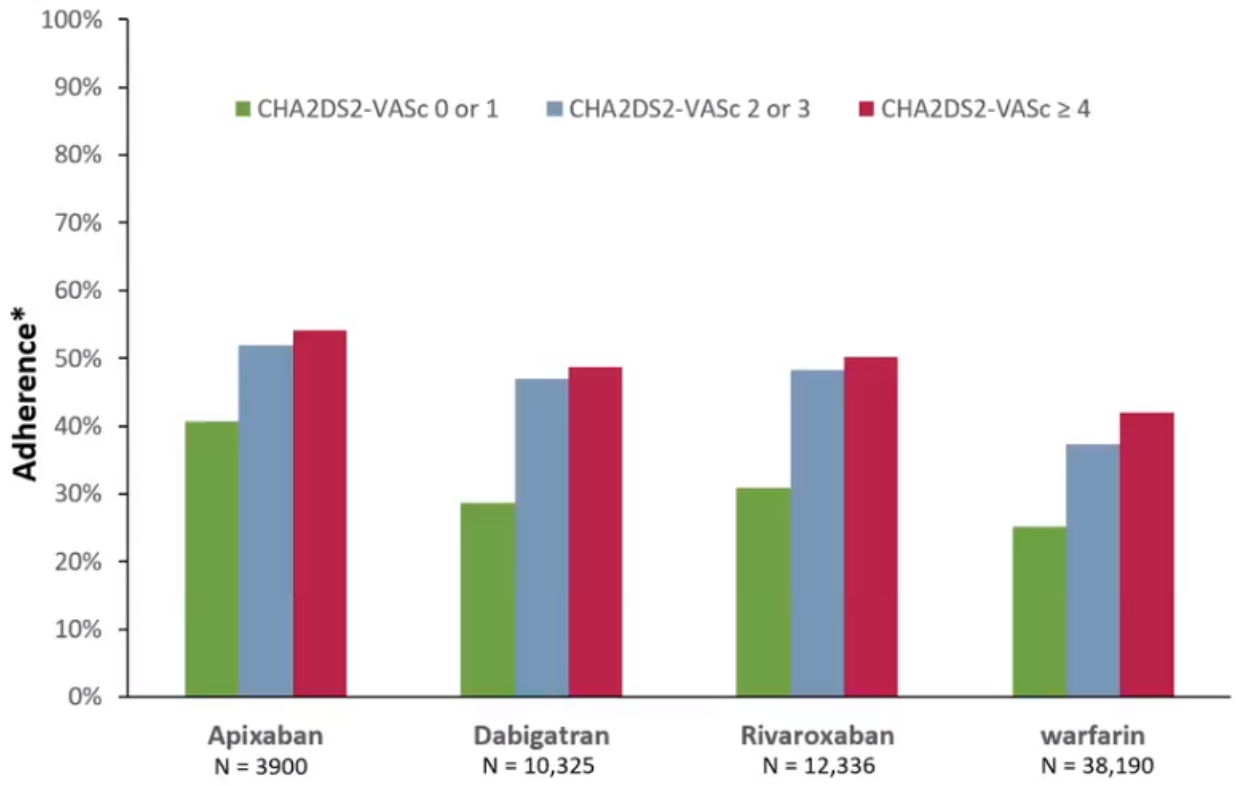
Hsu, J, et al. JAMA Cardiol. 2016;1(1):55-62. doi:10.1001/jamacardio.2015.0374

Adherence to Anticoagulation Remains a Challenge



*Predicted probability of adherence; reported adherence rates adjusted for confounders

Yao X et al. J Am Heart Assoc. 2016;5(2): e003074

A retrospective study of 64,661 patients found that only 47.5% of patients on DOACS had ≥80% adherence during a median follow-up period of 1.1 years

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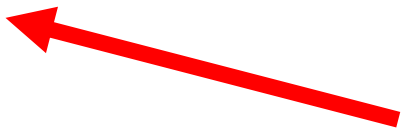
While DOACs offer many benefits and advantages over warfarin, issues of **poor compliance**, **sub-therapeutic dosing**, and **bleeding risk** persist.

This doesn't make sense – most afib patients don't get treated, the majority who do are subtherapeutic or non compliant and the bleeding risks can be prohibitive all in the number one disabling entity among adults!

Why not go to the source!



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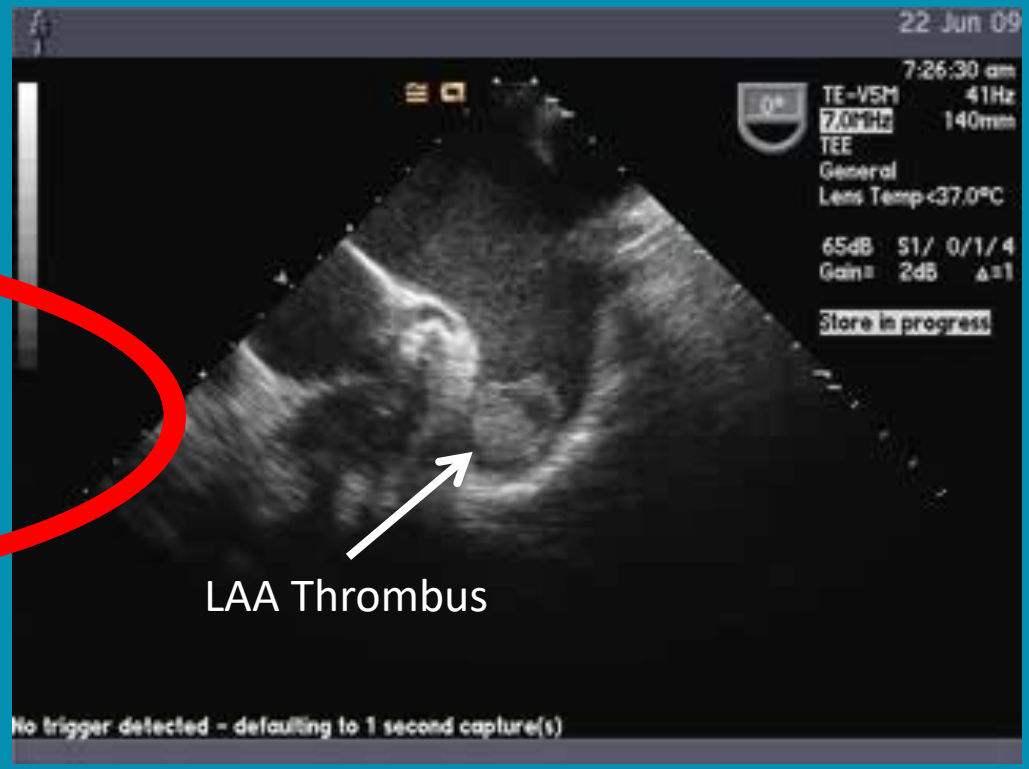
Connection Between Non-Valvular AF-Related Stroke and the Left Atrial Appendage

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].



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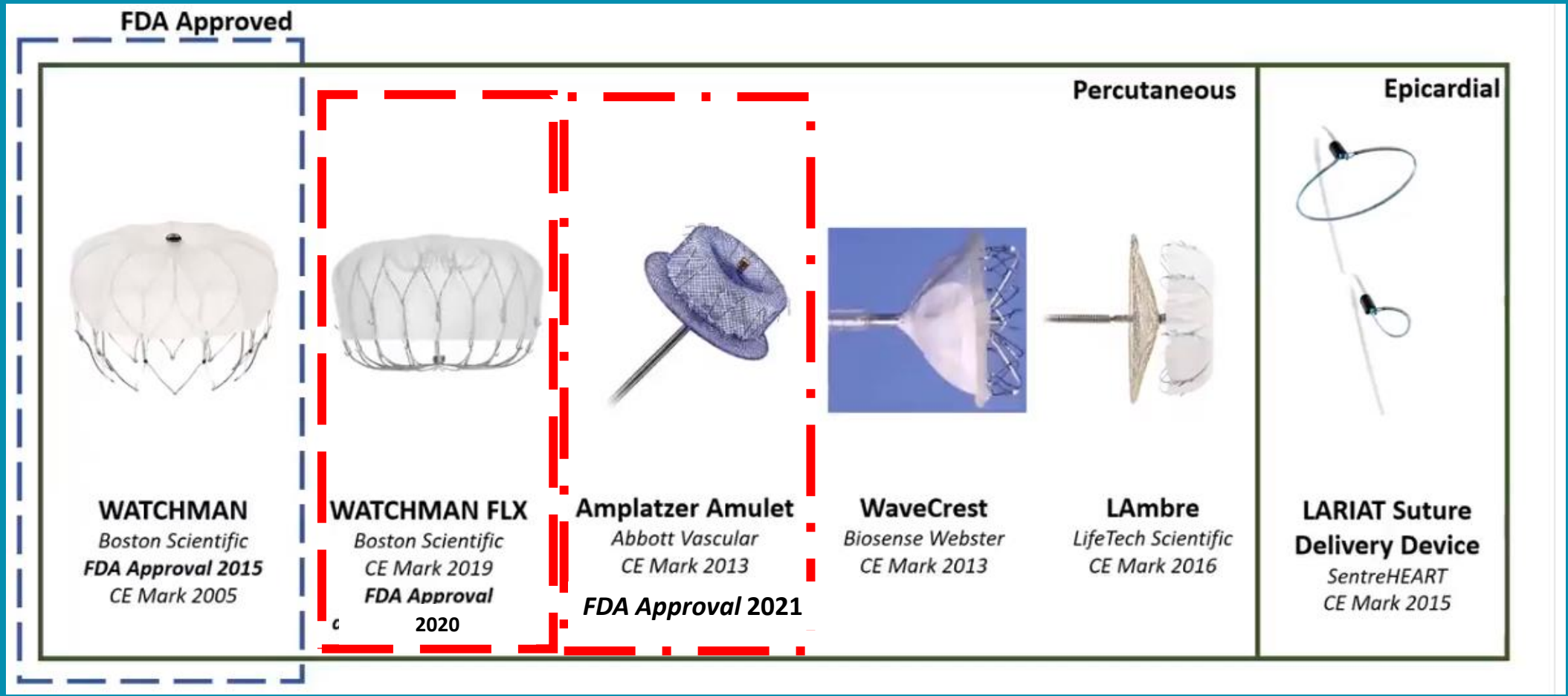
1. Stoddard et al. Am Heart J. (2003)
2. Goldman et al. J Am Soc Echocardiogr (1999)
3 Blackshear JL. Odell JA., *Annals of Thoracic Surg* (1996)

Left Atrial Appendage Occlusion Devices

Multiple devices approved in Europe, only two devices approved for use in the U.S.



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2019 ACC/AHA/HRS Focused Update on Atrial Fibrillation

Left Atrial Appendage Occlusion included in AF Guidelines

4.4. Nonpharmacological Stroke Prevention

4.4.1. Percutaneous Approaches to Occlude the LAA

Recommendation for Percutaneous Approaches to Occlude the LAA Referenced studies that support the new recommendation are summarized in Online Data Supplement 4.		
COR	**LOE**	**Recommendation**
IIb	**B-NR**	**1. Percutaneous LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation (S4.4.1-1–S4.4.1-5).** **NEW**: Clinical trial data and FDA approval of the Watchman device necessitated this recommendation.

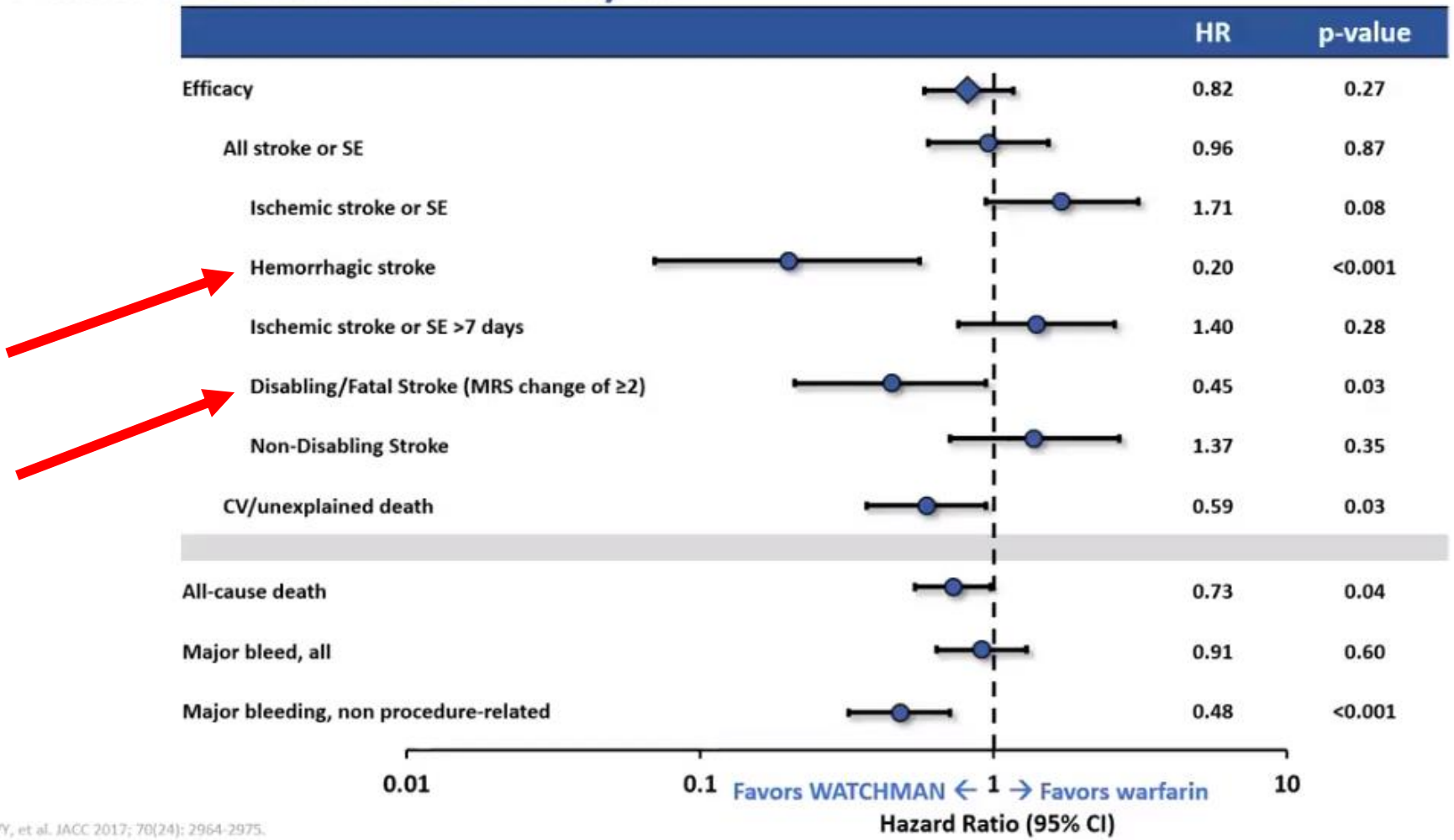
"Oral anticoagulation remains the preferred therapy for stroke prevention for most patients with AF and elevated stroke risk. However, **for patients who are poor candidates for long-term oral anticoagulation (because of the propensity for bleeding or poor drug tolerance or adherence)**, the Watchman device provides an alternative."

January, CT. et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. JACC. 2019; doi: 10.1161/CIR.0000000000000665

WATCHMAN Patient Criteria

1. Patient has Non-Valvular Atrial Fibrillation (NVAF)
2. Patient has an increased risk for stroke and is recommended for oral anticoagulation (OAC)
3. Patient is suitable for short-term warfarin therapy but deemed unable to take long-term OAC
4. Patient has an appropriate rationale to seek a non-pharmacologic alternative to warfarin.

PROTECT AF & PREVAIL 5 Year Patient Level Meta-Analysis



ddy VY, et al. JACC 2017; 70(24): 2964-2975.

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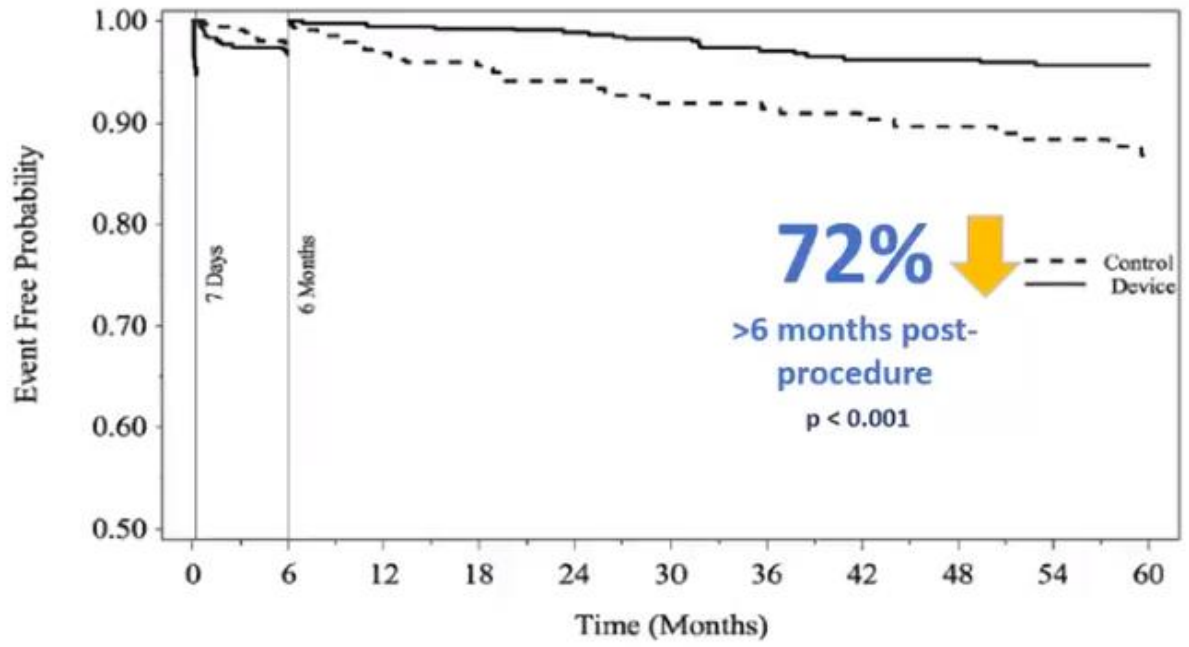
Bleeding Outcomes after Left Atrial Appendage Closure Compared with Long-term Warfarin

Freedom of Major Bleeding Over 3 Adjunctive Pharmacotherapy Intervals



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Price, MJ, et al. JACC: CV Interv 2015;8(15):1925-1932.

Note: This data is from 5 year results fro PROTECT AF and 2 year results from PREVAIL

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	87%	>93%
CAP	96%	>96%
PREVAIL	92%	>99%
CAP2[4]	96%	>96%

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; 54(1):1-12

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All-Cause Mortality

PROTECT AF/PREVAIL Meta-Analysis 5-Year Results

WATCHMAN arm reported
reduced all-cause mortality by 27%
compared to warfarin
(P=0.04)

Reddy, VY, et al. JACC 2017; 70(24);2964-2975.

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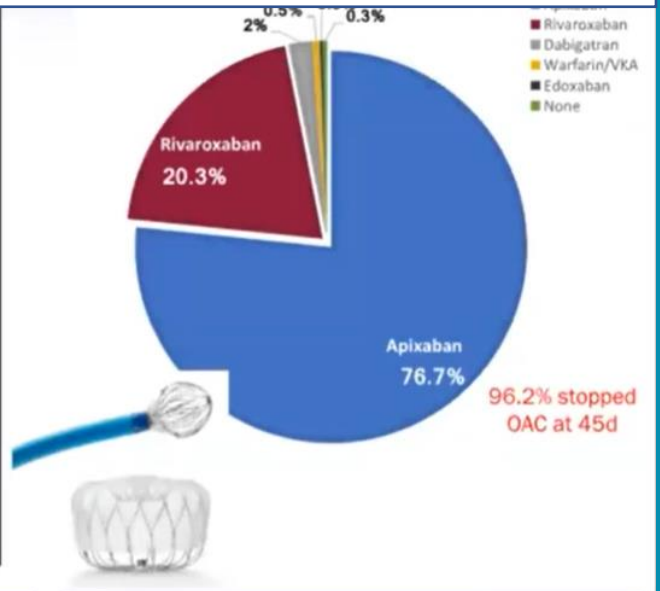
PINNACLE FLX Study Overview

A US-only IDE to evaluate the safety and efficacy of the new WATCHMAN FLX Device

Study Design	**Single arm non-randomized study design** • **Post-implant drug regimen - DOAC only** • **Compared to a performance goal based on the current generation WATCHMAN**
Enrollment	**400 Patients at 29 U.S sites, 58 roll-in subjects (2 per site)**
Objective	**To establish the safety and effectiveness of the WATCHMAN FLX Left Atrial Appendage Closure (LAAC) Device for patients with NVAF who are eligible for anti-coagulation therapy to reduce the risk of stroke**
Follow-Up	**45 d (+TEE), 6 mon., 12 mon. (+TEE), 18 mon., and 24 mon.**
Antithrombotic	**DOAC + ASA 45 day, Clopidogrel + ASA until 6 mon, ASA indefinitely**



	Implant	12 Months
Jet Size ≤ 5mm	100% (376/376)	100% (344/344)
Complete Seal	92.6% (348/376)	89.5% (308/344)
Jet Size > 0 and ≤ 5mm	7.4% (28/376)	10.5% (36/344)
Jet Size > 5mm	0% (0/376)	0% (0/344)
TEE deemed not evaluable for leak by Core Laboratory*	2.3% (9/385)	0.9% (3/347)

Implant Success*	**98.8% (395/400)**
Implant Unsuccessful	1.3% (5/400)
LAA Anatomy was not suitable	3/5
Did not meet device release criteria	2/5
Number of WATCHMAN FLX Devices Used	1.2 ± 0.4 (400)
All Devices Used (Implanted or Attempted)	
Number of Partial Recaptures	1.8 ± 2.8 (400)
Number of Full Recaptures	0.4 ± 1.1 (400)

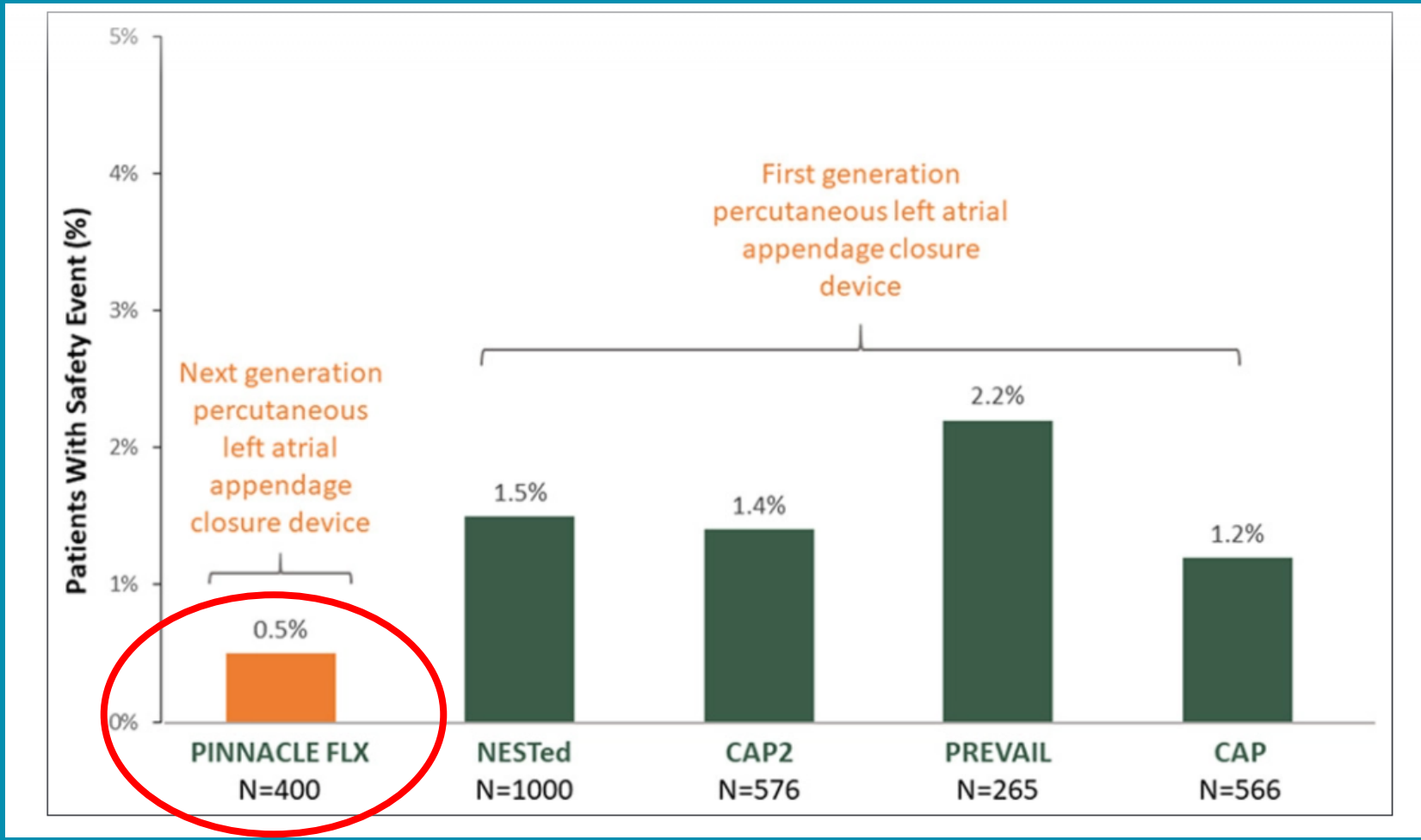
	Event Rate
Primary Safety Endpoint	**0.5% (2/400)**
All-Cause Death	0% (0/400)
Ischemic Stroke	0.5% (2/400)
Systemic Embolism	0% (0/400)
Device or Procedure Related Events Requiring Surgery or Major Endovascular Intervention	0% (0/400)

Doshi SK, et al. Circulation 2021 (in press).

Complications with LAA Closure

Procedural Complications	Post-Procedural Complications
1. Death (<0.2%)	1. Delayed pericardial effusion & tamponade
2. Stroke (<0.2%): - Ischemic: air or thromboembolism - Hemorrhagic	2. Device-related thrombus
3. Systemic embolism	3. Residual leak (LAA patency)
4. Pericardial effusion (~1%): - Cardiac perforation - Pericardial tamponade - Pericardial effusion (clinically insignificant)	4. Device migration/embolization
5. Device embolization (<0.2%): - Percutaneous retrieval - Surgical retrieval	5. Impingement of surrounding structures
6. Vascular complications: retroperitoneal bleed, AV fistula, pseudoaneurysm, hematoma	6. Device erosion
7. Other: bleeding, renal failure, respiratory failure, sepsis, MI, endotracheal /esophageal damage, interfering surrounding structures, device/contrast allergy, pericarditis	7. Iatrogenic atrial septal defects

Pinnacle FLX Study Safety Events



Kar, S, et al. Circulation 2021; 143(18), 1754-1762.

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PINNACLE FLX: Safety Profile

0.5%
Event Rate*[1]

0.5%	0%	0%	0%
Ischemic Stroke (2/400)	All Cause Death	Pericardial Effusions Requiring Open Cardiac Surgery	Device Embolization

*The low **0.5%** event rate demonstrates the **enhanced safety profile** of the **WATCHMAN FLX™** device, showing a statistically significant difference to the performance goal set for similar safety endpoints in the PREVAIL Trial and the CAP2 Registry[1].

1. PINNACLE FLX. Doshi, SK. Results presented at HRS 2020
2. 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
3. Price, M. J.; V. Y. Reddy, et al., JACC: CV Interventions 2015; 8(15): 1925-1932
*Two strokes in PREVAIL are excluded because the baseline MRI scans was unavailable

SURPASS Design

Objective

Assess **safety and efficacy outcomes** in patients in the NCDR-LAAO Registry who received **a commercial WATCHMAN FLX device**

Design

WATCHMAN FLX patients included in the NCDR-LAAO Registry from **August 2020 through August 2022** followed through 2 years post-implant. No exclusion criteria.

This Analysis

45-Day Outcomes

N=16,048
August 5, 2020 – March 31, 2021

Surpass Trial

Safety

0.37%

Major Procedural Adverse Event Rate*
(60/16,048)

Simplicity

98%

Procedural Success
(16,048/16,446)

Seal

82%

Complete LAA Closure
at 45 days

95%

LAA Closure <3mm
at 45 days

PRAGUE-17

A randomized trial of percutaneous LAAC versus DOAC agents in high-risk atrial fibrillation patients

Study Objective	To compare LAAC with DOAC in high risk AF patients
Study Design	Prospective, multicenter, open-label, randomized non-inferiority trial
Primary Endpoint	**Composite of:** • Stroke or TIA • Systemic embolism • Clinically-significant bleeding* • Cardiovascular death, or • Significant peri-procedural or device-related complication
Patient Population	415
Number of Sites	10 Cardiac Centers in the Czech Republic
Follow-up	6 weeks, 3 months, 6 months, 9 months, 12 months, then every 6 months
Status	Enrolling Complete

*defined as ISTH major or non-major clinically-significant bleeding

61% of LAAC procedures in this trial were performed with Abbott's Amulet LAA occluder

Osmancik et al. Presented at ESC 2019

LAAC

Amulet or Watchman/Watchman FLX

Post-implant antithrombotic treatment:

- DAPT for 3 months: aspirin (100 mg/day) + clopidogrel (75 mg/day)
- 3 month TEE; discontinue clopidogrel
- Continue aspirin indefinitely

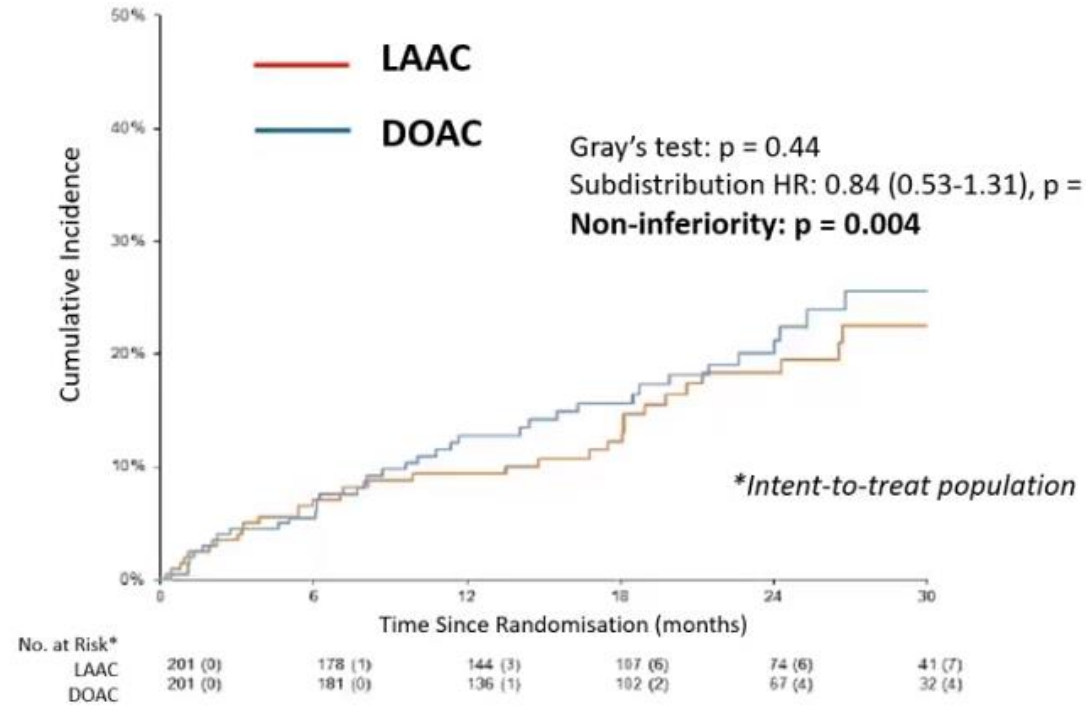
**Regimen could be individualized if needed*

DOAC

Rivaroxaban, Apixaban, or Dabigatran at manufacturer-recommended dose.

Apixaban preferred

LAAC Non-Inferior to DOAC for Primary Endpoint



Results of this trial show that LAAC is non-inferior to DOACs for the treatment of NVAF.

Future Randomized Clinical Trials will be conducted to study this finding in a larger patient population.

**61% of LAAC procedures in this trial were performed with Abbott's Amulet LAA occluder*

Osmancik et al. Presented at ESC 2019

Ongoing Indication Expansion Trials

CHAMPION-AF Trial

Expanding the Breath of Patients Who May Benefit from LAAC Therapy

Global Head-to-Head RCT comparing the safety and efficacy of WATCHMAN FLX to NOAs in a broader NVAF population, including of lower risk patients

Primary Endpoints:

- WATCHMAN FLX™ is non-inferior for the occurrence of stroke (including ischemic and/or hemorrhagic), cardiovascular (CV) death (including unexplained death), and systemic embolism at 36 months.
- WATCHMAN FLX is superior for non-procedural bleeding (ISTH major bleeding and clinically relevant non-major bleeding) at 36 months.
- WATCHMAN FLX is non-inferior for the occurrence of ischemic stroke and systemic embolism at 60 months.

Cost-Effectiveness of LAAC

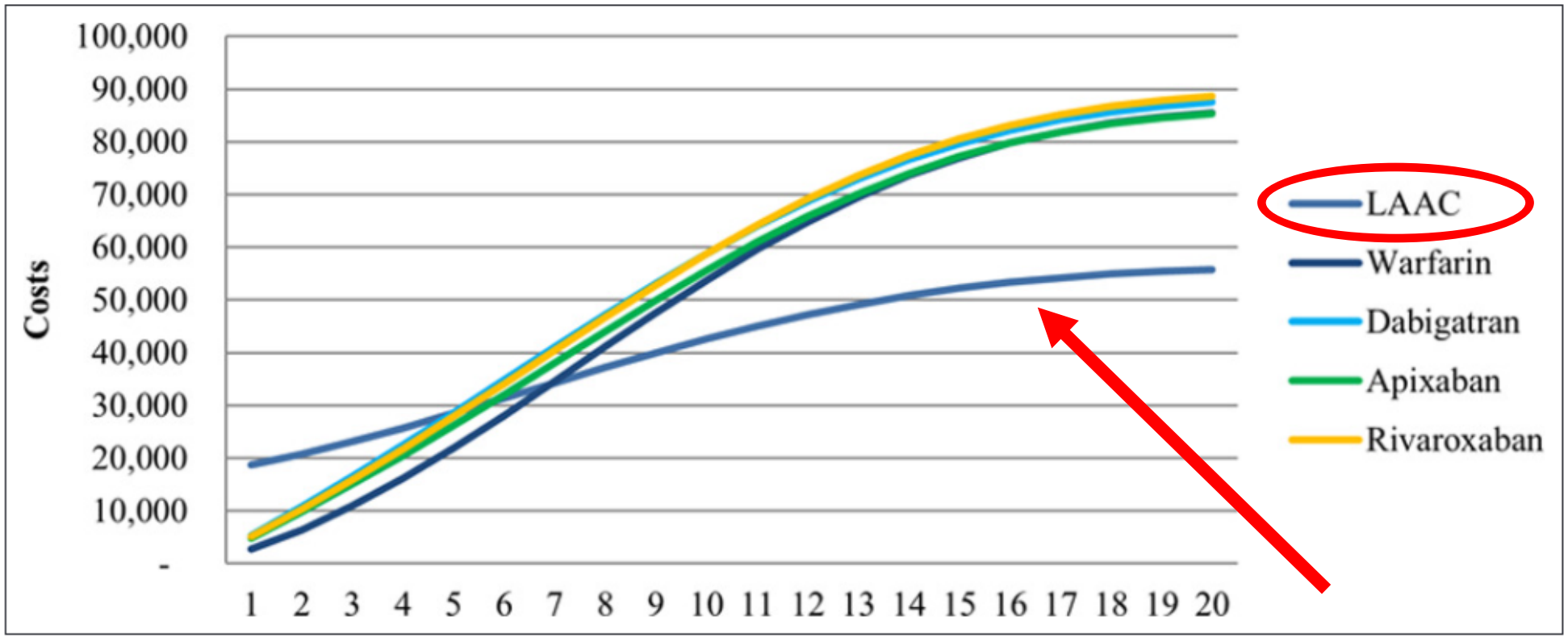


Figure 2. Cumulative costs by therapy over 20 years. LAAC indicates left atrial appendage closure.

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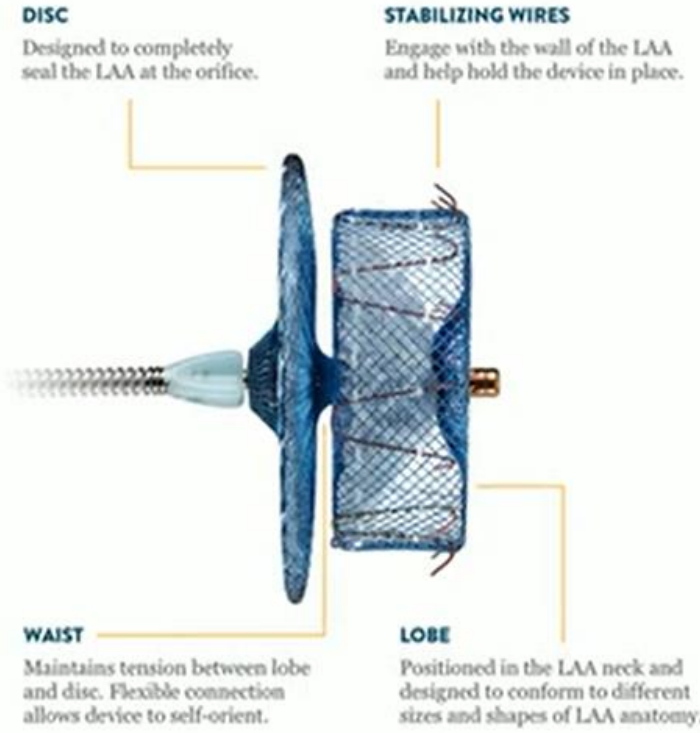
Reddy VY, et al. Stroke. 2018;49:1464-1470

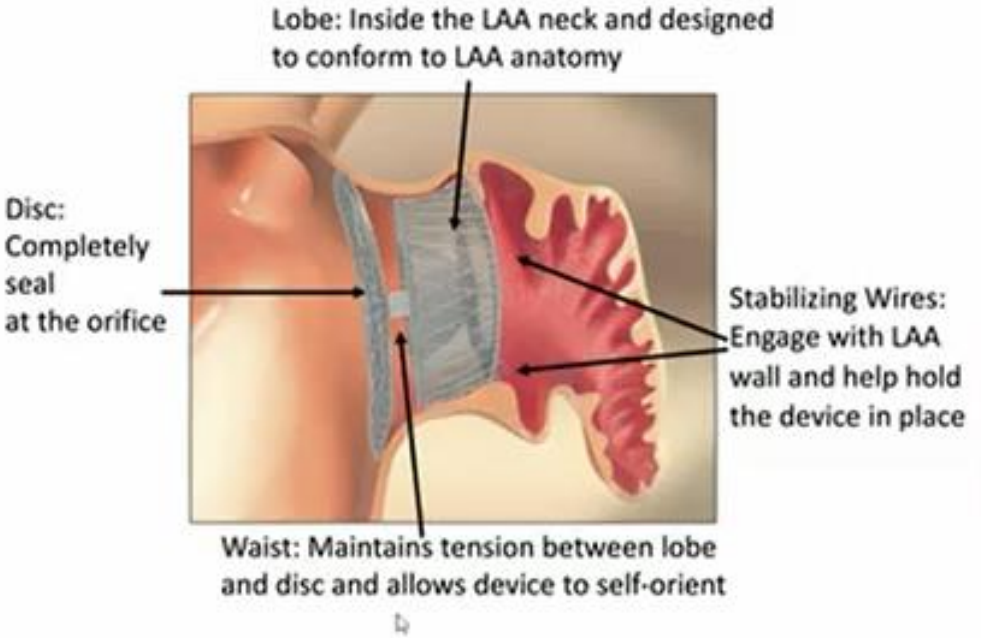
Amplatzer Amulet LAAO Device



Amulet LAA Closure Device

- FDA approved in August 2021
- CE Mark in Europe since 2013
- Length of device is shorter than the diameter
- Broadens the scope of anatomies that can be closed
- Amulet IDE Published in August 2021
- CATALYST trial evaluating Amulet vs AC is ongoing

Amulet LAAO Closure



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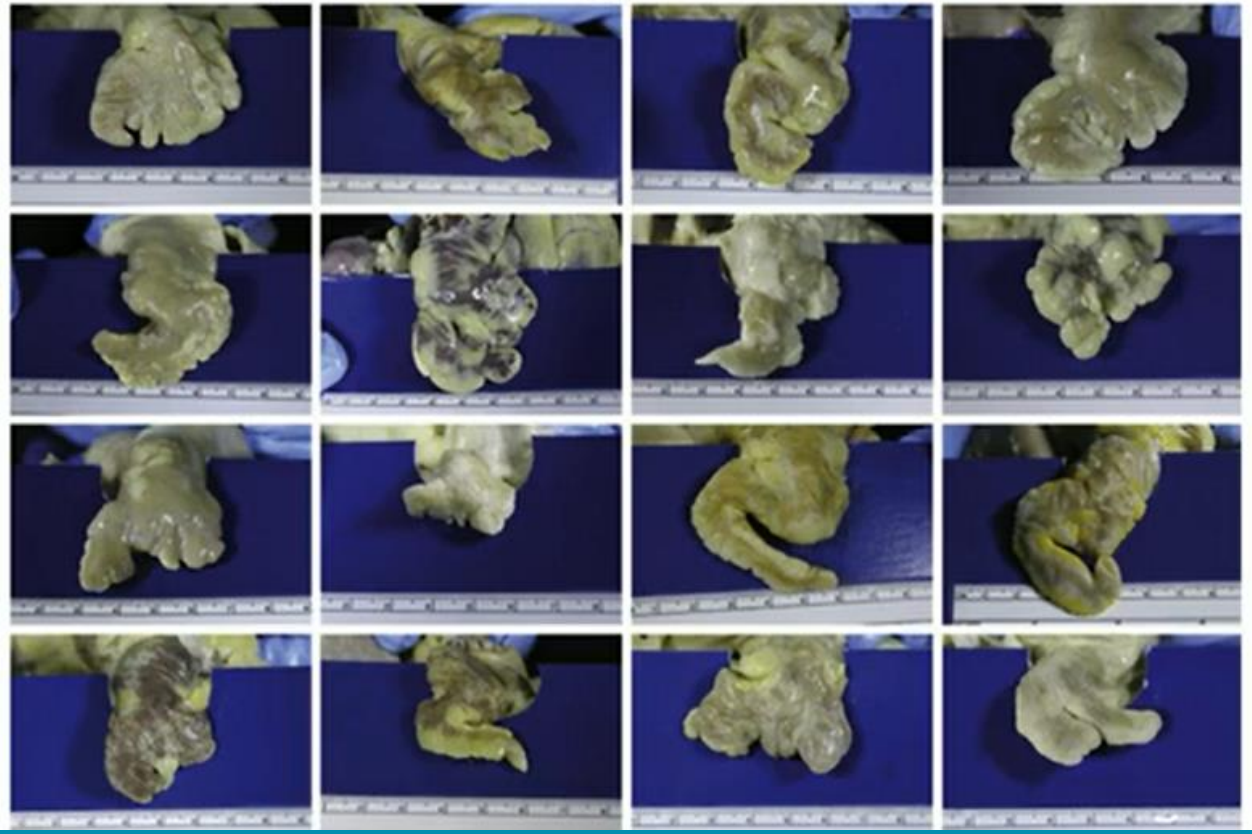
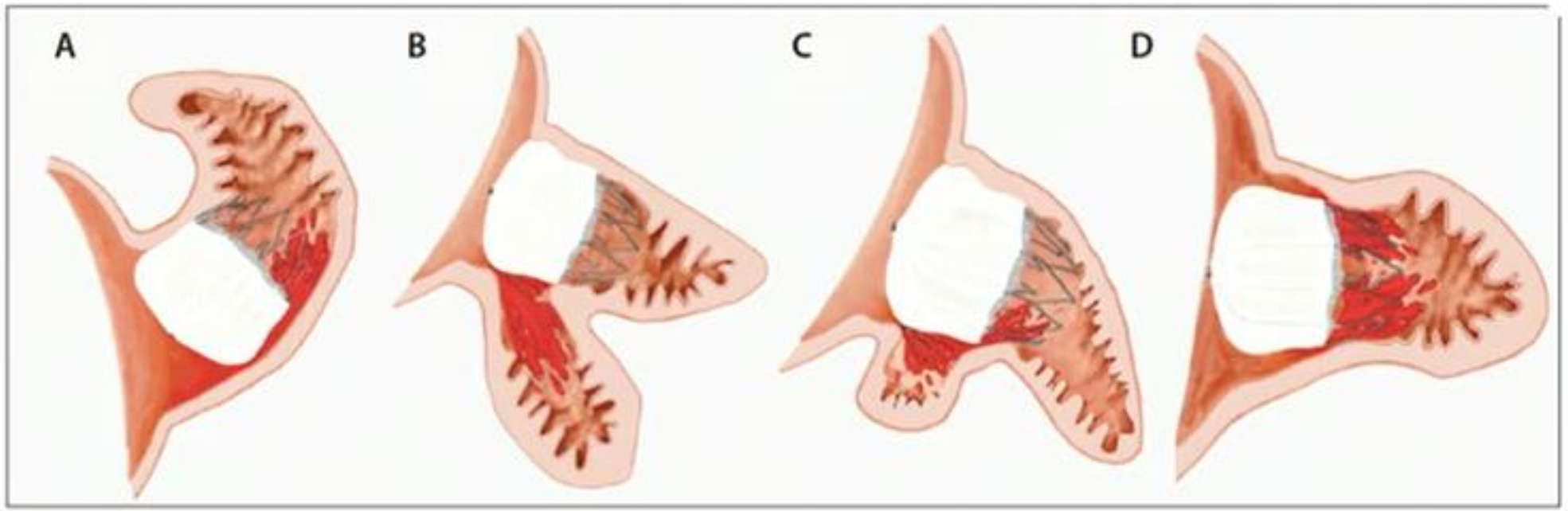
Left Atrial Appendage



M. Reisman et. al

Challenging LAA Anatomies for closure



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Amulet IDE Trial

- Initiated in 2016 to evaluate efficacy of the Amulet LAA closure device to reduce the risk of thrombus embolization from the LAA

- **Head to Head** trial evaluating the Amulet vs. Watchman (gen 2.5)
  - First Head to Head evaluating two different LAAO devices
  - N = 1878

- Patient Eligibility
  - Paroxysmal, persistent, and permanent AF
  - CHADSVASC ≥ 3 and CHASDS score ≥ 2
  - Short term candidate for AC, poor long-term candidate
  - Suitable anatomy for implantation based on TEE for both devices

Lakkireddy D, et al. Circulation. Nov 2021

Amulet IDE Trial

- Clinical follow up
  - Discharge, 45 day TEE, 6 months, 12 months with TEE, 18 m, 24, then annually for 5 years
- Discharge Medications
  - Amulet: **DAPT** or ASA + OAC (investigator discretion)
  - Watchman: ASA + Warfarin (per DFU)

Lakkireddy D, et al. Circulation. Nov 2021

Amulet IDE Primary Outcomes

- Primary safety endpoint: composite of all-cause mortality, procedure-related complications, or major bleeding at 12 months:
  14.5% with Amulet vs. 14.7% with Watchman ($p < 0.001$)

- Primary efficacy endpoint: composite of ischemic stroke or systemic embolism at 18 months:
  2.8% with Amulet vs. 2.8 % with Watchman (p for noninferiority < 0.001)

- Primary mechanism of action endpoint, residual jet around the device (<5 mm):
  98.8% with Amulet vs. 96.8% with Watchman (p for noninferiority <0.001)

Lakkireddy D, et al. Circulation. Nov 2021

Amulet IDE Secondary Outcomes

- Procedure-related complications (device embolization or pericardial effusion)
  - 4.5% with Amulet vs. 2.5% with Watchman (p = 0.02)
- Major bleeding at 18 months
  - 11.6% with Amulet vs. 12.3% with Watchman
- Device-related thrombus
  - 3.3% with Amulet vs. 4.5% with Watchman
- Moderate to severe peri-device leak at 12 months
  - 10% with Amulet vs. 22% with Watchman (p < 0.001)

Lakkireddy D, et al. Circulation. Nov 2021

Final LAAC Conclusions

- Watchman FLX has continued to improve the efficacy of the Watchman 2.5 device and significantly reduce complication rates to <1% in real-world registry data
- Amulet device provides a different design which may be better suited for particular appendage anatomy and may lead to less overall device leak
- Both devices can now be used with subsequent dual antiplatelet therapy
- LAAC offers a tremendous alternative option for patients who cannot tolerate long-term anticoagulants

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Is LAA Occlusion Ready to Fly??--------

- My Opinion:---------Yes!!!

-As effective as anticoagulation

-Highly safe procedure

-Less costly than anticoagulation

-Eliminates cost and bleeding risk

-Eliminates issues with compliance

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