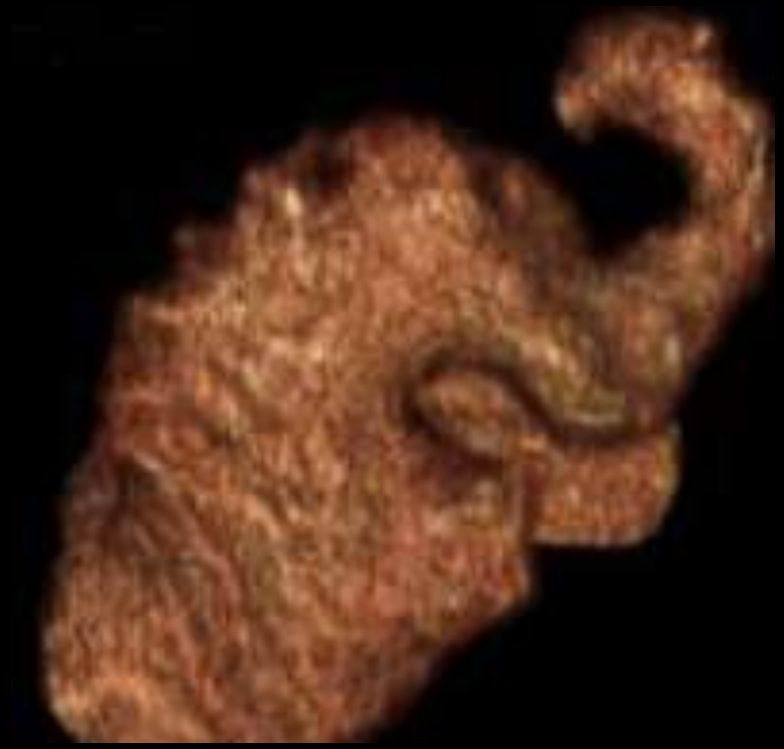
Stroke Prevention in Atrial Fibrillation: A 2021 Update



Rakesh Gopinathannair, MD, MA, FAHA, FACC, FHRS

EP Medical Director, Research Medical Center

Director, Cardiac EP Laboratories, The Kansas City Heart Rhythm Institute

Professor of Medicine, University of Missouri-Columbia

Associate Professor of Medicine (Adjunct), University of Louisville

Email: rakesh.gopinathannair@hcahealthcare.com

@drrakeshg1

9/17/2021

RMC Stroke Symposium
9-17-2021

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Disclosures

- Consultant/speaker: Abbott Medical, Boston Scientific, Pfizer, Zoll Medical
- Physician Advisor: Altathera, PaceMate

None relevant to the content of this presentation

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Outline

- Atrial fibrillation: The problem, Prevalence, Impact and Gender differences
- Risk of stroke – Scoring systems
- Stroke Prevention Strategies:
    - Anticoagulation – Guideline Recommendations
    - Novel Oral Anti-Coagulants (NOACs)
    - Gender Differences in Stroke Prevention Strategies
    - Left atrial appendage closure
- Conclusions

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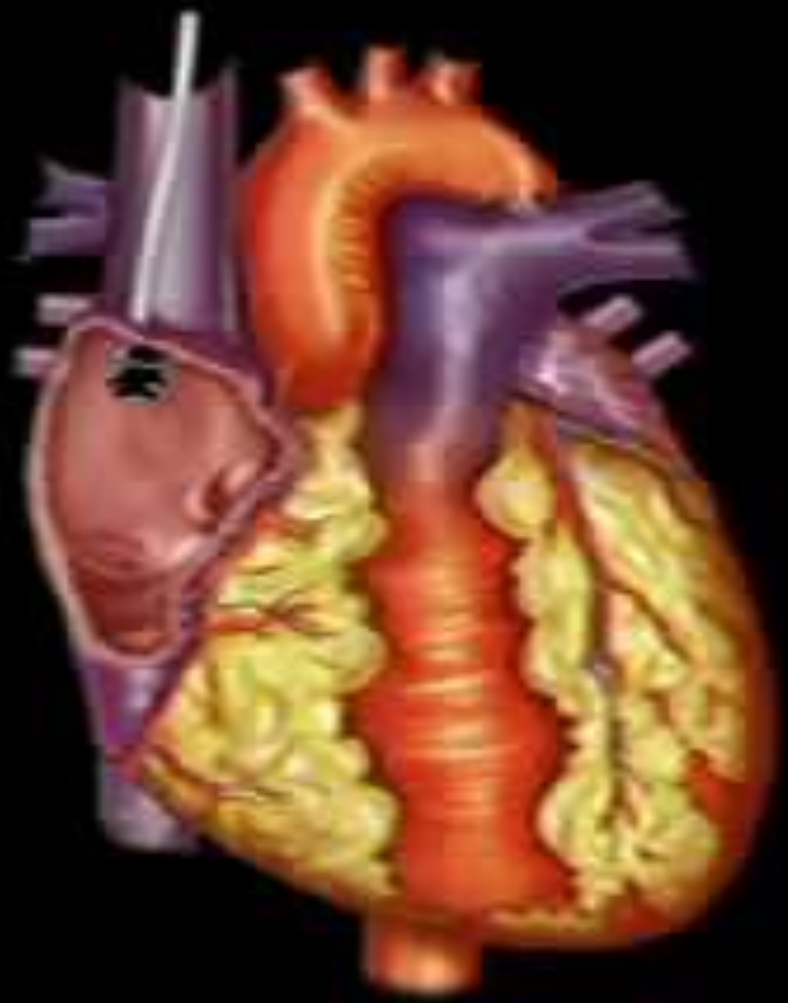
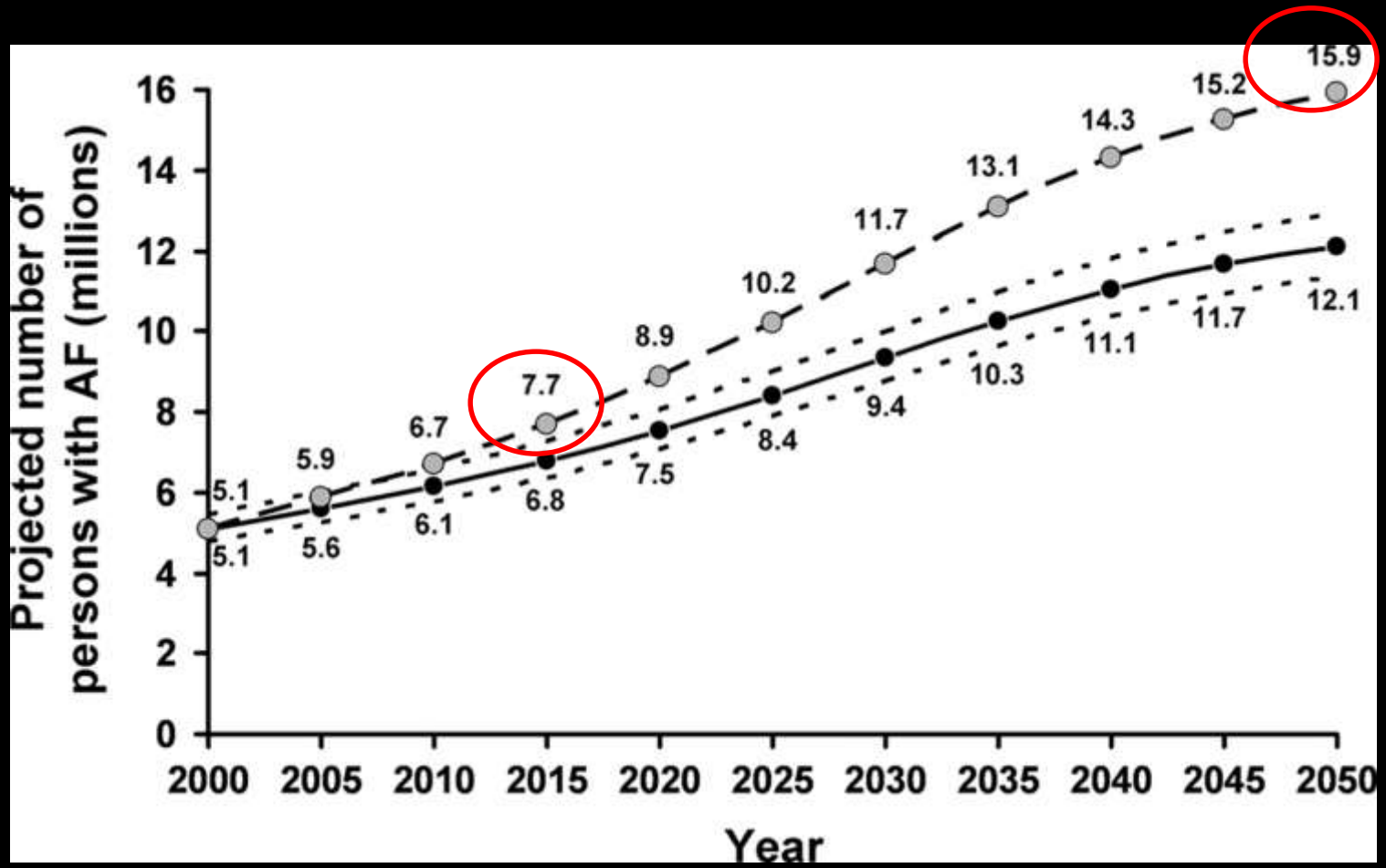


AF – A big problem

Trends in AF incidence, Olmsted county, MN



Miyasaka, Y. et al. Circulation 2006;114:119-125

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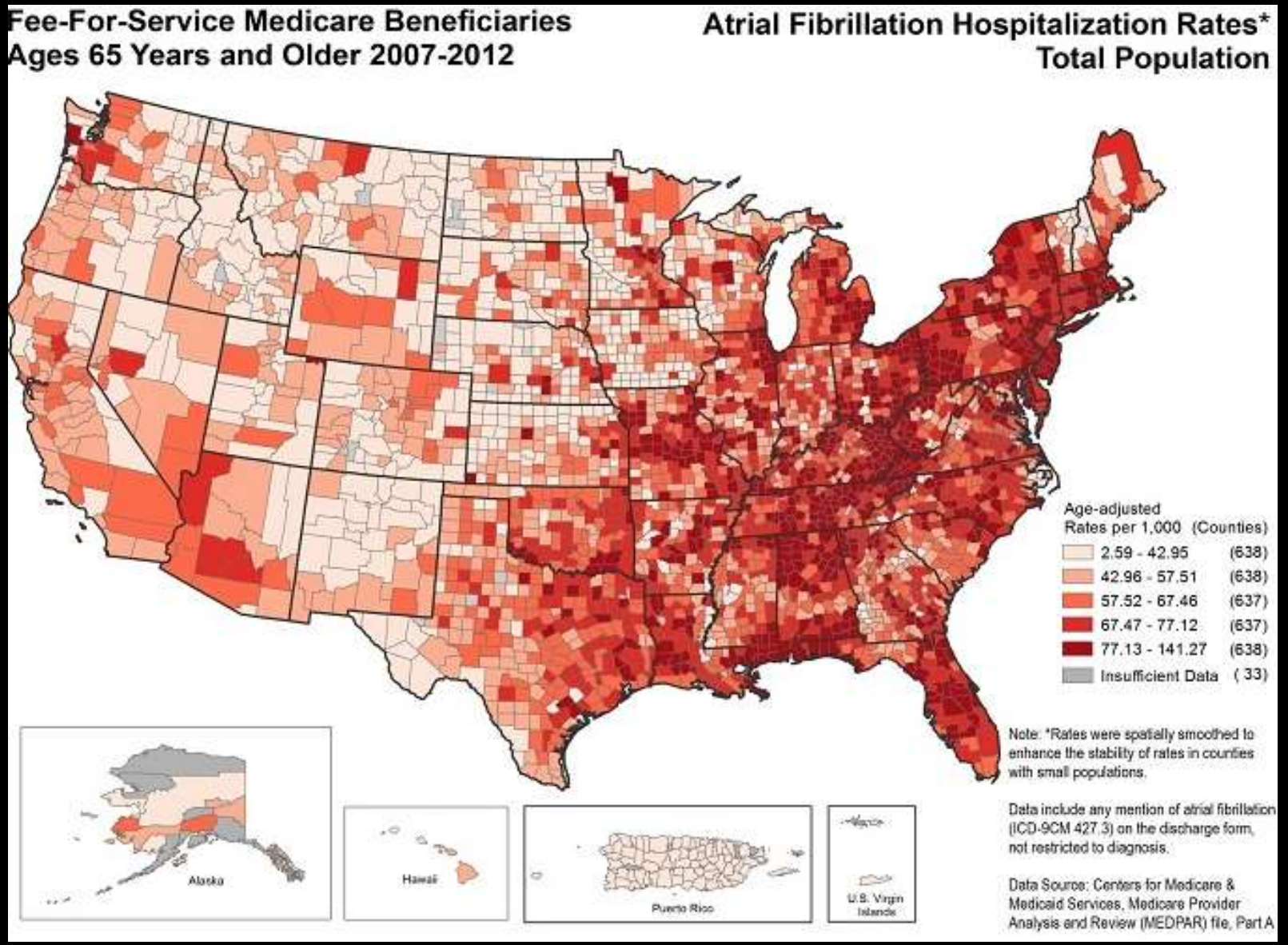
AF – The Problem

- Common – 10% over age 80
- Every hour, 15 patients with AF will have a stroke (15-20% of all strokes)
- Prevalence: ~8 million in North America
- By 2050: ~16 million in America and 33 million worldwide
- 5-times increased risk of stroke (20% of all strokes are due to AF)
- AF accounted for ≈1.5% of strokes in individuals 50-59 years of age and
- ≈23.5% in those 80-89 years of age.
- AF is independently associated with mortality, heart failure, and arrhythmia-induced cardiomyopathy
- Medicare spending for new AF diagnoses has reached $15.7 billion per year

Go AS, et al. AHA Heart Disease and Stroke Statistics, Circulation 2014
Mozaffarian D, et al. AHA Heart Disease and Stroke Statistics, Update Circulation2015
Virani S et al. Circulation. 2021 Feb 23;143(8):e254-e743
Gopinathannair R, Olshansky B et al. J Am Coll Card. 2015;66:1714–28

Burden of Atrial Fibrillation

Atrial Fibrillation Hospitalization Rates/year



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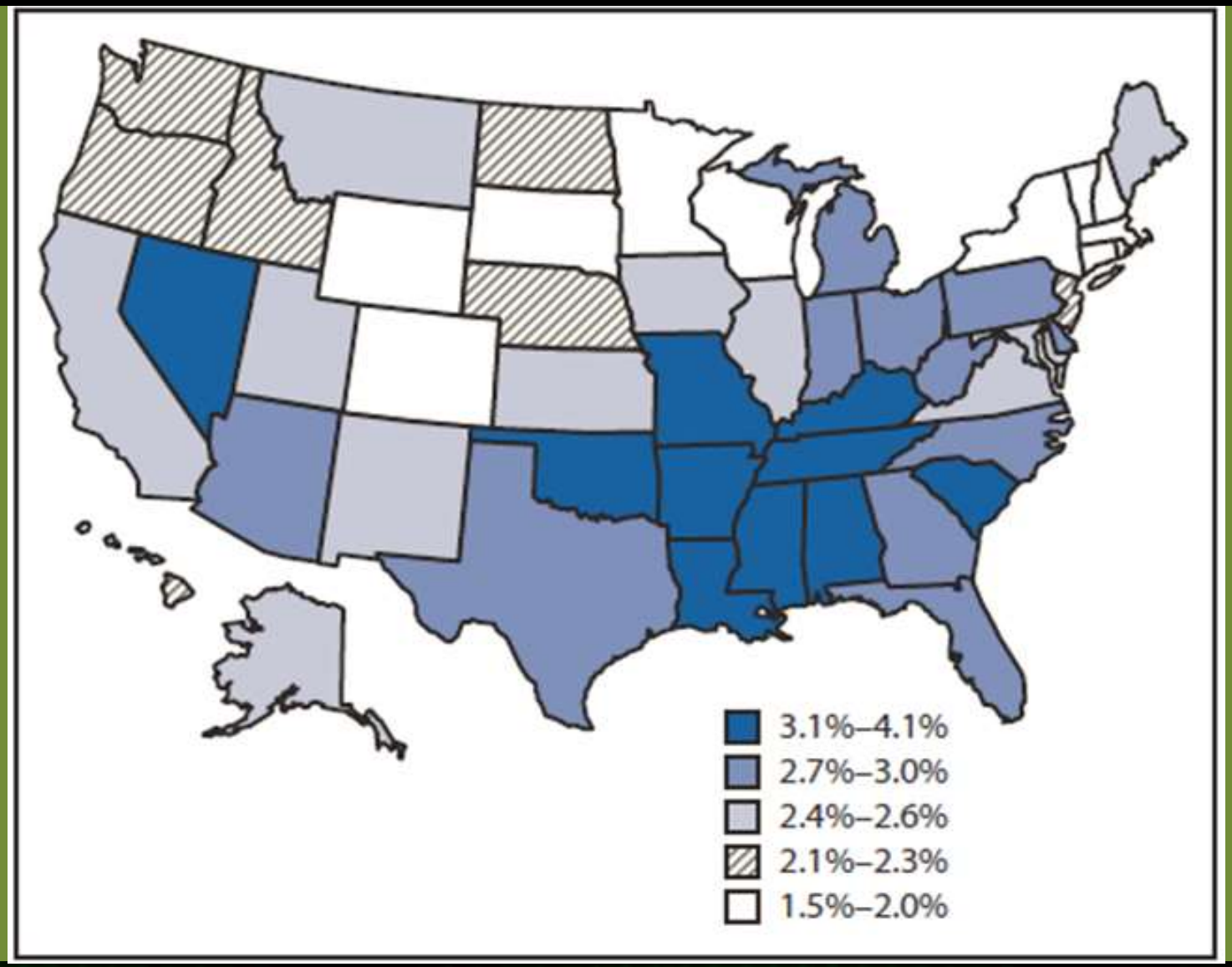
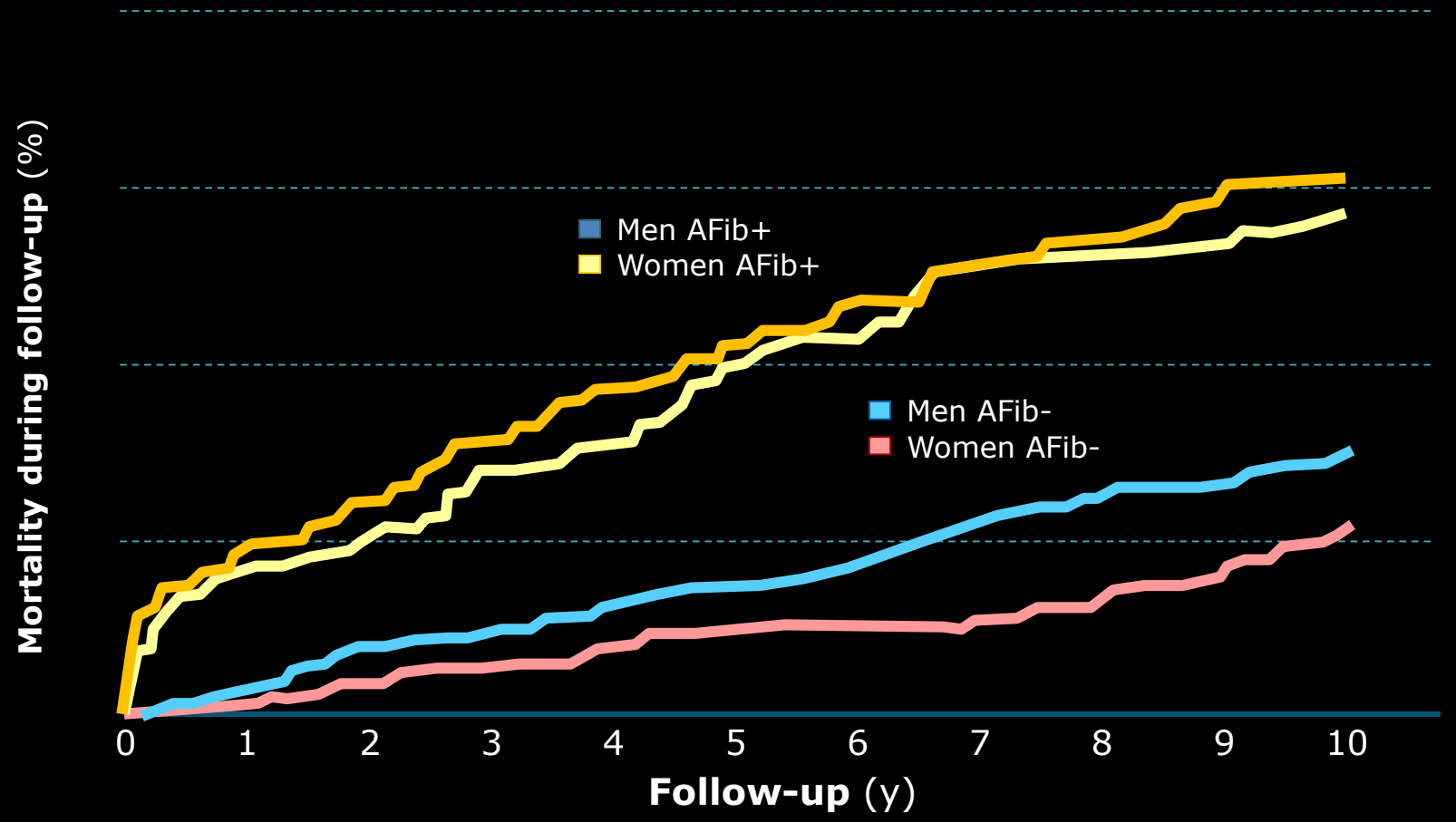
Stroke Prevalence Rates/population 2010



Mortality Associated with AFib

Framingham Heart Study, n=5209

The age-adjusted mortality rate attributable to AF was 6.4 per 100 000 people in 2018 (NHLBI data)



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Benjamin EJ, et al. *Circulation* (1998) 98: 946

Gender and Stroke Risk in AF

- Stroke risk (RR 1.9) and systemic embolism risk from AF is higher for women
- Remains high in women despite anticoagulation (and despite adequate TTR for warfarin)
- Women were less likely to receive anticoagulation
- Women have worse functional outcome following a stroke
- Mortality after stroke remains same (~23% at 30-days)
- Bleeding risk remains the same (~1% for warfarin)
- Women with AF taking warfarin had ↑ residual risk of CVA/SE compared with men (OR 1.279, 95% CI 1.111 to 1.473, p = 0.001)
- No gender difference in residual risk of CVA/SE was seen in patients receiving NOAC agents (OR 1.146, 95% CI 0.97 to 1.354, p = 0.11)
- Major bleeding was less frequent in women with AF treated with NOAC

Michelena HI et al . Gend Med 2010; 206-217
Fang MC, et al. Circulation 2005; 112: 1687-91
Pancholy SB et al. Am J Cardiol. 2014 Feb 1;113(3):485-90.
Thompson LE et al . Am Heart Assoc. 2017;6:e005801
Virani S et al. Circulation. 2021 Feb 23;143(8):e254-e743

AF -Definitions

- **Paroxysmal:** Recurrent AF (≥ 2 episodes) that terminates spontaneously within 7 days
- **Persistent:** AF sustained beyond 7 days, or lasting <7 days but needing electrical/pharmacological cardioversion
- **Long-standing persistent:** Continuous AF > 1 year duration
- **Permanent:** AF in which cardioversion has either failed or not been attempted
- Overlapping patterns can be seen in the same patient.
- **Non-Valvular AF:** AF in the absence of moderate to severe mitral stenosis, and a mechanical heart valve

HRS/ACC/ECAS consensus statement. Heart Rhythm 2007; 4(6): 816-858
2014 AHA/ACC/HRS AF Guidelines. Circulation. 2014 Apr 10.

A word on Subclinical AF/AF screening

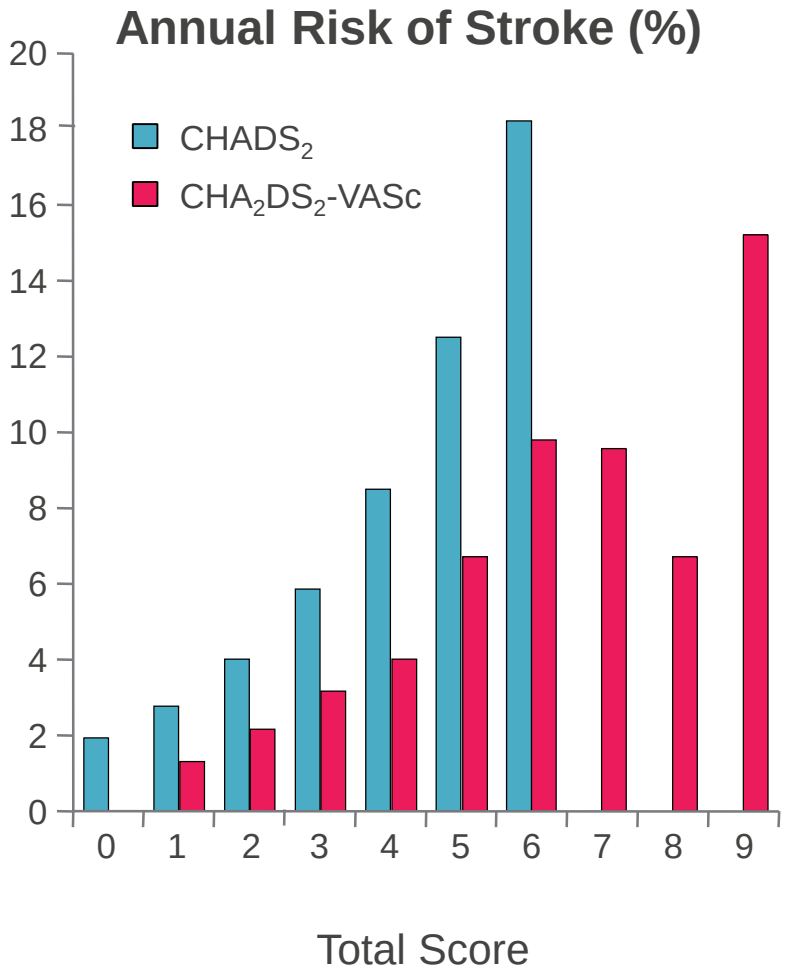
Recommendations for screening to detect AF

Recommendation	Class[a]	Level[b]
Opportunistic screening for AF by pulse taking or ECG rhythm strip is recommended in patients ≥65 years of age.[188,211,223,225]	I	B
It is recommended to interrogate pacemakers and implantable cardioverter defibrillators on a regular basis for AHRE.[c224,226]	I	B
When screening for AF it is recommended that:[217,218] • The individuals undergoing screening are informed about the significance and treatment implications of detecting AF. • A structured referral platform is organized for screen-positive cases for further physician-led clinical evaluation to confirm the diagnosis of AF and provide optimal management of patients with confirmed AF. • Definite diagnosis of AF in screen-positive cases is established only after physician reviews the single-lead ECG recording of ≥30 s or 12-lead ECG and confirms that it shows AF.	I	B

- New-onset device-detected atrial tachyarrhythmias were observed in 23%; 3 times ↑ risk of stroke; more with longer episodes (>5, OR 3.88 vs. <1 min, OR 1.77)
- Temporal relationship: The OR for stroke was the highest within a 5-day period after a qualifying AF episode (>5.5. hrs)
- Number needed to screen to identify 1 treatable new AF case varied by age: 83 for ≥65 years of age, 926 for 60 to 64 years of age, and 1089 for <60 years of age
- ILR screening post- cryptogenic stroke: 30% have AF
- To date, no studies have demonstrated that AF screening reduces mortality or incidence of thromboembolic complications.

Hindricks G et al. ESC 2020 Guidelines. European Heart Journal (2020) 00, 1;125
Belkin MN et al. Circ Arrhythm Electrophysiol. 2018

Stroke Prevention in Atrial Fibrillation



CHA_2DS_2-VASc

Risk Factor	Score
Cardiac failure	1
Hypertension	1
Age ≥75 years	2
Diabetes	1
Stroke	2
Vascular disease (MI, peripheral arterial disease, aortic atherosclerosis)	1
Age 65-74 years	1
Sex category (female)	1

MI=myocardial infarction.

- **Nonparoxysmal AF was associated with an increased risk of thromboembolism (HR, 1.38 [95% CI, 1.19–1.61]; P<0.001)**
- **The risk of stroke was significantly lower in patients with atrial flutter than in those with AF (HR, 0.69 [95% CI, 0.61–0.79]).**

Ganesan AN et al. Eur Heart J. 2016;37:1591–1602
Al-Kawaz M et al. J Stroke Cerebrovasc Dis. 2018;27:839–844

Bleeding Risk - HASBLED

Risk factors and definitions		Points awarded
H	**Uncontrolled hypertension** SBP >160 mmHg	1
A	**Abnormal renal and/or hepatic function** Dialysis, transplant, serum creatinine >200 µmol/L, cirrhosis, bilirubin > × 2 upper limit of normal, AST/ALT/ALP >3 × upper limit of normal	1 point for each
S	**Stroke** Previous ischaemic or haemorrhagic[a] stroke	1
B	**Bleeding history or predisposition** Previous major haemorrhage or anaemia or severe thrombocytopenia	1
L	**Labile INR[b]** TTR <60% in patient receiving VKA	1
E	**Elderly** Aged >65 years or extreme frailty	1
D	**Drugs or excessive alcohol drinking** Concomitant use of antiplatelet or NSAID; and/or excessive[c] alcohol per week	1 point for each
Maximum score		**9**

Hindricks G et al. 2020 ESC AF Guidelines. European Heart Journal (2020) 00, 1-125

Stroke Prevention in AF: Guideline Recommendation

- Antithrombotic therapy substantially ↓ stroke risk
- Selection of antithrombotic should be based on stroke risk, irrespective of whether AF is paroxysmal, persistent or permanent
- **CHA_2DS_2–VASc**: is recommended for assessment of stroke risk
- For CHA_2DS_2–VASc score ≥ 2 (men) or ≥ 3, anticoagulation is recommended
- NOACs are recommended in preference to VKAs
- If warfarin is used, a target INR of 2-3 and TTR of ≥70% is recommended
- Renal function should be evaluated prior to initiation of direct thrombin or factor Xa inhibitors and should be re-evaluated at least annually
- For Atrial flutter, similar recommendations apply
- OAC should be considered for stroke prevention in AF patients with a CHA2DS2-VASc score of 1 in men or 2 in women. Treatment should be individualized based on net clinical benefit and consideration of patient values and preferences

Hindricks G et al. 2020 ESC AF Guidelines. European Heart Journal (2020) 00, 1-125
2014 AHA/ACC/HRS AF Guidelines. Circulation. 2014 Apr 10.

Stroke Prevention in AF: Guideline Recommendations

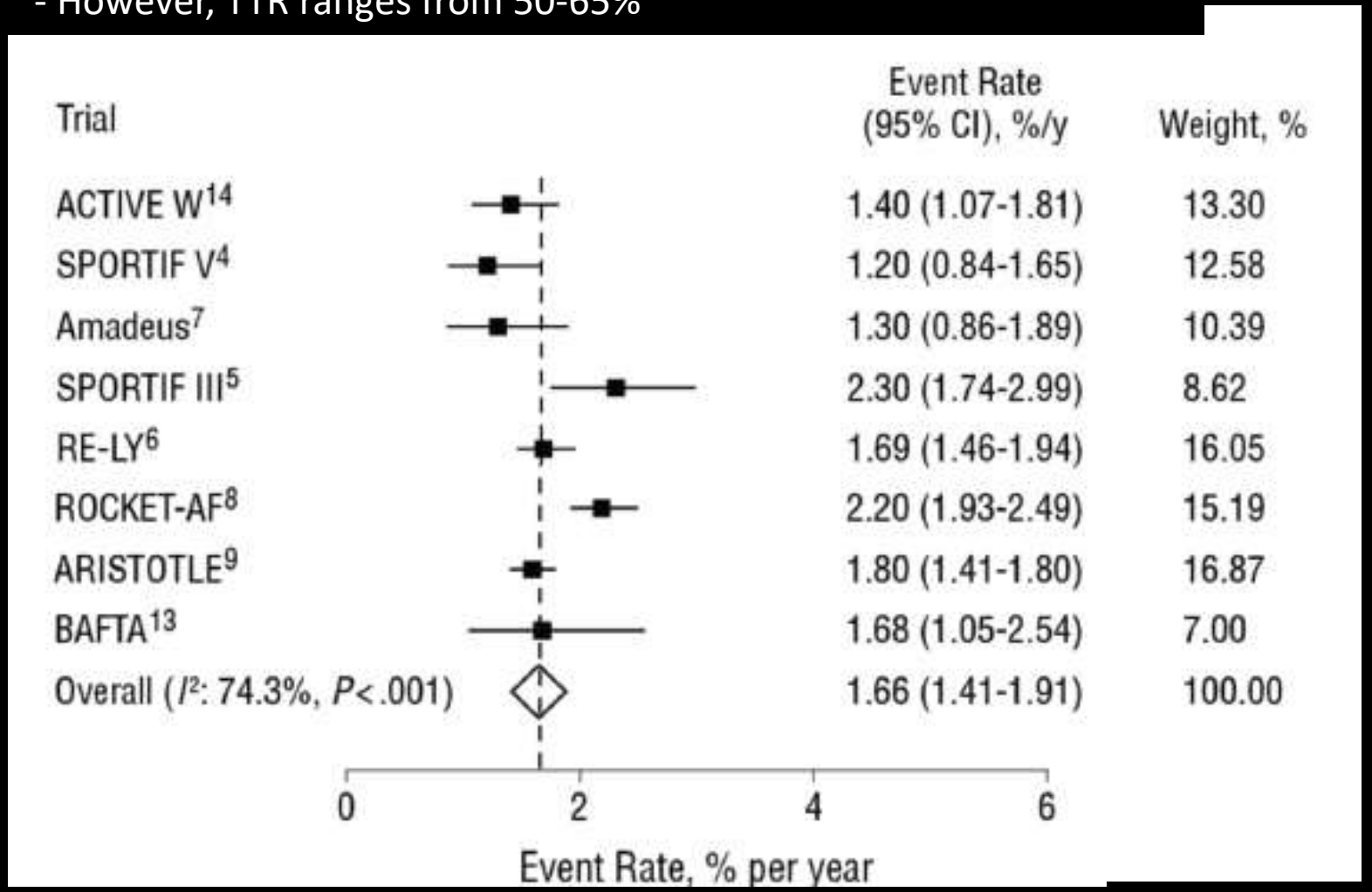
- **Nonvalvular AF and a CHA2DS2-VASc score of 0 (1 in female)**: reasonable to omit antithrombotic therapy
- **Nonvalvular AF and a CHA2DS2-VASc score of 1 (2 in female)**: OAC should be considered. Treatment should be individualized based on net clinical benefit and consideration of patient values and preferences

- Dabigatran, edoxaban and Rivaroxaban are not recommended in patients with AF and end-stage CKD or hemodialysis
- Dabigatran should not be used in patients with AF and a mechanical heart valve

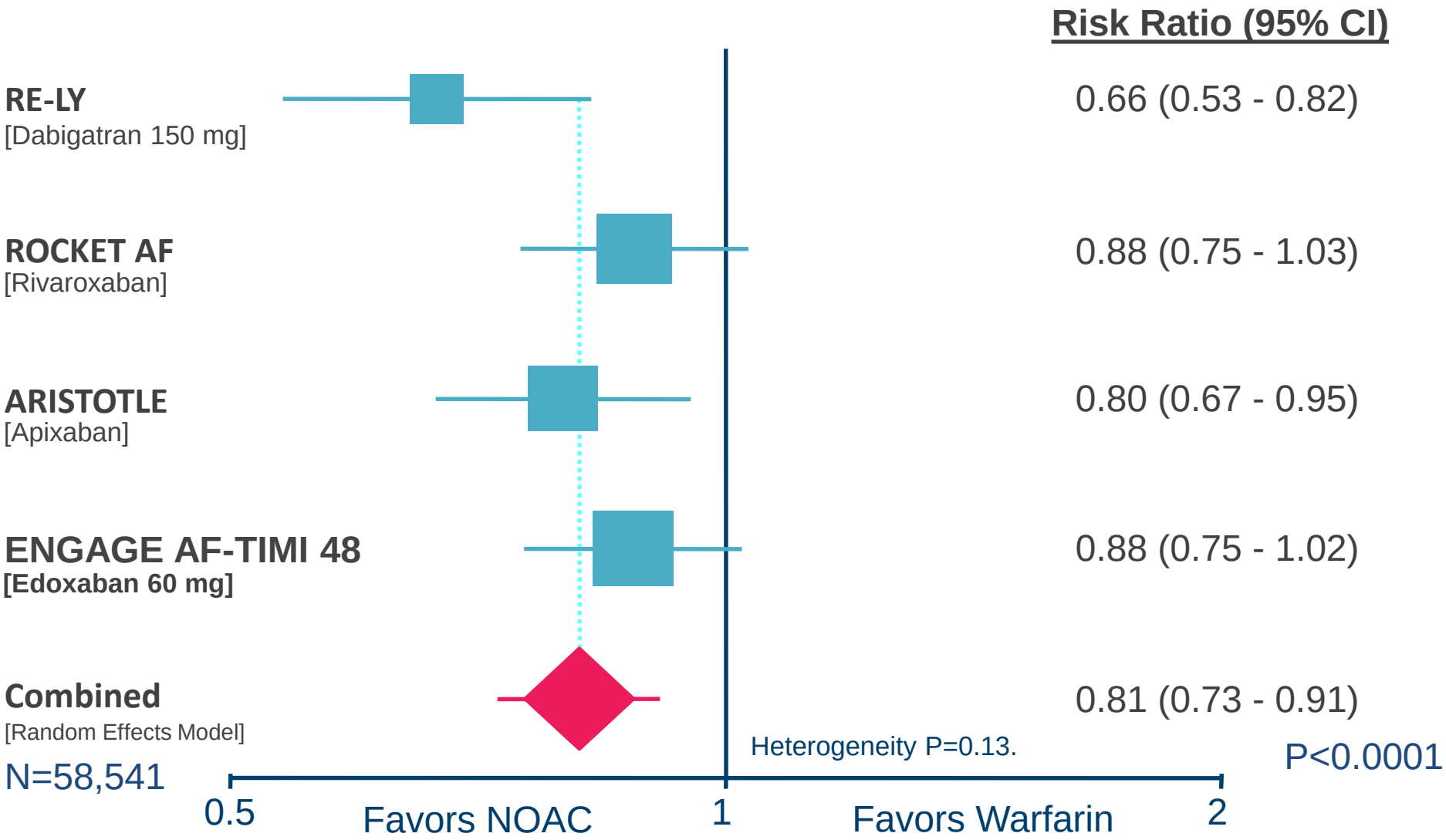
Hindricks G et al. 2020 ESC AF Guidelines. European Heart Journal (2020) 00, 1-125
2014 AHA/ACC/HRS AF Guidelines. Circulation. 2014 Apr 10.

Stroke reduction in AF patients treated with Warfarin: A meta-analysis

- Risk of stroke/systemic embolism in AF patients = 1.6 for warfarin
- However, TTR ranges from 50-65%



Agarwal S. Arch Intern Med. 2012;172:623-31.



Ruff CT, *et al.* Lancet. 2014

	RE-LY (Dabigatran)	ROCKET-AF (Rivaroxaban)	ARISTOTLE (Apixaban)	ENGAGE AF TIMI 48 (Edoxaban)
Efficacy % Warfarin vs. OAC (CVA or SE)	1.69 vs. 1.11 p<.001 NNT = 167 *150 mg shown	2.42 vs. 2.12 p=.12 (2.2 vs 1.7 on treatment)	1.60 vs. 1.27 p < .001 NNT = 303	1.80 vs. 1.57 p=.08 (1.5 vs. 1.18 on treatment) *High-dose (60 mg)
Major Bleeding %	3.57 vs. 3.32 p=0.31	3.45 vs. 3.6 p=0.58	3.09 vs. 2.13 p<.001	3.43 vs. 2.75 p<.001
ICH%	0.74 vs. 0.30 p< .001	0.74 vs. 0.49 p=.019	0.47 vs. 0.24 p< .001	0.85 vs. 0.39 p< .001
All-cause mortality %/yr	4.13 vs. 3.64 p = 0.051 NNT = 204	4.91 vs. 4.52 p=NS	3.94 vs 3.52 p = 0.05 NNT = 238	4.35 vs. 3.99 p=0.08 NNT = 277
Conclusion vs. warfarin	Superior efficacy, similar bleeding, less ICH	Non-inferior on efficacy and safety measures	Superior efficacy, less major bleeding and ICH, lower mortality	Non-inferior on efficacy; less bleeding

NOACs: key similarities

- All are noninferior to warfarin for prevention of total stroke and systemic embolism
- All reduce the risk of intracerebral hemorrhage
- Outcomes of major bleeding are generally better than with warfarin
  - Outcome differences may in part be explained by variations in dosing, study design, intrinsic risk, concurrent treatment and other factors
- Reductions in mortality are comparable and appear to be related to lower rates of cardiovascular death and fatal bleeding.

NOACs in Renal Disease

Agent	Standard AF Dose (Prescribing info)	Renal Dosing	Trial and Other Experience

Dabigatran	**150mg Twice Daily** (CrCl > 30ml/min)	75mg Twice Daily **(CrCl 15-30ml/min)**	• **RE-LY trial: 150mg or 110mg BID if CrCl > 30ml/min**
			• **No trial experience in pts w/ CrCl < 30ml/min**
			• **75mg dose not studied in RCTs**
			• **European dosage:**
			  • **150mg BID if CrCl >50ml/min**
			  • **110mg BID if CrCl 30-50ml/min**
			  • **Contraindicated if CrCl < 30ml/min**

Rivaroxaban	**20mg Once Daily (CrCl > 50ml/min)**	**15mg Once Daily** (CrCl 15-50ml/min)	• **ROCKET-AF trial:**
			  • **20mg Daily if CrCl > 50ml/min**
			  • **15mg Daily if CrCl 30-50ml/min**
			• **No trial experience in pts w/ CrCl < 30ml/min**

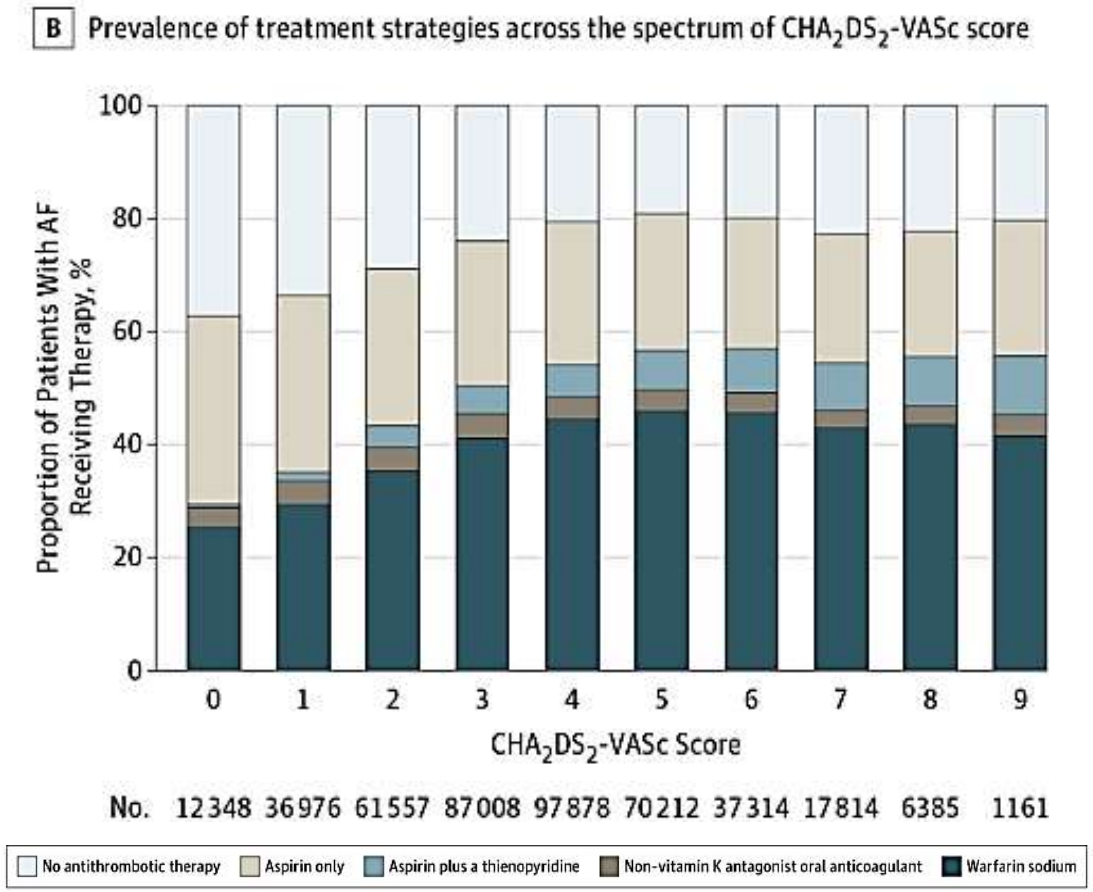
Apixaban	**5mg Twice Daily**	**2.5mg Twice daily if at least 2 of the following: ≥ 80 y/o, Weight ≤ 60kg, SCr ≥ 1.5ml/dL** **Dosing guidance for ESRD (with or without hemodialysis)**	• **ARISTOTLE trial: Renal dose studied as per prescribing information.** • **No trial experience in pts w/ CrCl < 25ml/min** • **No trial experience with ESRD patients**

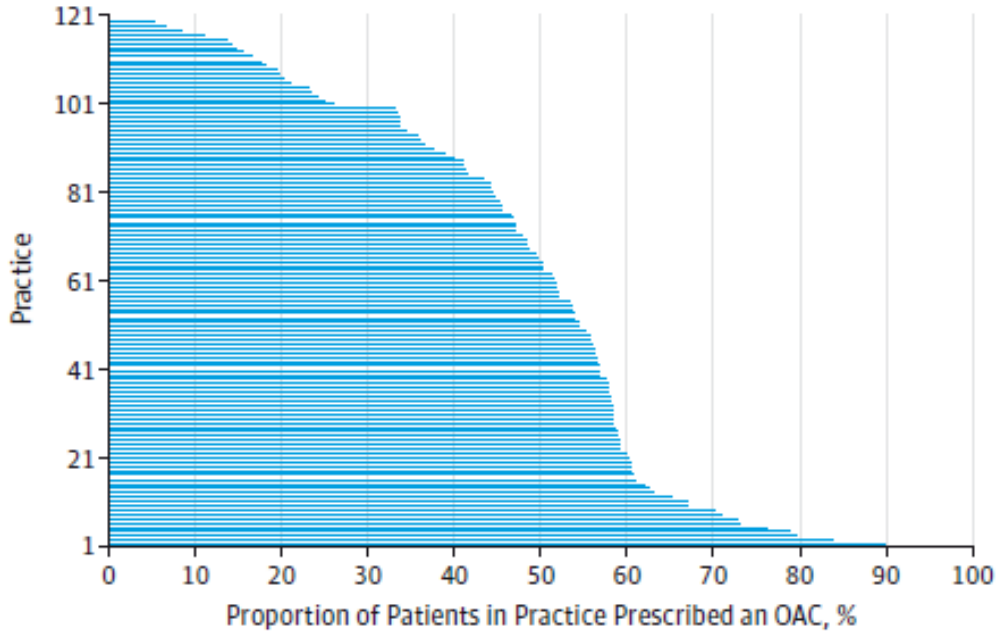
Edoxaban	**60mg Once Daily (CrCl 50-95ml/min)**
	BLACK BOX WARNING: Avoid use if CrCl > 95ml/min
		30mg Once Daily (CrCl 15-50ml/min)	• **TIMI-ENGAGE: Randomized to 60mg or 30mg Daily**
			  • **Dose halved if**
			  • **CrCl 30-50ml/min, Weight ≤ 60kg, or**
			  • **Concomitant verapamil, quinidine, or dronedarone (strong P-gp inhibitors)**
			• **No trial experience in pts w/ CrCl < 30ml/min**
			• Worse outcomes in patients with CrCl > 95ml/min

- Among patients with atrial fibrillation and CrCl 25 to 30 mL/min, apixaban caused less bleeding than warfarin
- Even greater reductions in bleeding than in patients with CrCl >30 mL/min.

Stanifer JW. 2020 Apr 28;141(17):1384-1392.

Challenges With Oral Anticoagulation (OAC)





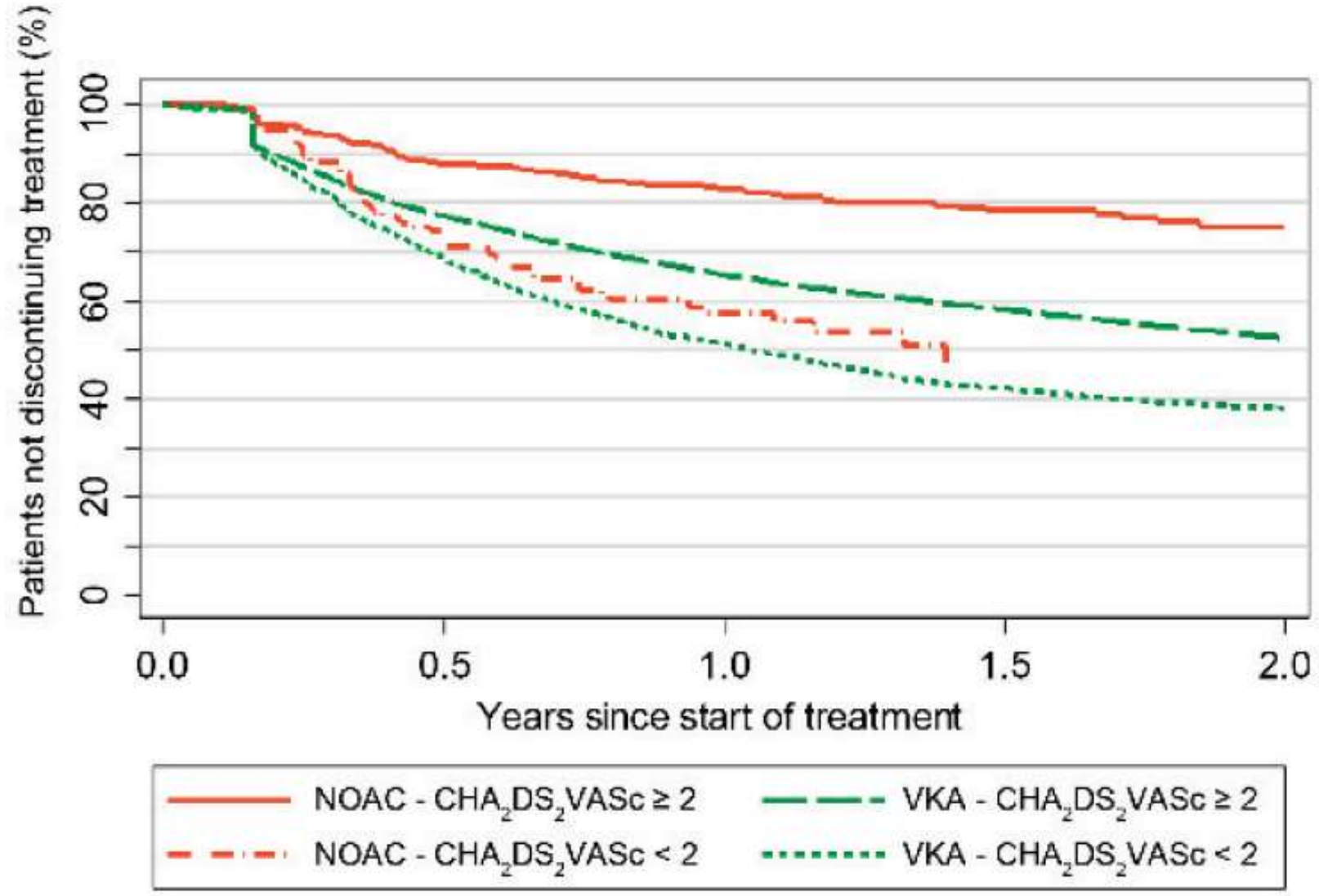
- Bleeding risk
- Drug and diet interactions (VKA)
- Non-adherence
- Issues with monitoring (VKA)

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

Hsu JC et al. *JAMA Cardiol. 2016;1(1):55-62.*

OAC Adherence

NOACs better than VKA but still ~30% of NOAC patients stop taking the drug at 2 years



Martinez C et al. Thromb Haemost 2016; 115: 31–39

Warfarin Ineligible Patient: ROAR Study

- Multicenter study (n=263)of the use of direct oral antagonists (DOACs) in Warfarin ineligible (major bleed or stroke) patients
- **63% (166 of 263) patients had a repeat major bleed on DOACs**
- **Repeat major bleed was significantly higher in patients with prior gastrointestinal bleeding (74.5% vs. 30%, P < 0.0001**)
- Five percent (12 of 263) developed repeat stroke/TE
- 34% (57 of 166) of patients had an intervention to manage repeat major bleed

Turagam MK, Gopinathannair R, Lakkireddy D. J Cardiovasc Electrophysiol. 2017 Aug;28(8):853-861

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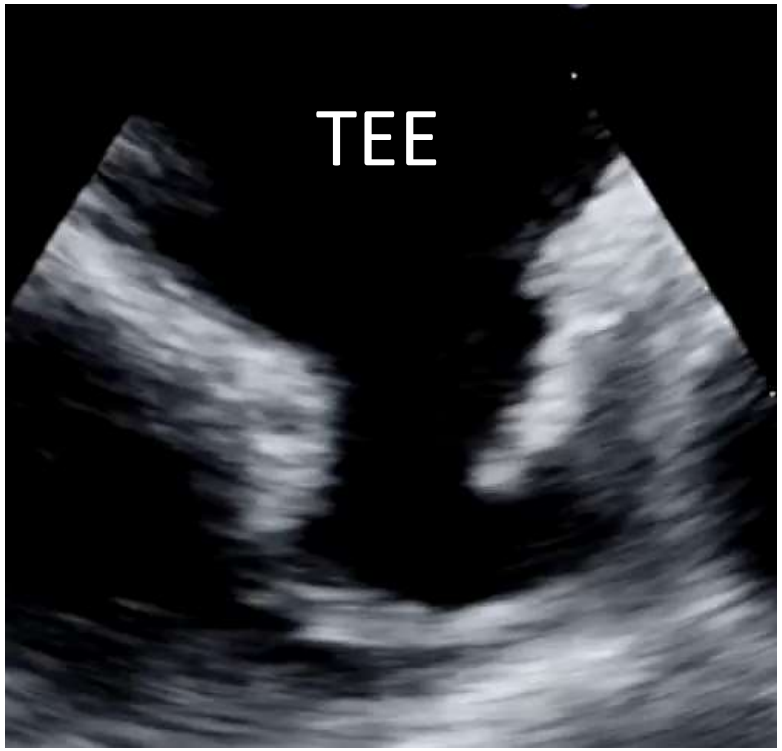
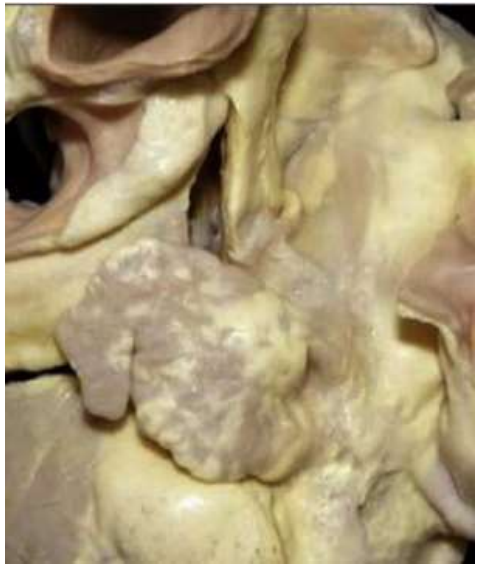
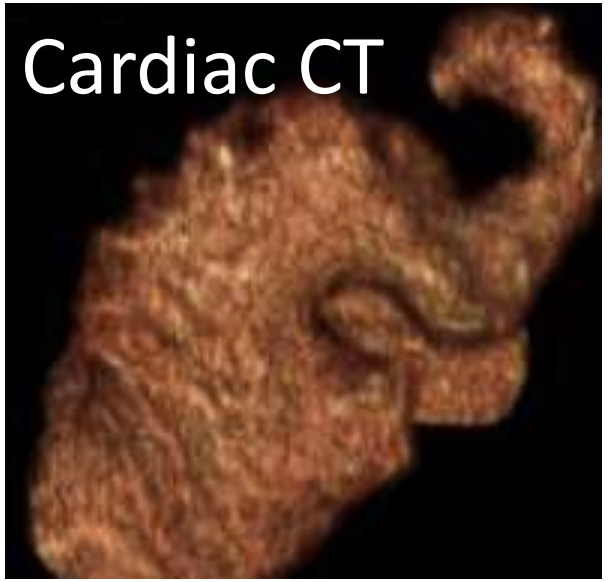
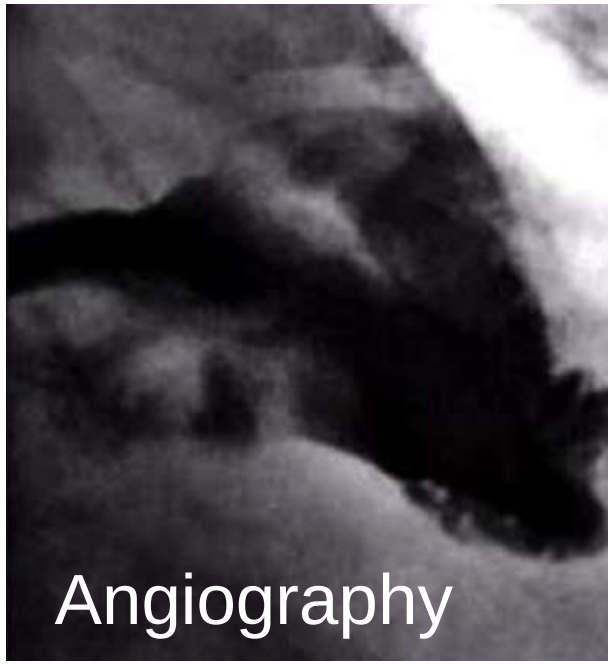


Gross Anatomy







Courtesy: Dr. Marcus Stoddard

Beigel et al.: JACC Img. 2014;7(12):1251-1265

Left Atrial Appendage: What Does It Do?

- Major source or AF-related cardiac thromboembolism (91%) in non-valvular AF
- LAA – source of focal firing & AF triggers in 27% of AF patients undergoing re-do ablation

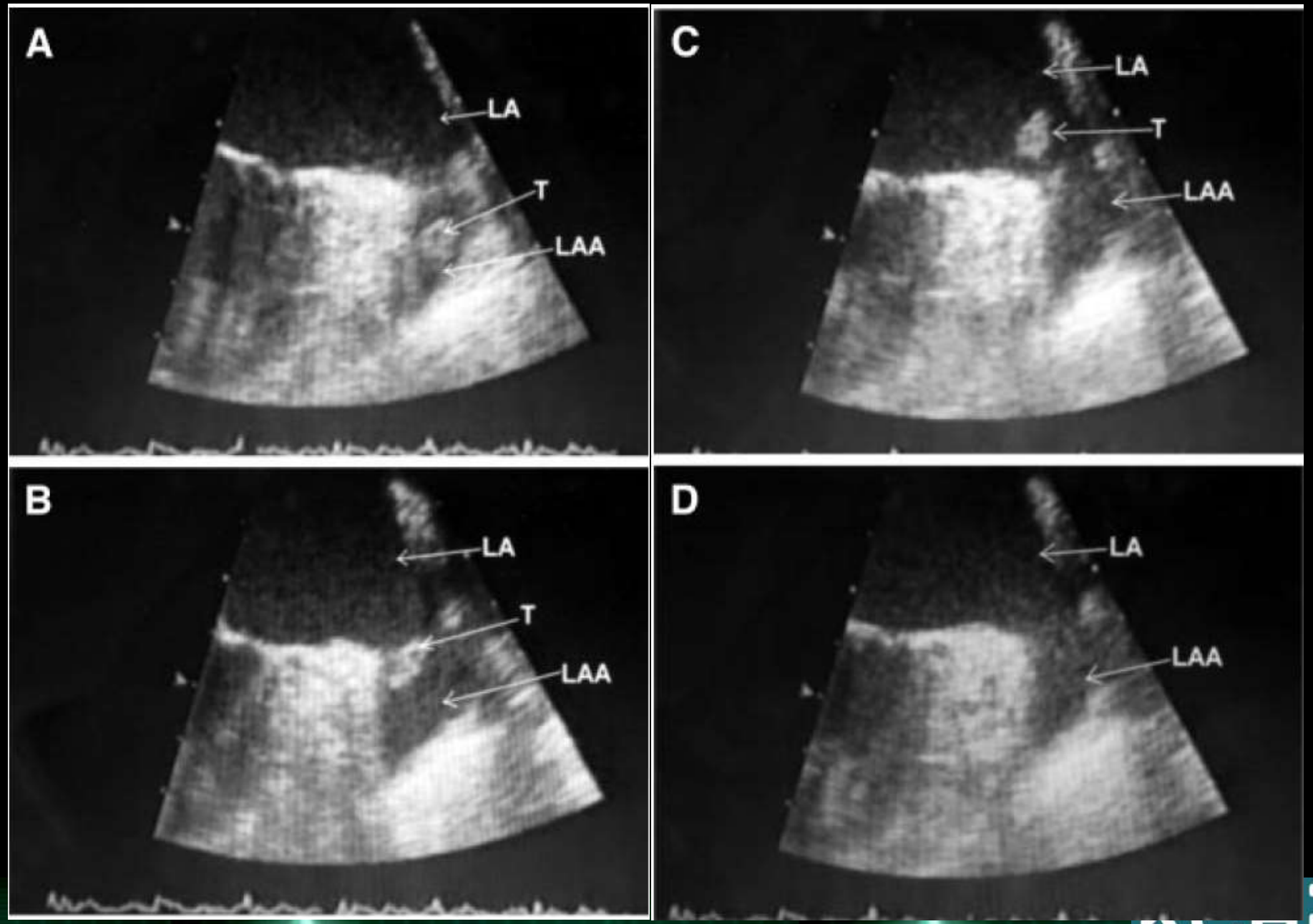
Blackshear JL et al. Ann Thorac Surg 1996;61:755-9
Di Biase et al. Circulation 2010 Jul 13;122(2):109-18.

Left Atrial Appendage: What does it do?

- Conduit, reservoir and neurohormonal
- Major source or AF-related cardiac thromboembolism (91%) in non-valvular AF
- Complex architecture with pectinates facilitate slow conduction and arrhythmogenecity, especially when fibrosis present
- LAA – source of focal firing & AF triggers in 27% of AF patients undergoing re-do ablation

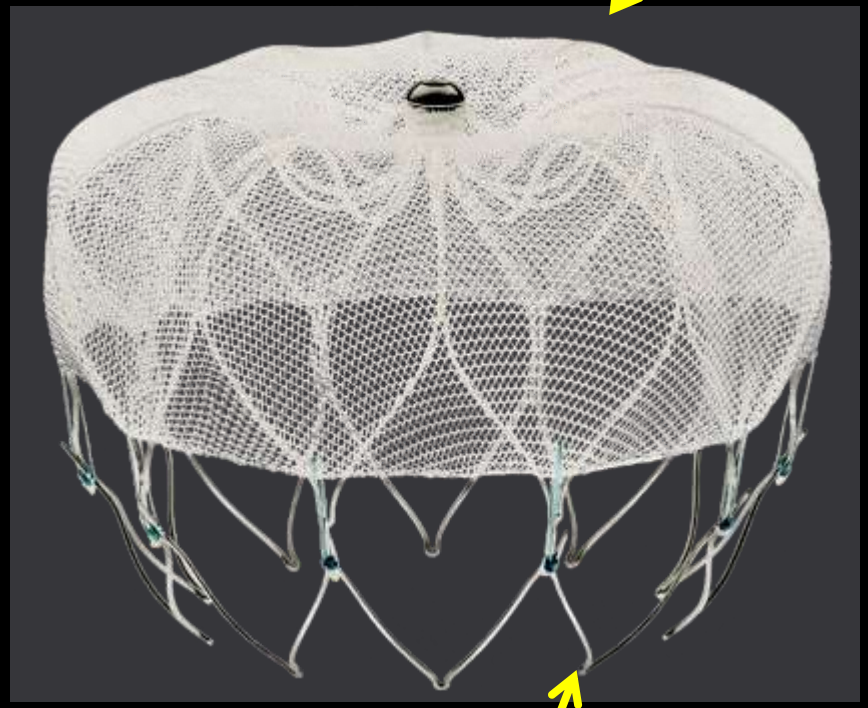
Blackshear JL et al. Ann Thorac Surg 1996;61:755-9
Di Biase et al. Circulation 2010 Jul 13;122(2):109-18.

52 year-old Female with Persistent Atrial Fibrillation Undergoing TEE



Parekh A et al. Circulation. 2006 Sep 26;114(13):e513-4

WATCHMAN™ Left Atrial Appendage Closure (LAAC) Device Overview



Nitinol Frame

- Radially expands to maintain position in LAA
- Available sizes:
  - 21, 24, 27, 30, 33 mm (diameter)
- 10 Active fixation anchors around device perimeter engage LAA tissue for stability and retention

160 Micron Membrane

- Polyethylene terephthalate (PET) cap
- Designed to block emboli from exiting the LAA

LAAC Indications: US vs International

US (CMS)- WATCHMAN™

- NVAF
- CHADS2VASC≥ 3
- Suitable for short-term warfarin but appropriate rationale exists to seek non-pharmacologic alternative to long-term OAC
- Formal shared decision-making with an independent non-interventional physician

International

- LAAC is intended to prevent thrombus embolization from the LAA and reduce the risk of life-threatening bleeding events in patients with NVAF who are eligible for OAC (IIb B)
- Or who have a contraindication to anticoagulant therapy (IIBC)

2014 AHA/ACC/HRS AF Guidelines. Circulation. 2014 Apr 10
Masoudi FA et al. J Am Coll Cardiol 2015; 66:1497–1513
Meier B et al. EHRA/EAPCI expert consensus statement. Europace 2014; 16:1397–1416

LAA Closure – Indications (AHA/ACC/HRS 2019 & ESC Guidelines 2020)

Section 4.4.1 - Percutaneous Approaches to Occlude the Left Atrial Appendage

Percutaneous LAAO should be considered for those AF patients at an increased risk of stroke who have contraindications to long-term anticoagulation and who are at high risk of thromboembolic events.

Recommendations for occlusion or exclusion of the LAA		
LAA occlusion may be considered for stroke prevention in patients with AF and contraindications for long-term anticoagulant treatment (e.g. intracranial bleeding without a reversible cause).[448,449,481,482]	IIb	B
Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery.[459,483]	IIb	C

Hindricks G et al. Eur Heart J. 2020
January CT et al. J Am Coll Cardiol. 2019

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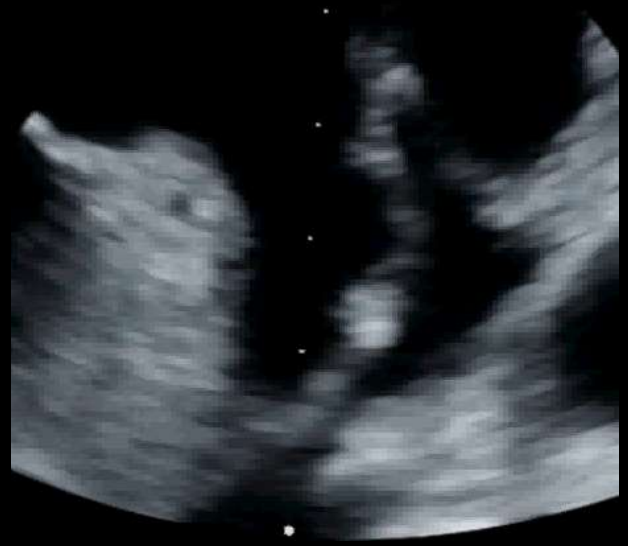
Rationale to seek non-pharmacologic alternative

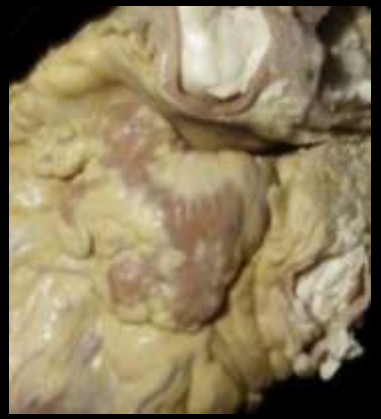
- Major bleeding from OAC
- Inability to maintain INR/Non-compliance/refuses OAC
- Medical condition, occupation, or lifestyle placing patient at high risk of major bleeding secondary to trauma
- HASBLED score ≥3
- Fall risk
- CAD patients needing triple therapy

LAA anatomy is complex- Windsock

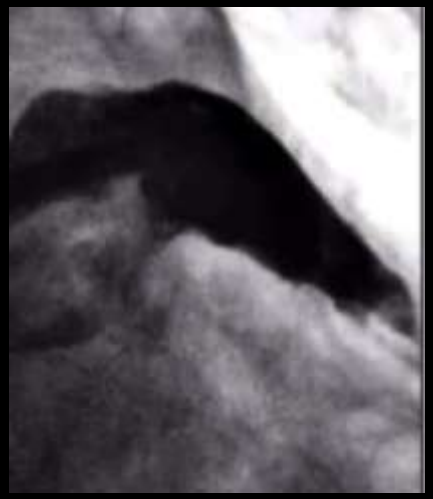
Endocast



TEE

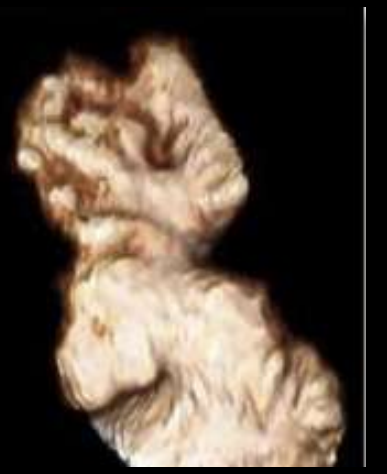


Gross Anatomy



Angiography

Courtesy: Dr Marcus Stoddard

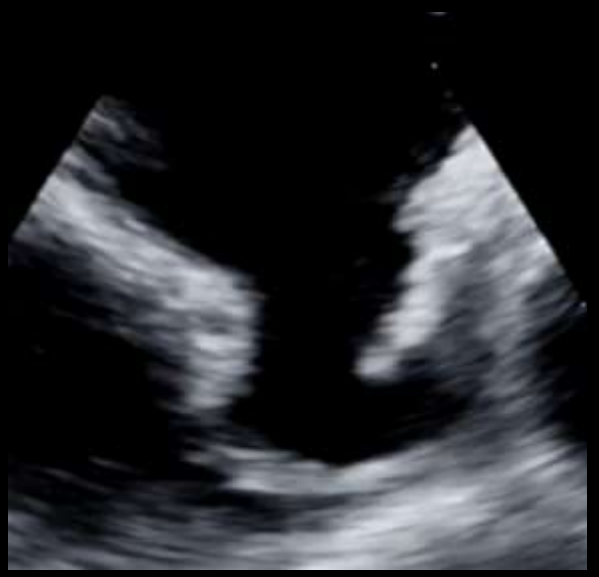


Cardiac CT

Beigel et al.: JACC Img. 2014;7(12):1251-1265

LAA anatomy is complex- Chicken Wing

Endocast



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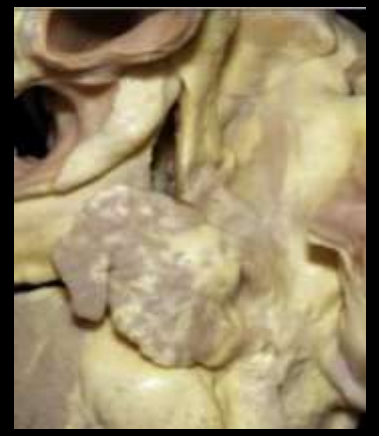
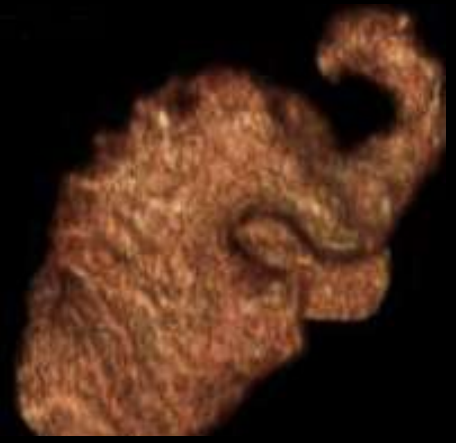


Gross Anatomy

Angiography

Courtesy: Dr. Marcus Stoddard

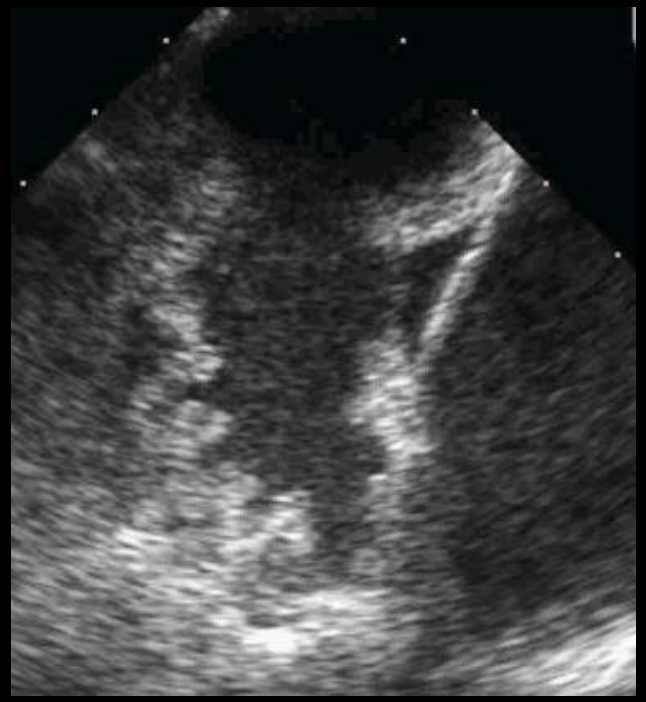


Cardiac CT

Beigel et al.: JACC Img. 2014;7(12):1251-1265

LAA anatomy is complex- Cactus

Endocast



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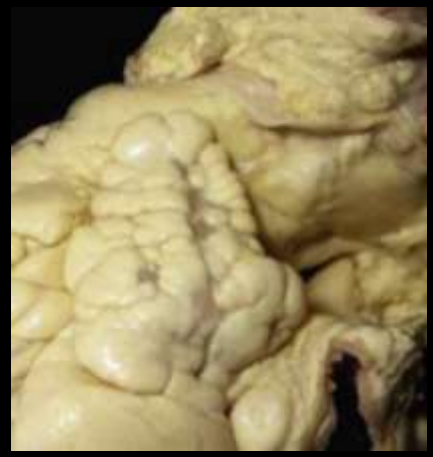
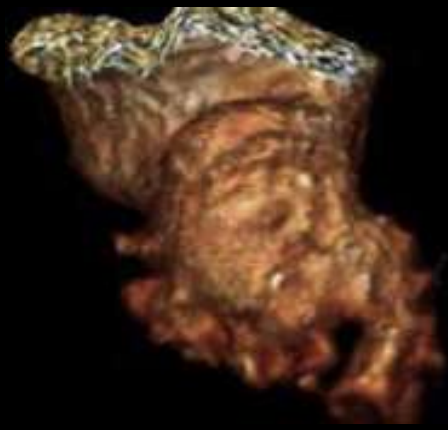


Gross Anatomy

Angiography

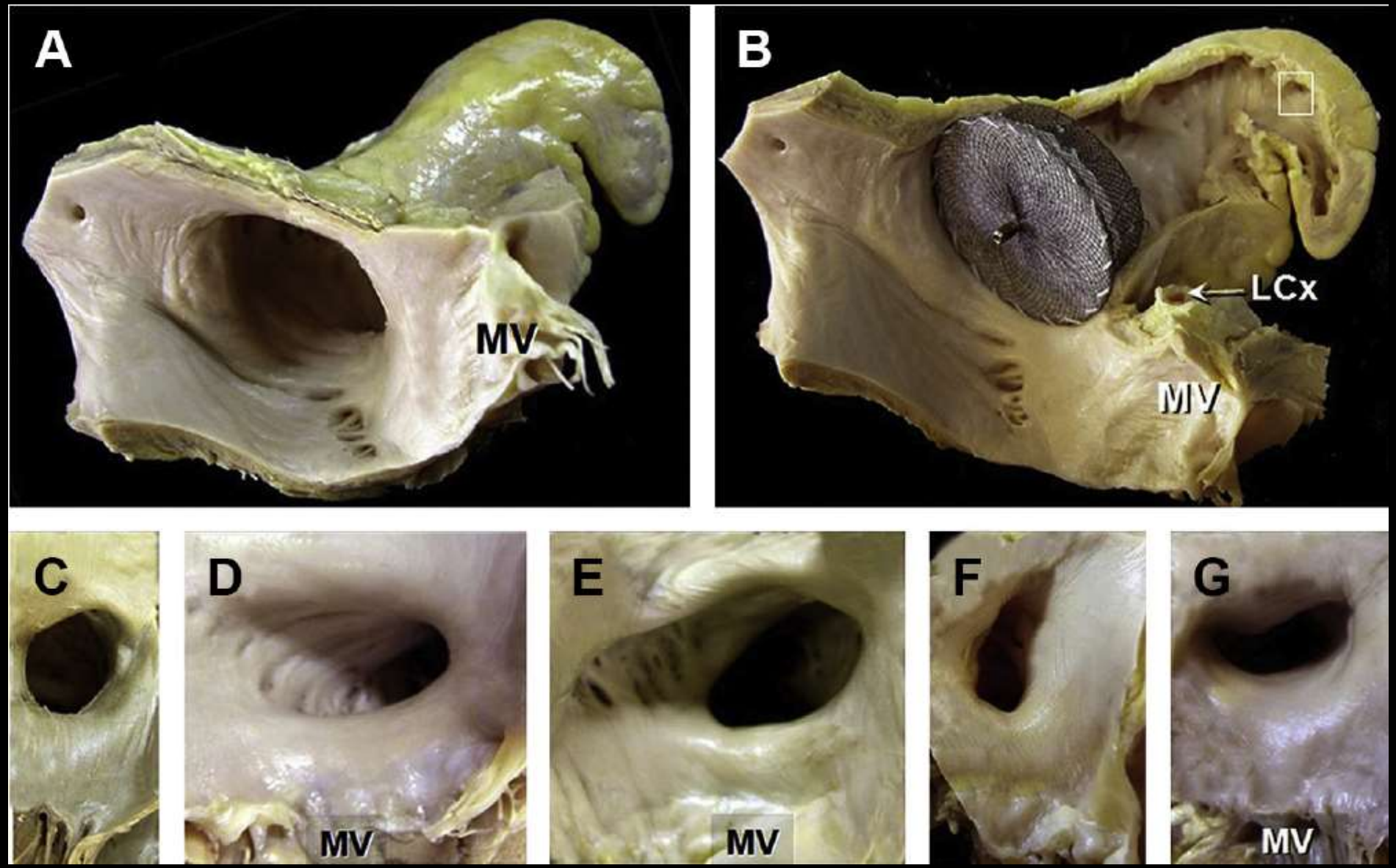
Courtesy: Dr. Marcus Stoddard

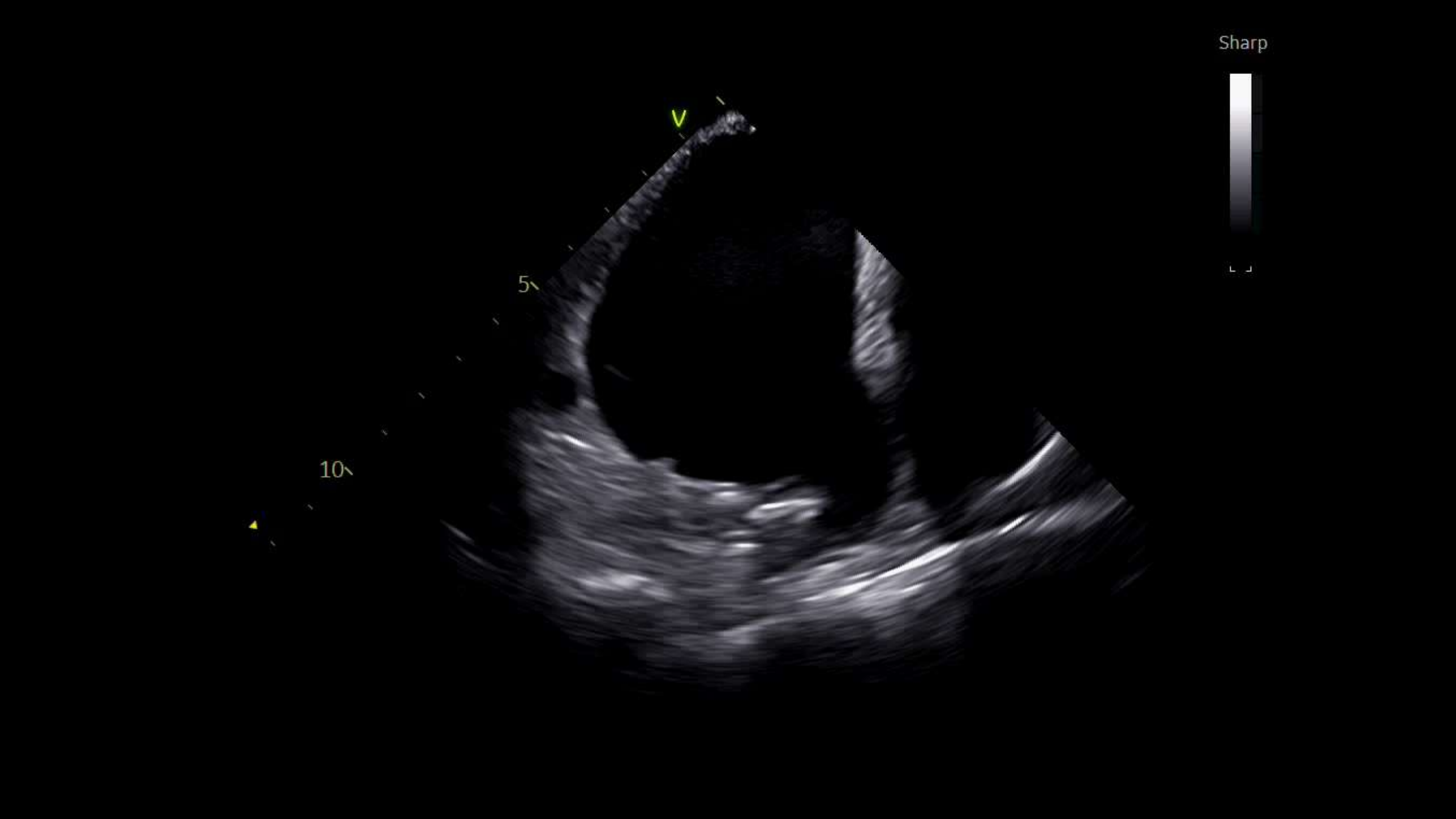


Cardiac CT

Beigel et al.: JACC Img. 2014;7(12):1251-1265

LAA Ostial Variations

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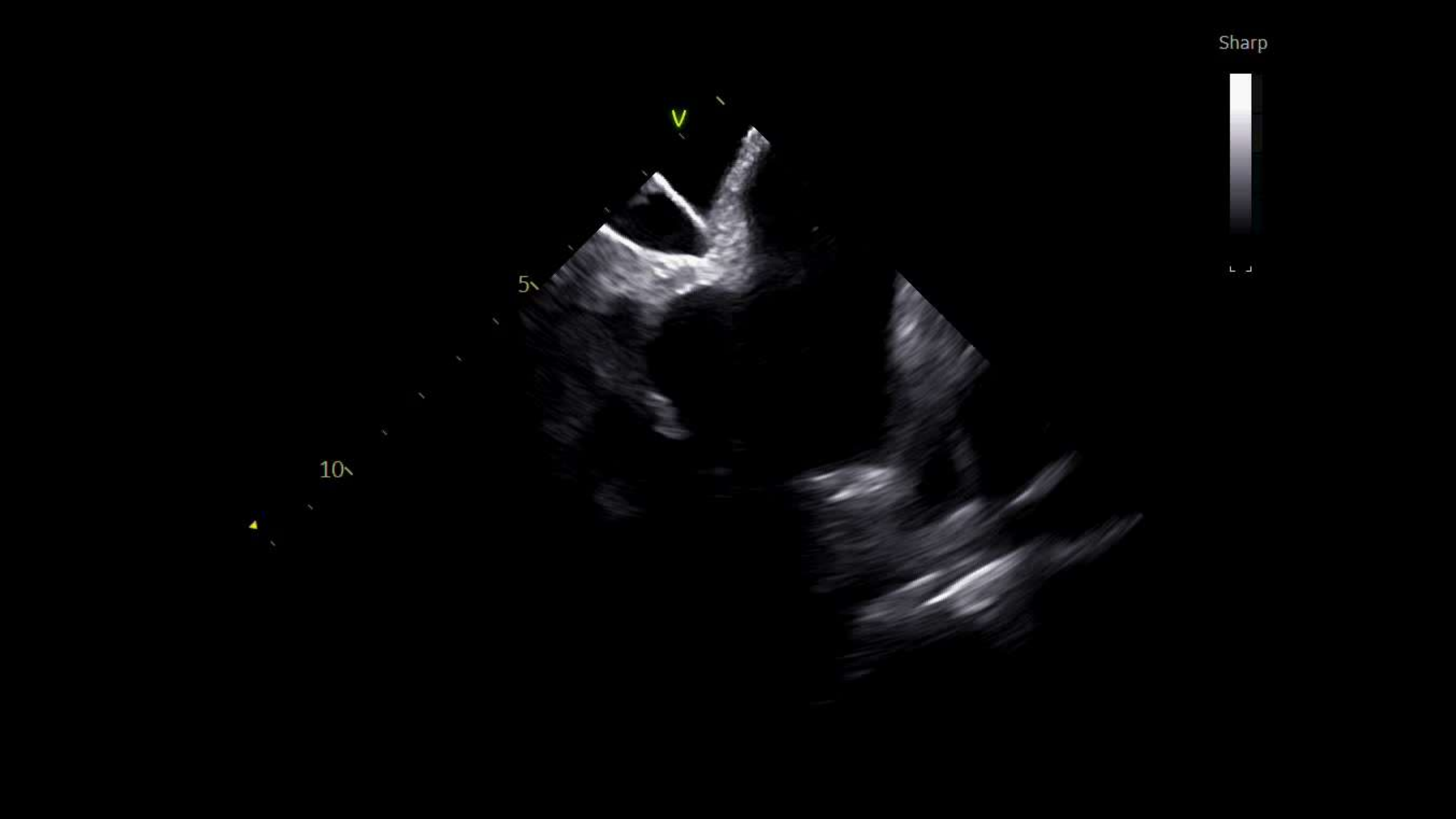
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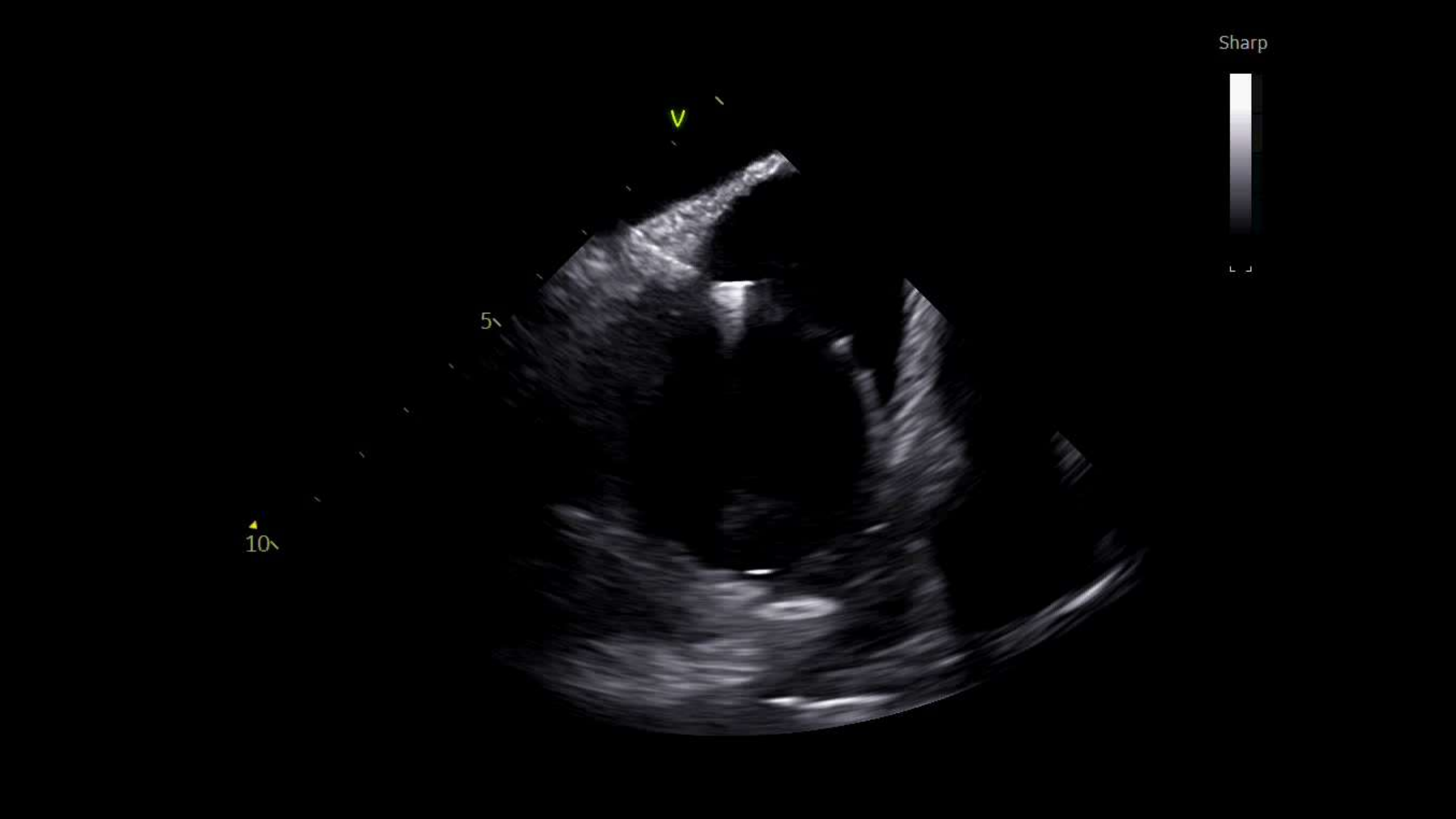
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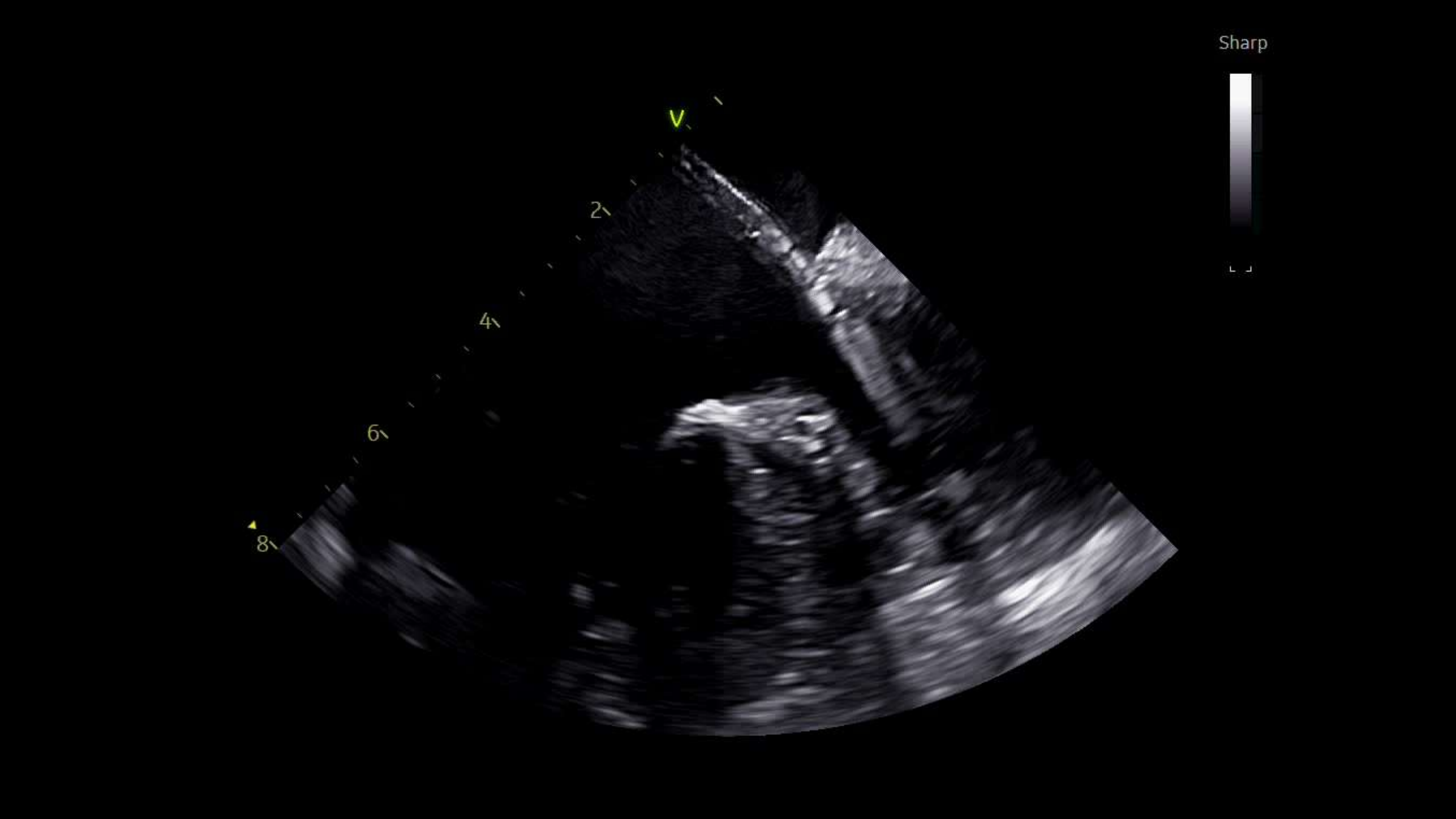
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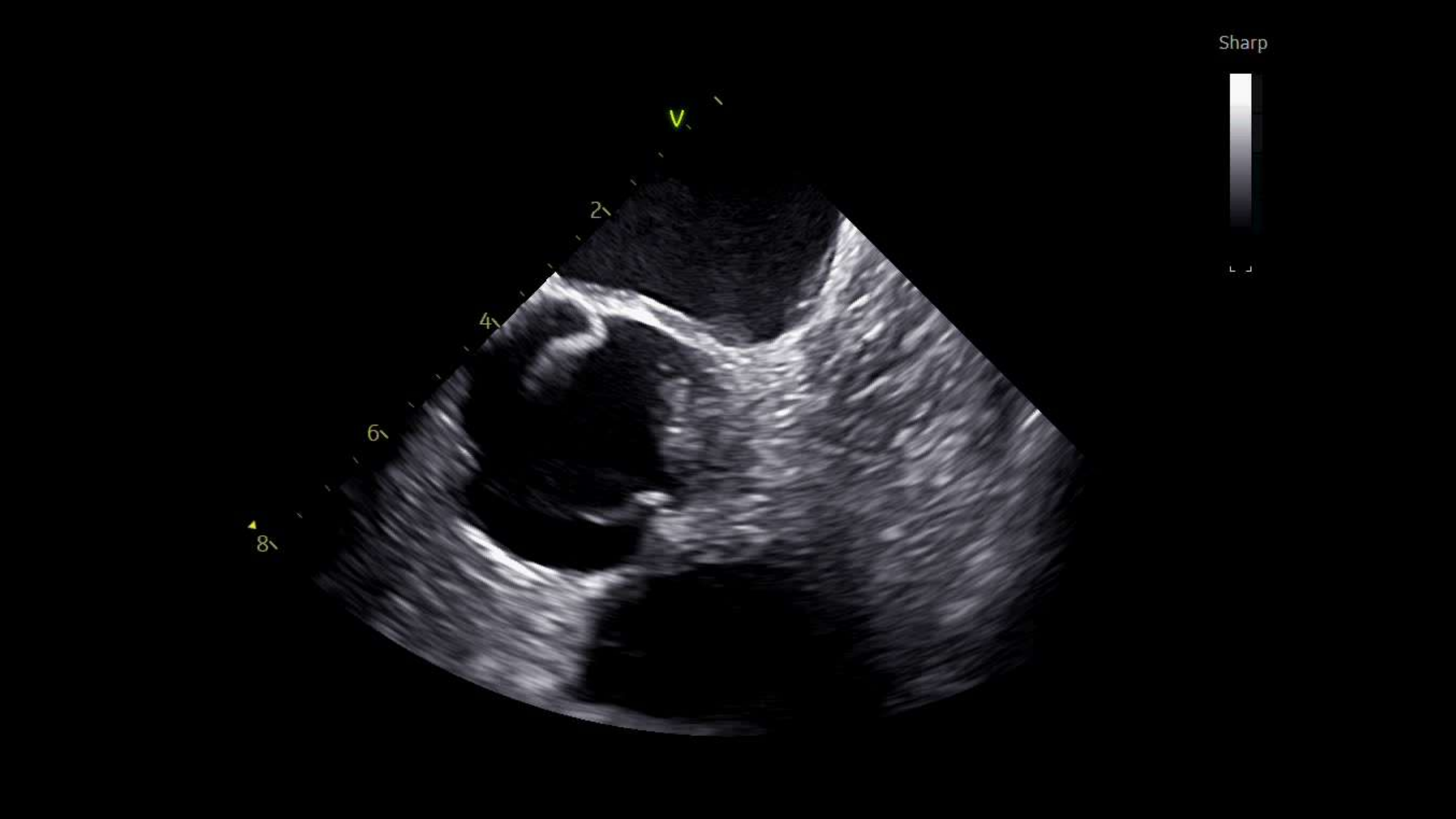
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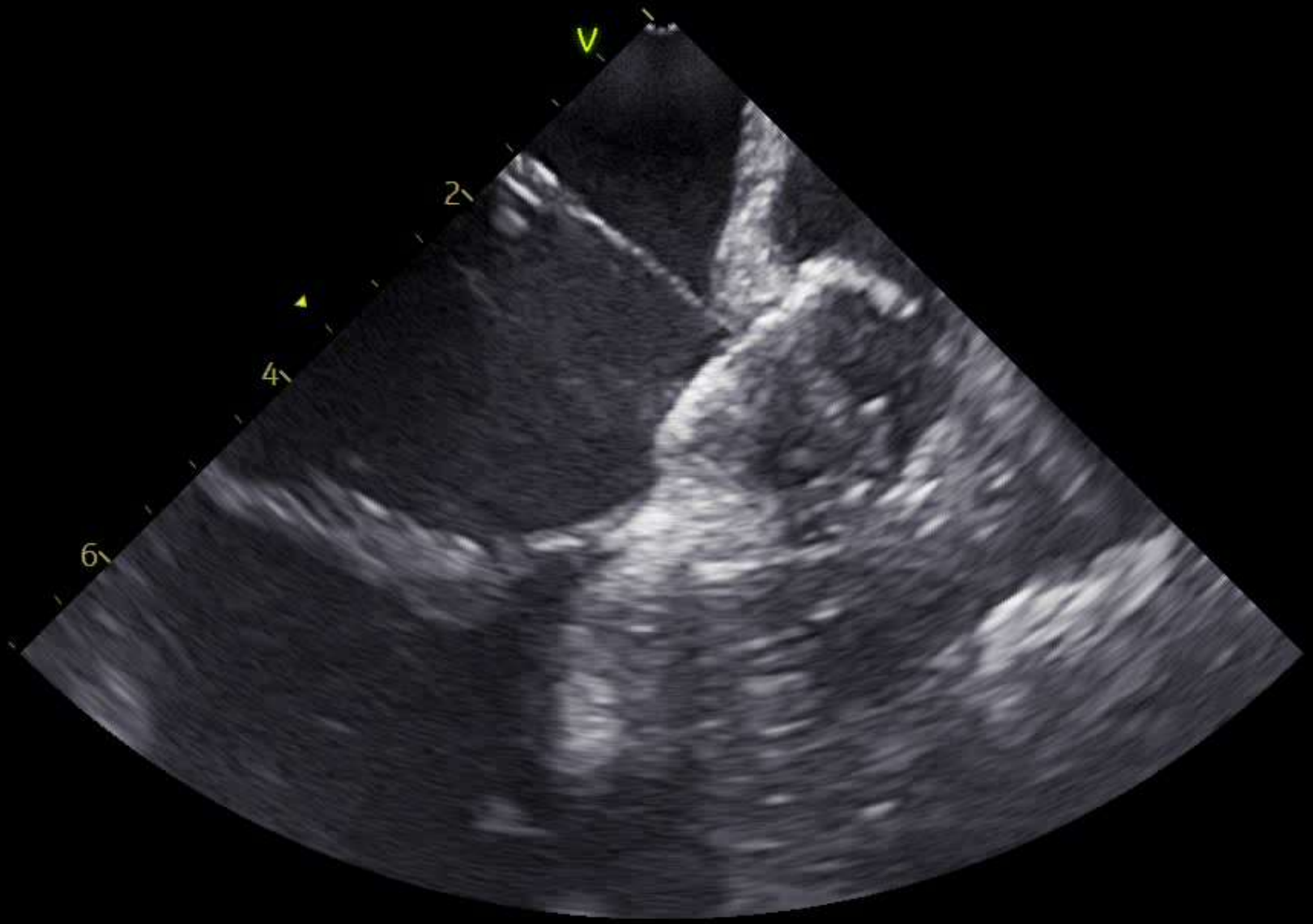
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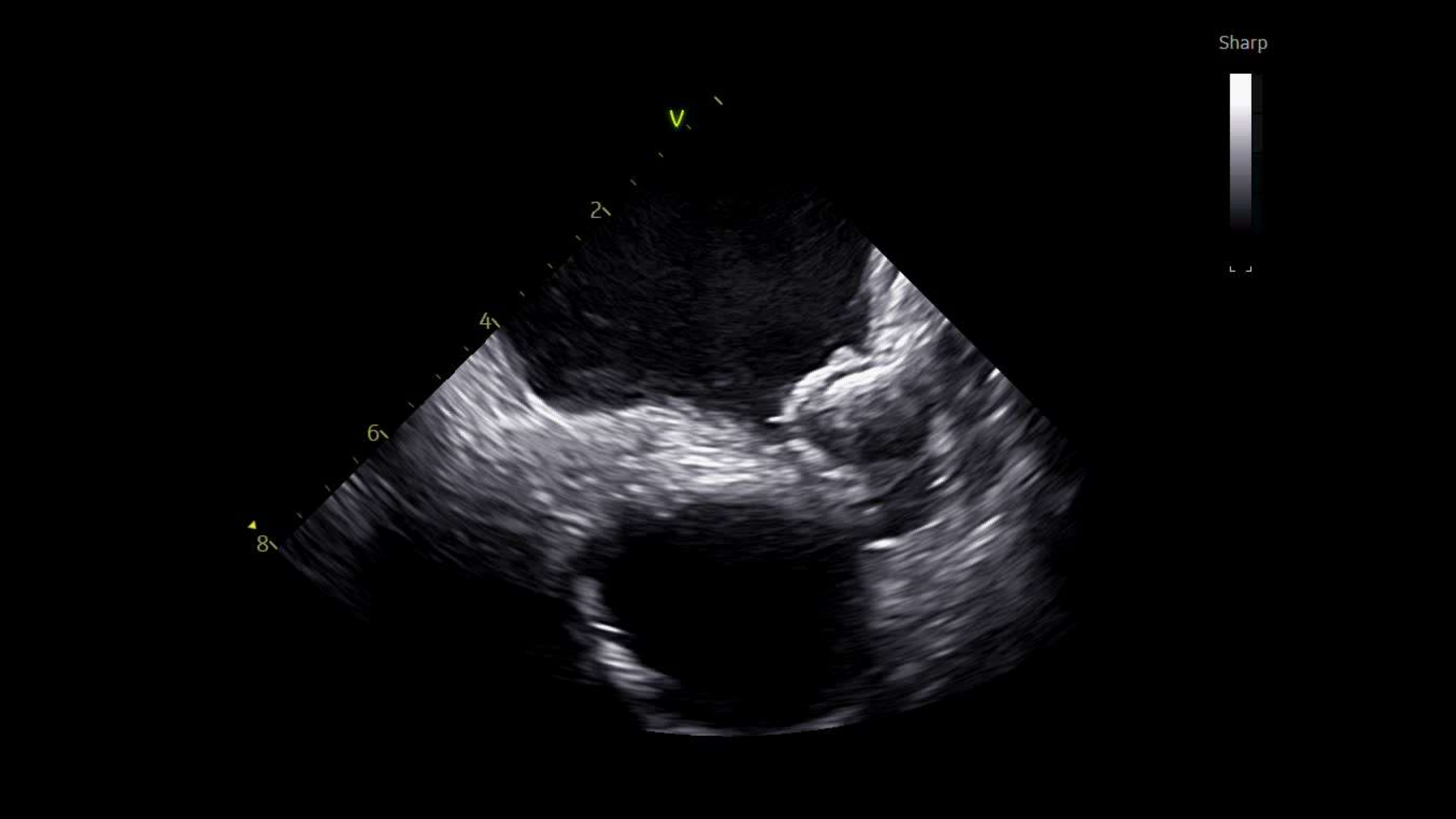
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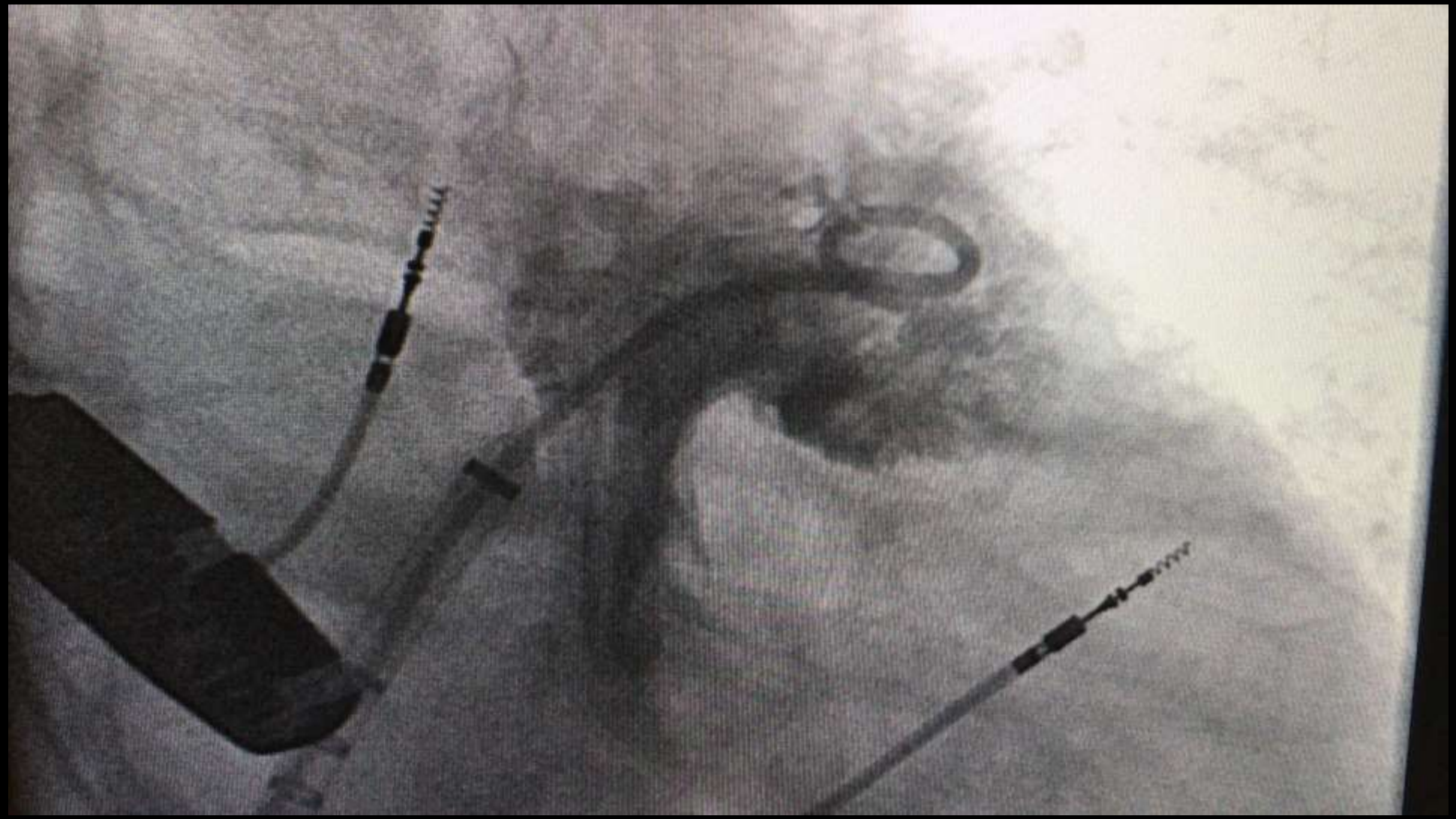

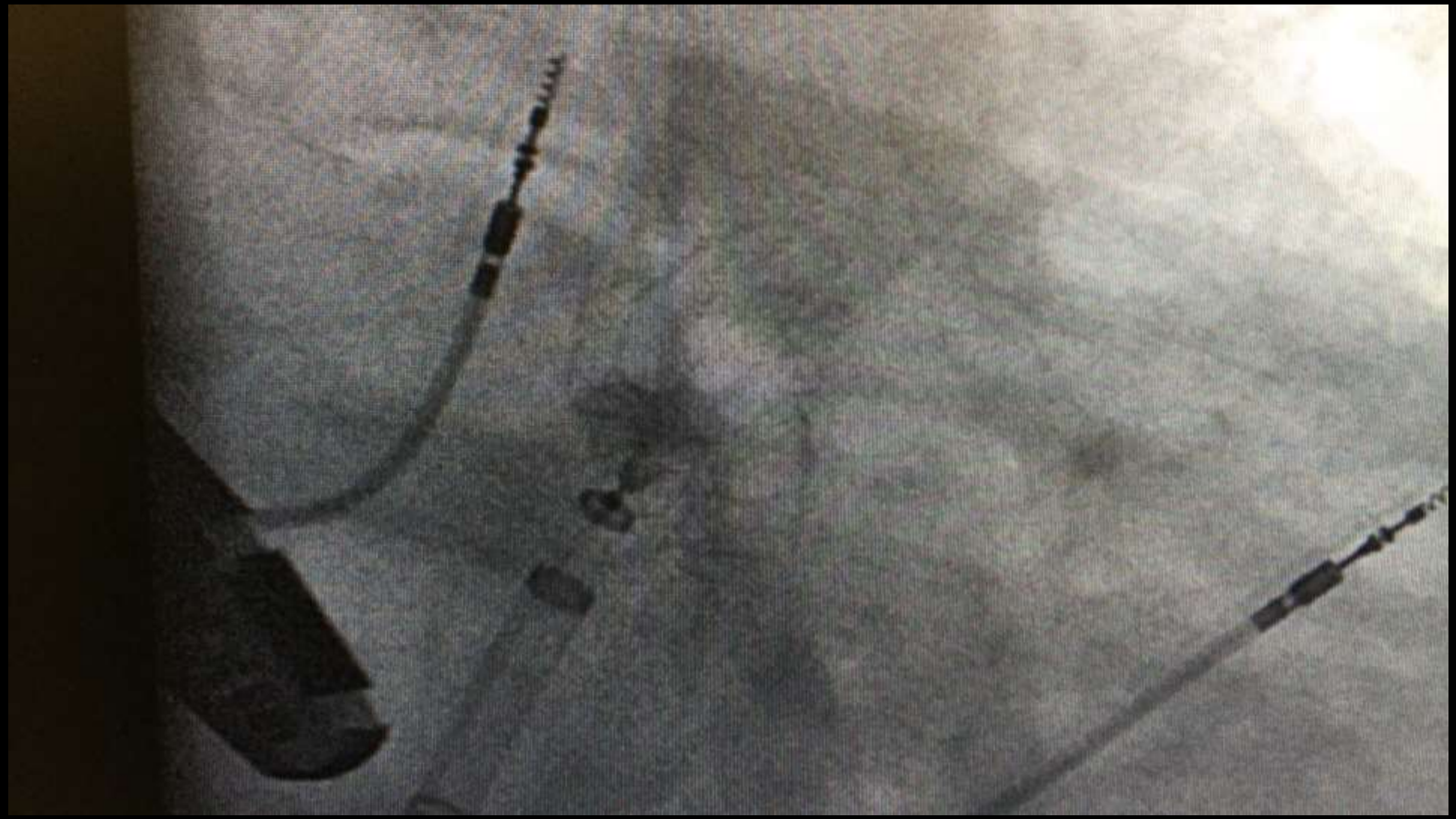

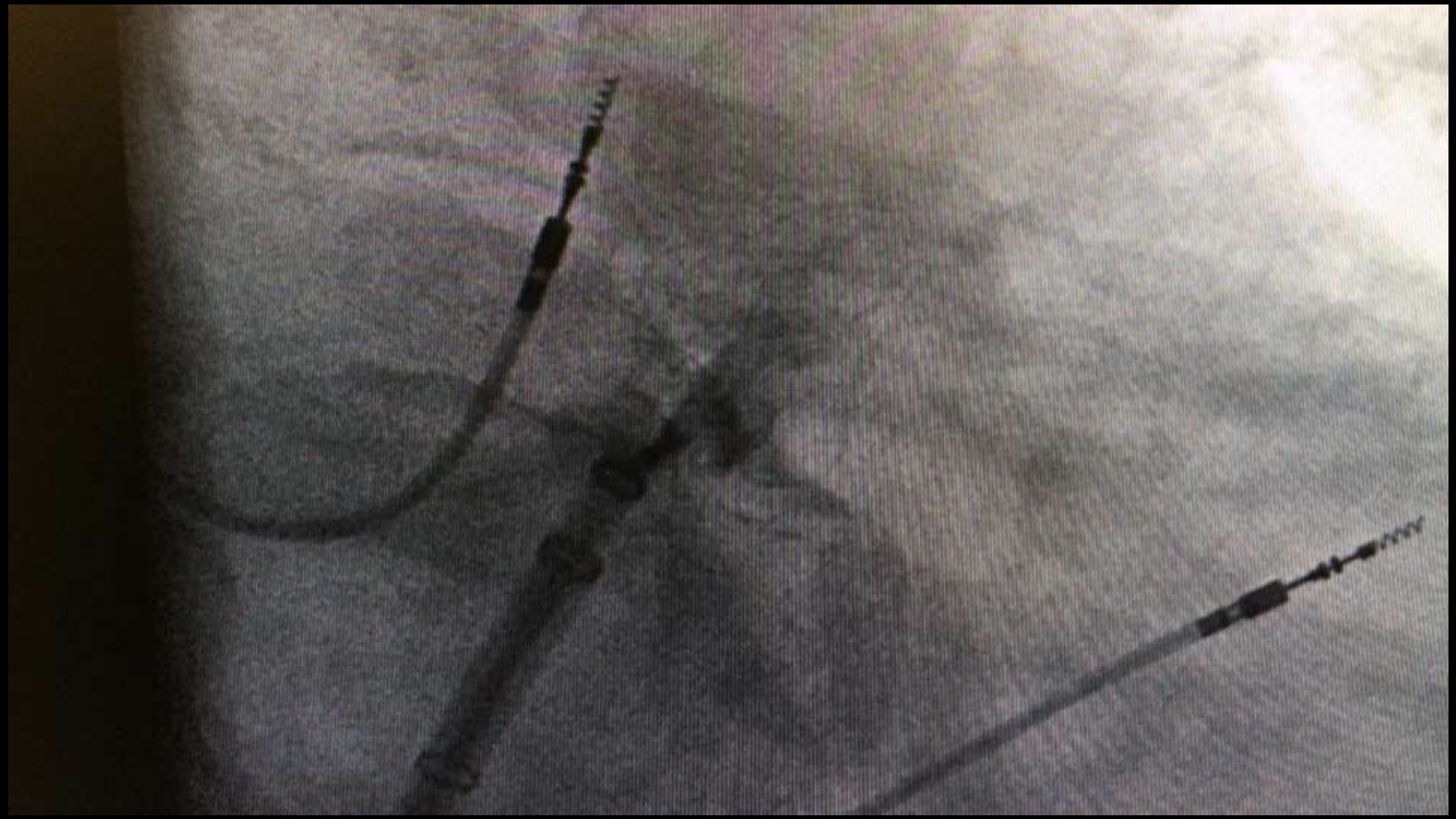

Efficacy and Safety Data

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WATCHMAN Clinical History

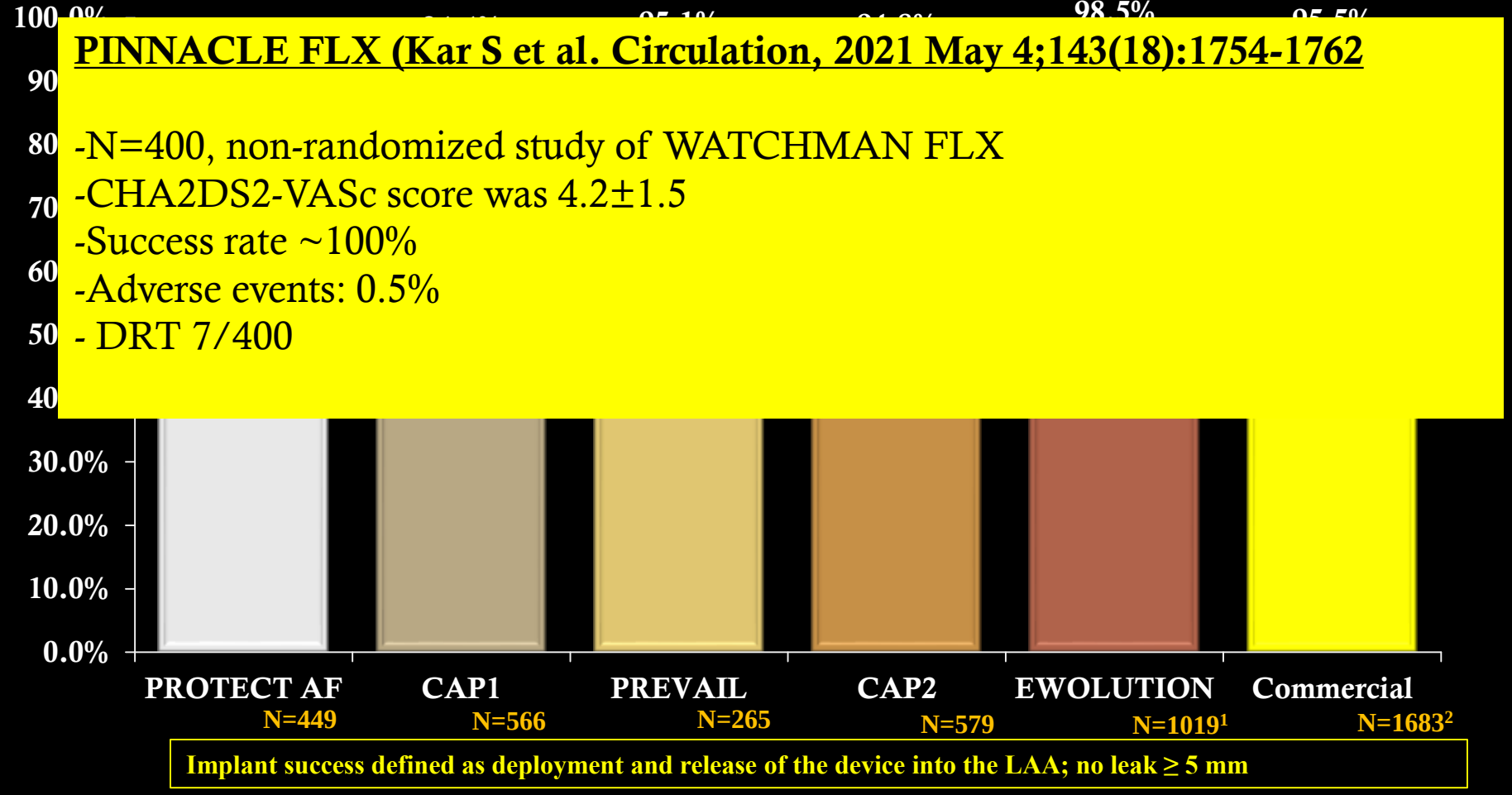
Over 2,000 patients with 4,800 patient years follow-up

Pilot	*Early feasibility with > 6 years of follow up*
PROTECT-AF	*Superior to warfarin for primary efficacy, CV death, and all-cause mortality at 4 years*[1]
CAP Registry	*Significantly improved safety results*[2]
ASAP	*Expected rate of stroke reduced by 77% in patients contraindicated to warfarin*[3]
PREVAIL	*Improved success and procedural safety confirmed with new and experienced operators*[4]
CAP2	*Currently enrolling up to 1500 patients at ~60 sites*

Procedural Success

~50% new operators

~70% new operators



PINNACLE FLX (Kar S et al. Circulation, 2021 May 4;143(18):1754-1762

-N=400, non-randomized study of WATCHMAN FLX
-CHA2DS2-VASc score was 4.2±1.5
-Success rate ~100%
-Adverse events: 0.5%
- DRT 7/400

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

Boersma, L.et al. *EHJ*; published online Jan 2016; 2 Holmes DR, Reddy VY, et al. ACC 2016. Chicago, IL USA

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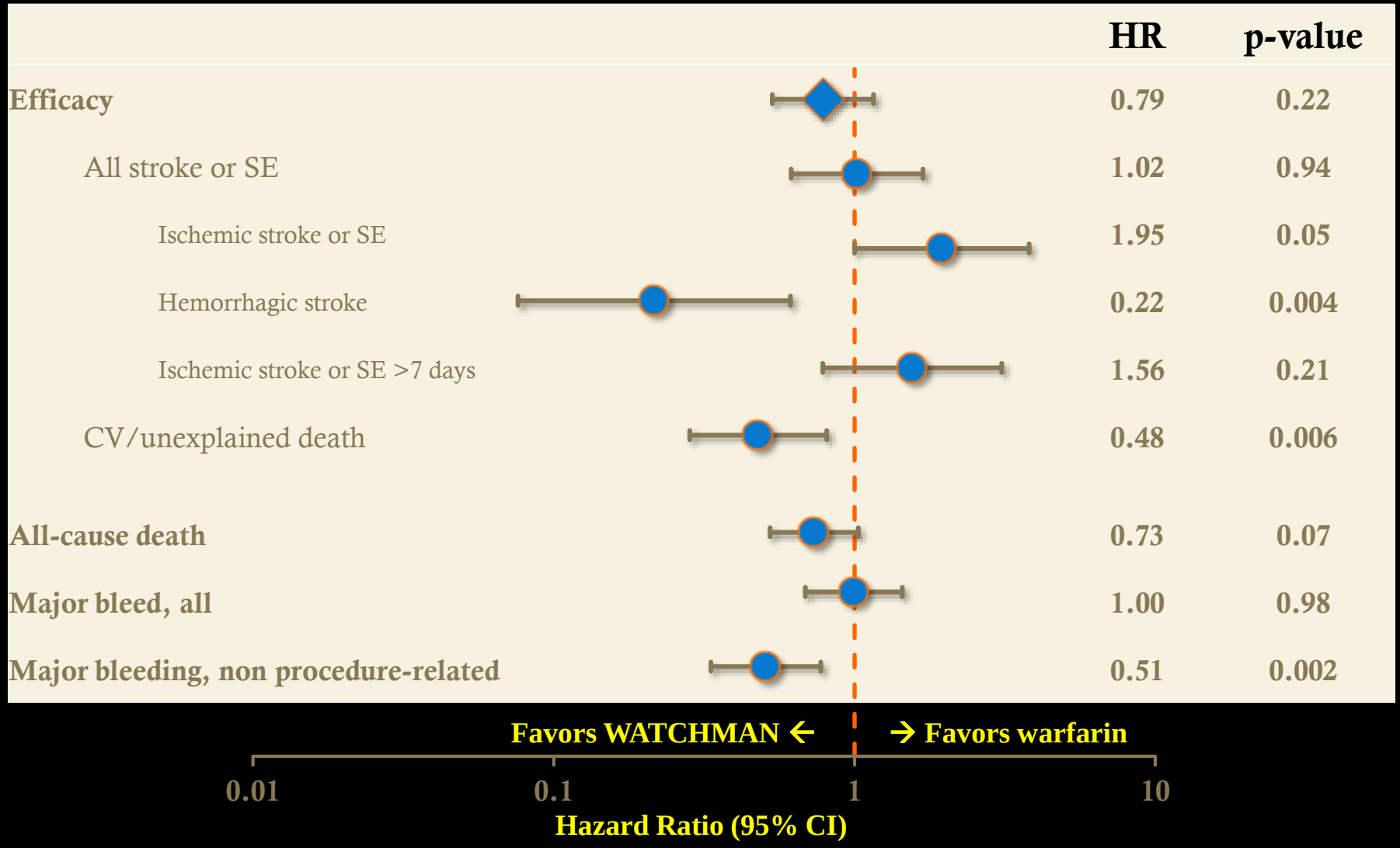
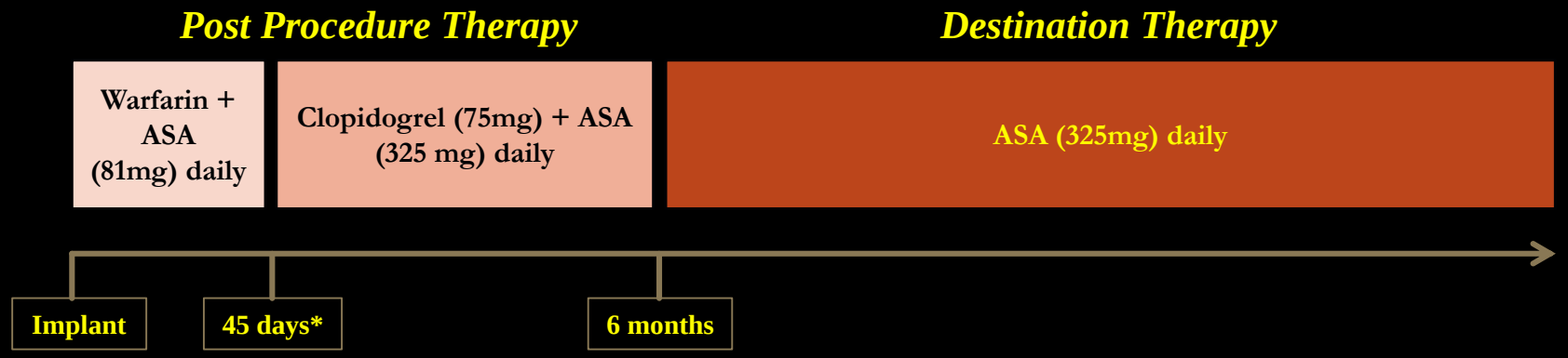
Patient-Level Meta-analysis of PROTECT AF, PREVAIL, and CAP Registries

2406 patients with 5931 patient-years of follow-up (Mean follow-up 2.69 years)



Holmes DR et al. J Am Coll Cardiol 2015;65:2614–23

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

LAAC in Patients with Absolute OAC Contraindication

- ASAP Study (Multicenter observational; n=150)
- Warfarin ineligible (hemorrhagic/bleeding tendencies in 93%); CHADS2VASC 4.4 ±1.7
- **ASAP –TOO RCT prematurely terminated due to poor enrollment**

	Entire Cohort Events/Patient-Years*
Primary efficacy	8/175.0 (4.6%)
Death, all cause	9/180.0 (5.0%)
All stroke	4/176.0 (2.3%)
Ischemic stroke	3/176.9 (1.7%)
Hemorrhagic stroke	1/179.1 (0.6%)

Reddy VY et al. J Am Coll Cardiol 2013;61:2551–6

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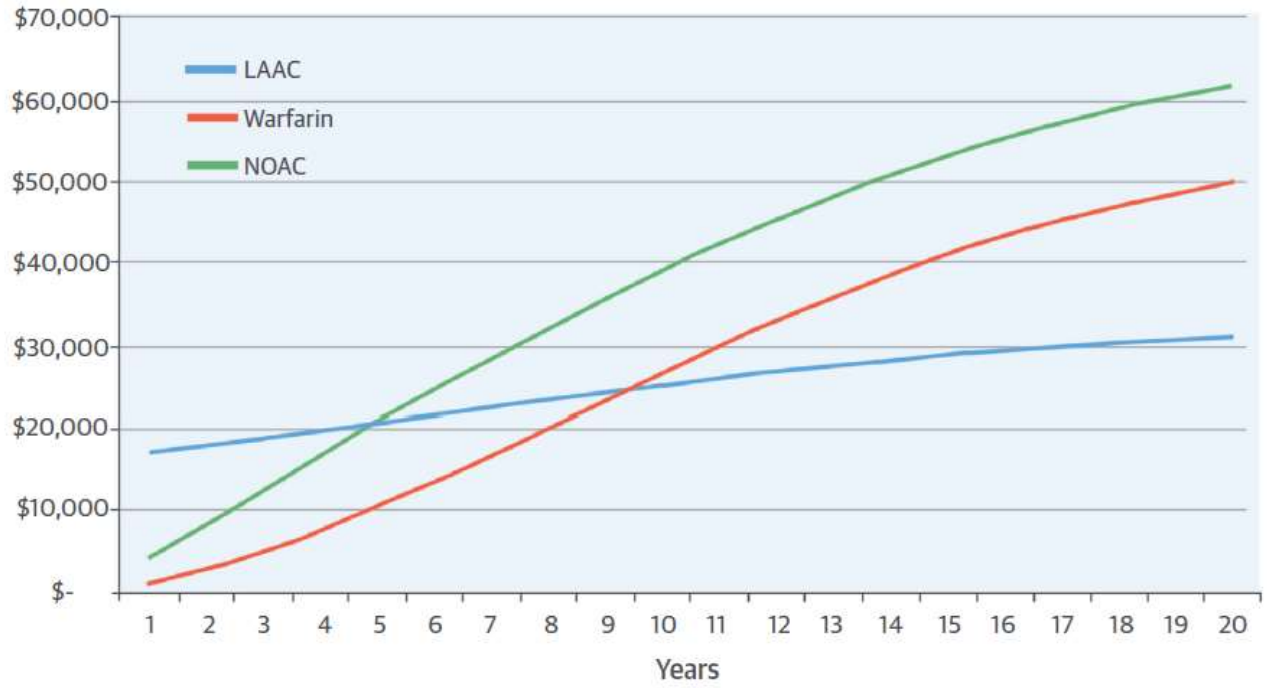
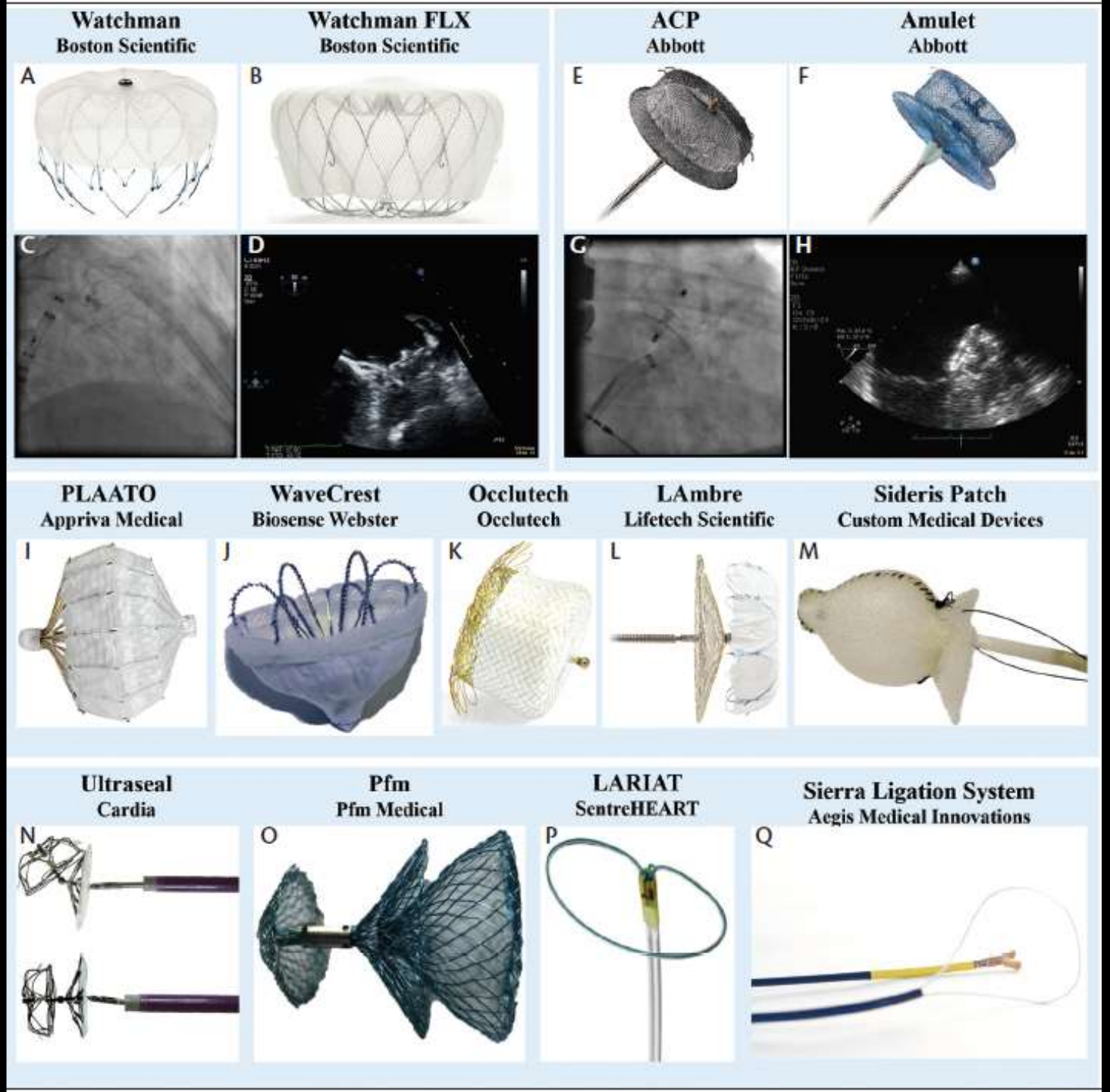
Cost-Effectiveness

CENTRAL ILLUSTRATION **Warfarin Versus NOACs Versus LAAC: Cumulative Cost and Time to Cost-Effectiveness Following Treatment Initiation**

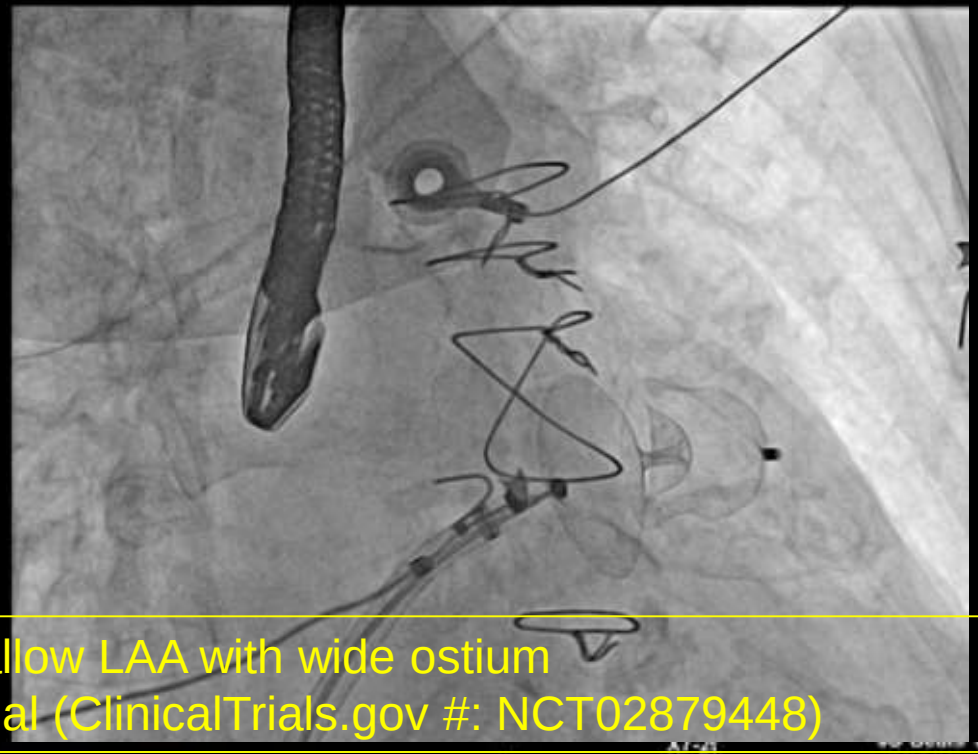


	Time to Clinical Effectiveness (Incremental QALYs)	Time to Cost-Effectiveness (Cost per QALY)	Time to Dominance (More Effective, Less Costly)
LAAC vs. warfarin	Year 3 (0.015)	Year 7 ($42,994/QALY)	Year 10
NOACs vs. warfarin	Year 1 (0.008)	Year 16 ($48,446/QALY)	N/A
LAAC vs. NOACs	Year 5 (0.007)	Year 5 (Dominant)	Year 5

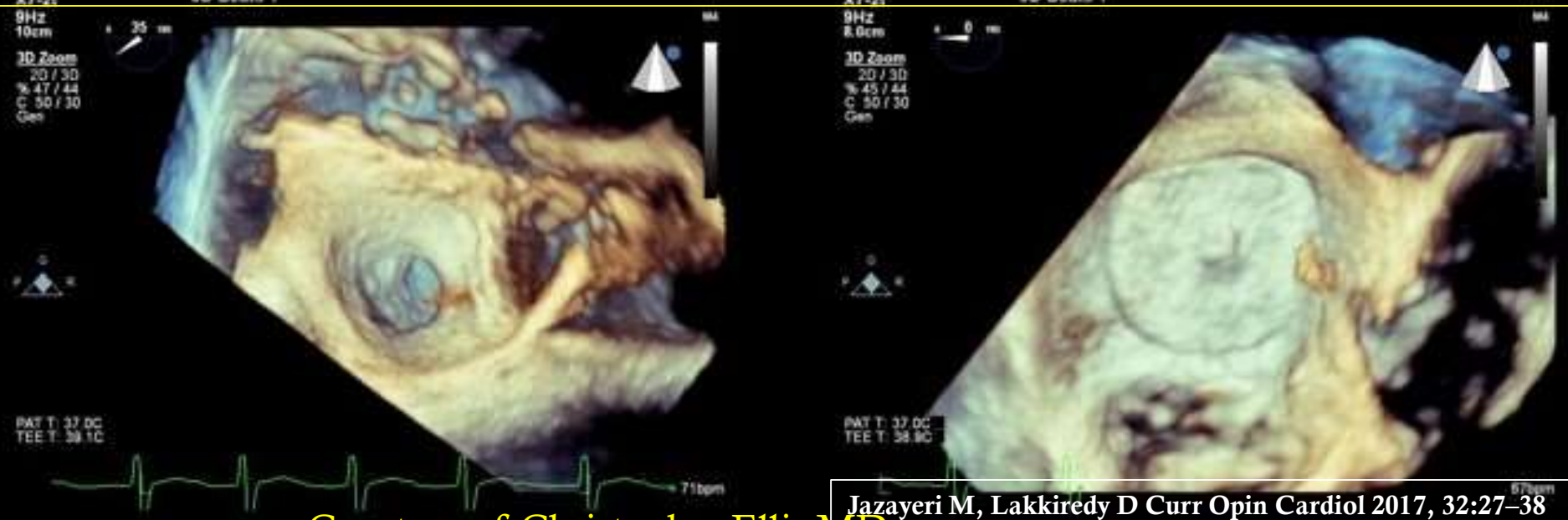
Reddy, V.Y. et al. J Am Coll Cardiol. 2015; 66(24):2728-39.



Asmarats L et al. Cardiac interventions today may/june 2018 vol. 12, no. 3



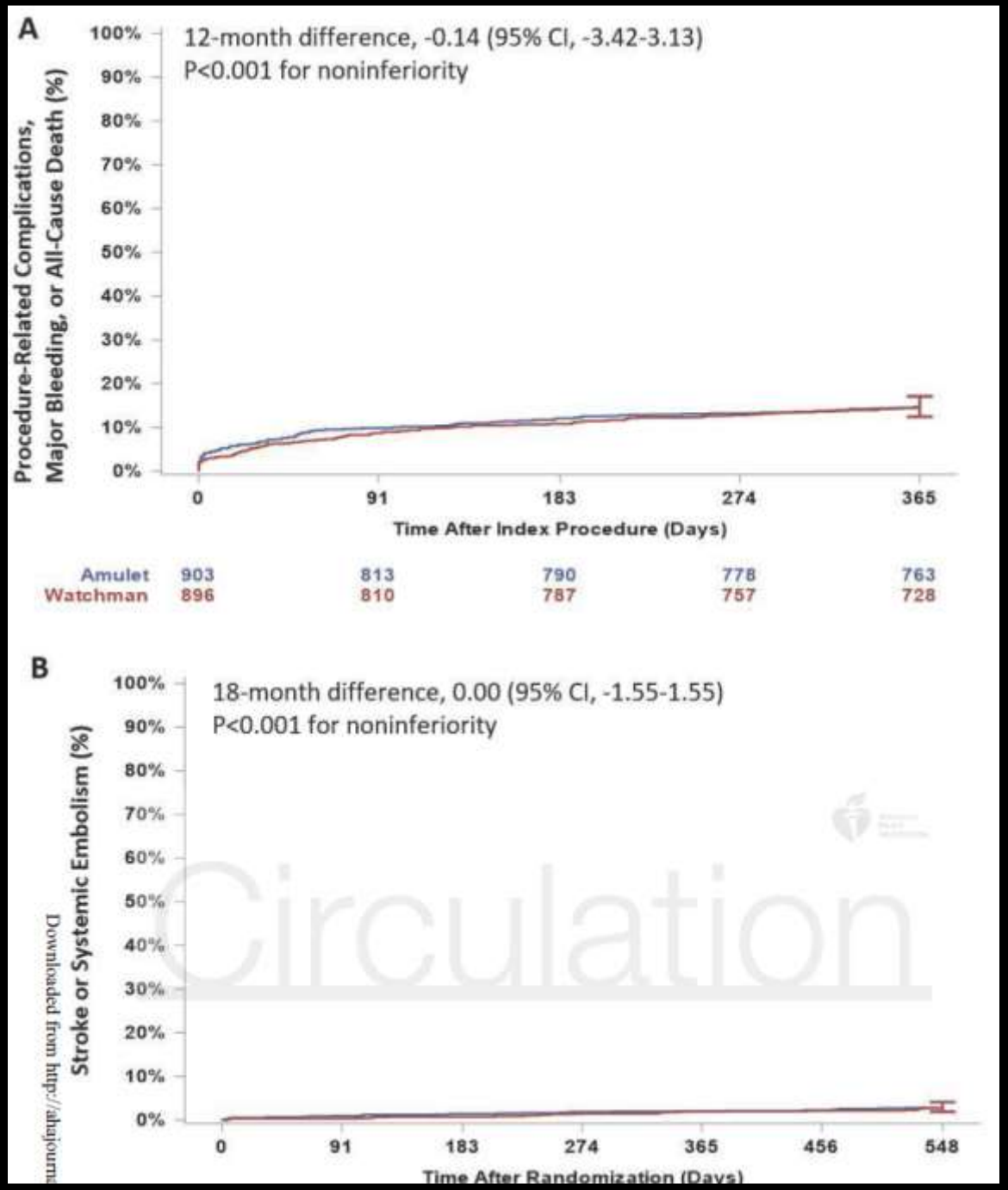
1. Useful for shallow LAA with wide ostium
2. Amulet IDE trial (ClinicalTrials.gov #: NCT02879448)



Courtesy of Christopher Ellis MD

Jazayeri M, Lakkiredy D Curr Opin Cardiol 2017, 32:27–38

AMULET IDE Trial



- The Amulet occluder was non-inferior for safety and effectiveness of stroke prevention for NVAF compared with the Watchman device, and superior for LAA occlusion (↓ leaks).
- Procedure-related complications were higher with the Amulet device (pericardial effusions and device embolization) and decreased with operator experience.

Lakkireddy D et al. Circulation . 2021 Aug 30.

Conclusions

- AF in increasing in incidence and prevalence
- Substantially increases risk of stroke and thromboembolism (accounts for ~20% for all strokes)
- Highly effective therapies are available to prevent or reduce the risk for stroke in patients with AF
- NOACs are preferred over warfarin for stroke prevention in non-valvular AF
- Compared to warfarin, target specific oral anticoagulants are: a) at least as good at preventing stroke, b) substantially reduce risk of intracranial hemmorhage, and c) may be associated with improved survival
- Many issues need to be considered: Bleeding risk, renal disease, drug interactions, cost, compliance, patient preferences etc.

Conclusions

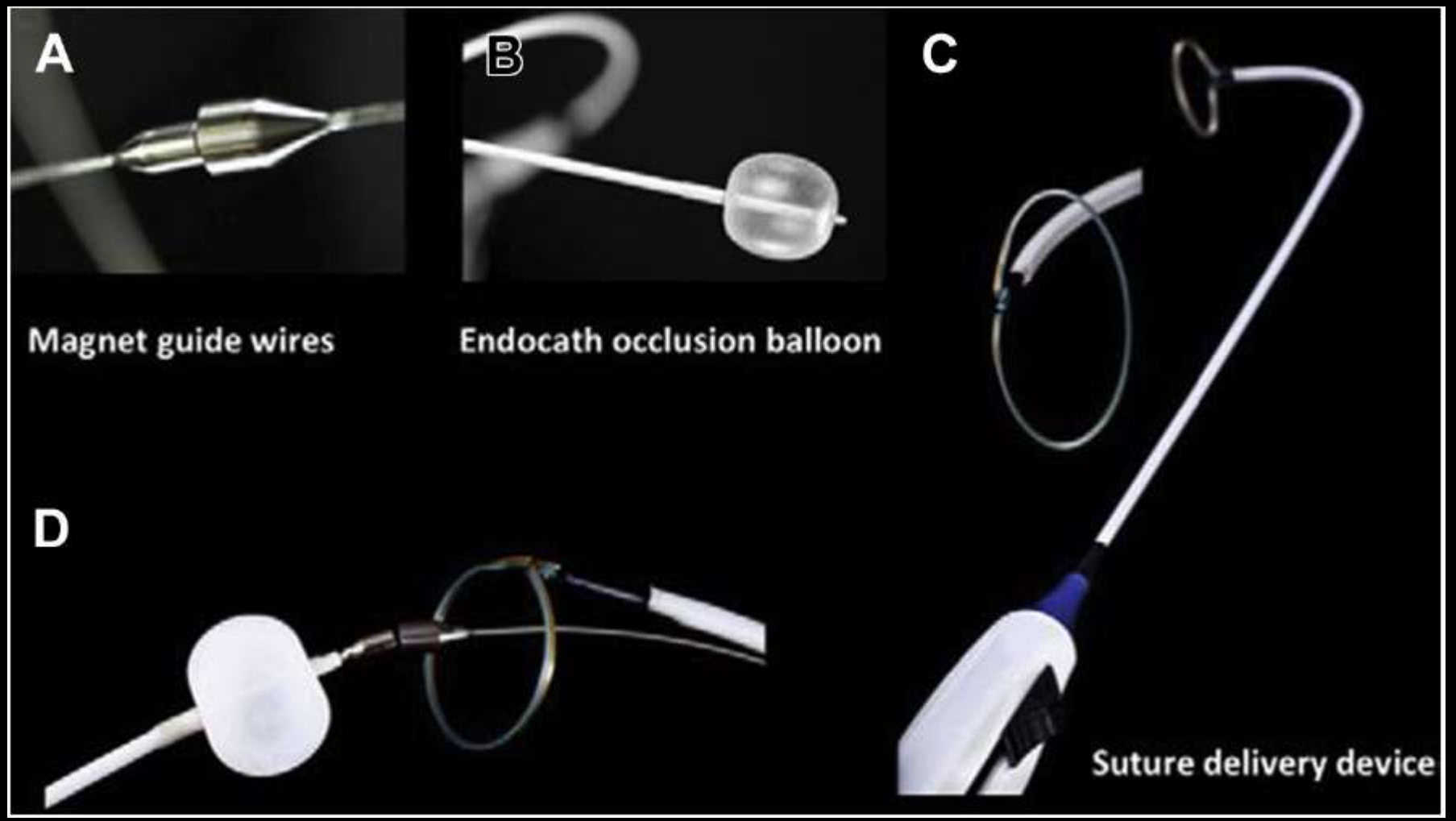
- A significant proportion of NVAF patients who need OAC are either not on it or cannot take it long-term
- LAA is primary source for NVAF-related thromboembolism
- Percutaneous LAAC is an established alternative to anticoagulation in patients with NVAF at high risk for bleeding or having contraindications to OAC
- WATCHMAN™ and Amulet ™: FDA-approved percutaneous LAAC devices in the US
- Indication: **Moderate to high risk of stroke with appropriate rationale to seek alternative to long-term anticoagulation**
- Randomized trials have proved efficacy and safety of Watchman compared to warfarin ⟶ Equivalent for total stroke; superior for hemorrhagic stroke and cardiovascular mortality. Amulet equivalent to watchman for efficacy & safety

Thank you!

Contact Info:
Email:
rakesh.gopinathannair@hcahealthcare.com
Twitter: @drrakeshg1
Cell: 301-641-6062
www.kcheartrhytm.com

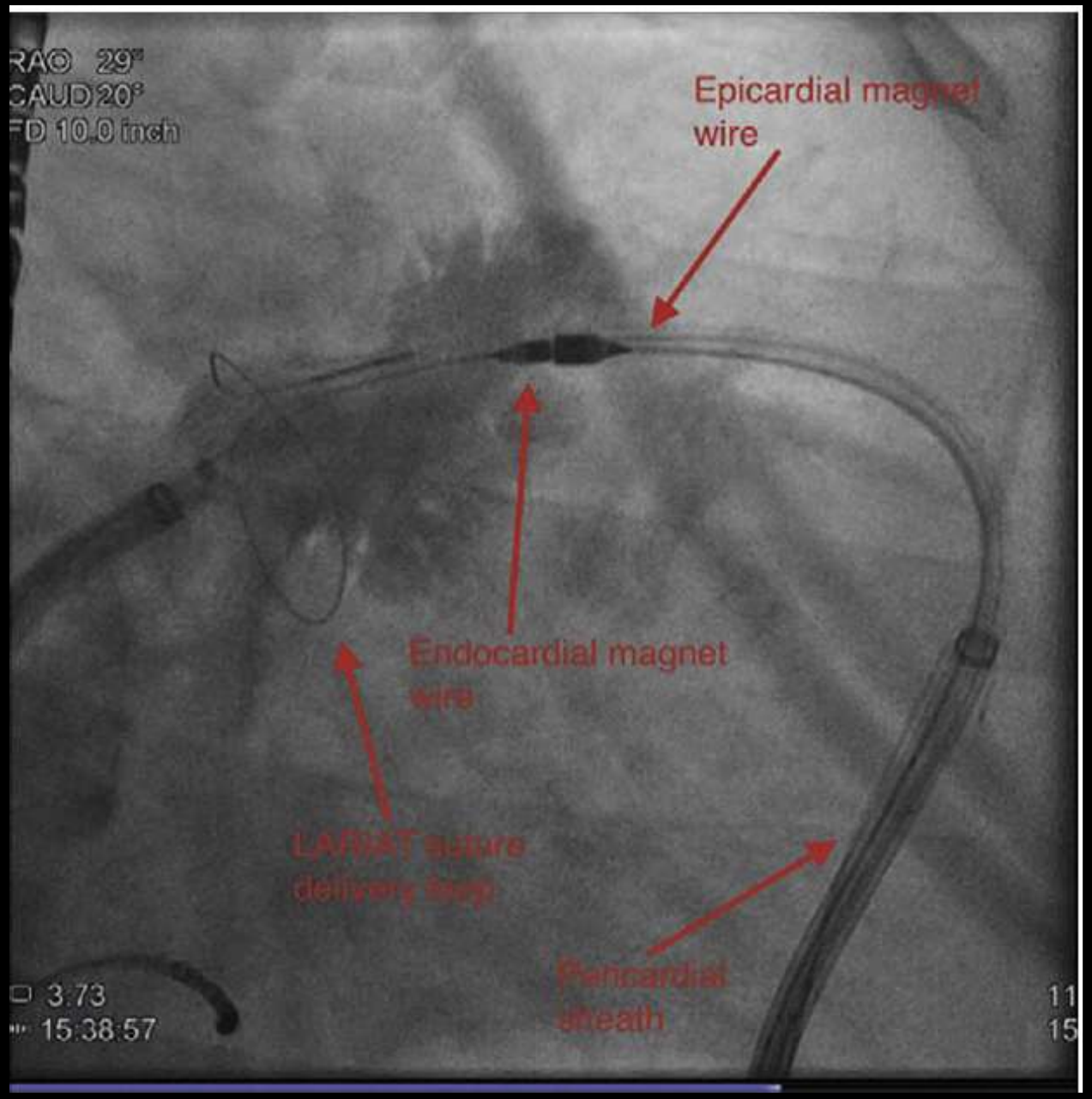
Supplementary Slides

LARIAT Suture Delivery System



1. Advantageous in patients with absolute contraindication to OAC
2. Electrical isolation of LAA may provide arrhythmic benefit

Jazayeri M, Lakkireddy D. Curr Opin Cardiol 2017, 32:27–38



AMAZE trial: Evaluating the efficacy of LAA ligation along with pulm vein isolation for long-standing persistent AF

Iskander S et al. Cardiol Clin 34 (2016) 329–351

Device	Advantages	Limitations	Current status	Future
WATCHMAN	- Most data - **2 Randomized studies and registry data**	- Unsuitable for shallow, wide appendage - Need for OAC or DAPT post-op	**FDA approved** **CE Mark**	- **Trial comparing against NOACs (OCCLUSION-AF)** - **Management of leaks and DRT** - **Use with DAPT only (In absolute OAC CI)** - **Post-AF ablation (OPTION)** - **Alternative to OAC as first line (CHAMPION-AF)** - **Post-TAVR (WATCH-TAVR)**
AMULET	- Shallow, wide appendages - Lobe & Disc design can account for ostial variation	- DAPT post-op	**CE Mark** **FDA Approved**	- **AMULET-IDE (LBCT at ESC2021)** - **CATALYST (Alternative to OAC as first line)**
LARIAT	- Can be used in patients with absolute CI to OAC - LAA Electrical isolation	- Technically challenging procedure - Limited by LAA anatomy & prior surgery	- **FDA 510 K** - **FDA safety communication**	- **Randomized data for use in persistent AF ablation (AMAZE)** - **Improving procedural safety**

Anti-thrombotic therapy after left atrial appendage occlusion

Device/patient	Aspirin	OAC	Clopidogrel	Comments
Watchman/low bleeding risk	75 - 325 mg/day indefinitely	Start warfarin after procedure (target INR 2 - 3) until 45 days or continue until adequate LAA sealing is confirmed[a] by TOE. NOAC is a possible alternative	Start 75 mg/day when OAC stopped, continue until 6 months after the procedure	Some centres do not withhold OAC at the time of procedure (no data to support/deny this approach)
Watchman/high bleeding risk	75 - 325 mg/day indefinitely	None	75 mg/day for 1 - 6 months while ensuring adequate LAA sealing[a]	Clopidogrel often given for shorter time in very high-risk situations
ACP/Amulet	75 - 325 mg/day indefinitely	None	75 mg/day for 1 - 6 months while ensuring adequate LAA sealing[a]	Clopidogrel may replace long-term aspirin if better tolerated

Hindricks G et al. ESC 2020 Guidelines. European Heart Journal (2020) 00, 1;125

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PROTECT AF

- 707 NVAF patients (n=463 to WATCHMAN and n=244 to Warfarin)
- Efficacy – Primary composite endpoint of stroke, cardiovascular death, and systemic embolism
- 88% had successful implant; 86% successfully discontinued warfarin at 45 days
- **At 1065 Pt-years follow-up:**

  Efficacy - 3% vs. 4.3% for warfarin; RR 0.62, 95% CI 0.35-1.25

  Safety - 7.4% vs. 4.4% for warfarin; RR 1.69; 95% ci 1.01-3.19
- Pericardial Effusion 4.8%; Major bleeding 3.5%
- Met non-inferiority for primary efficacy endpoint

Holmes DR et al. Lancet 2009; 374: 534–42

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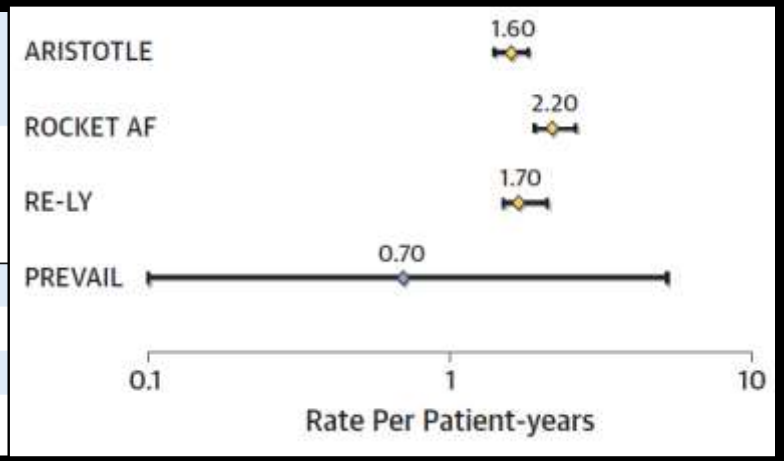
PREVAIL

Holmes DR et al. J Am Coll Cardiol 2014;64:1–12

- 407 patients in a 2:1 randomization to Watchman vs. Warfarin
- 25% of patients treated by new operators
- Implant Success: 95% had successful implant
- Watchman did not meet primary efficacy endpoint (0.063 vs 0.064%; RR1.07; 95% CrI: 0.57-1.89)
- 2.2% early safety events (non-inferior to warfarin)

TABLE 3 Coprimary Efficacy Endpoint Observed Events by Type: PREVAIL Subjects Only (Intention-to-Treat)*

	Device Group			Control Group		
	No. of Events	% of Subjects	% of Endpoints	No. of Events	% of Subjects	% of Endpoints
Ischemic stroke	5	1.9	35.7	1	0.7	25.0
Hemorrhagic stroke	1	0.4	7.1	0	0.0	0.0
Death (cardiovascular/unexplained)	7	2.6	50.0	3	2.2	75.0
Systemic embolism	1	0.4	7.1	0	0.0	0.0



Watchman – Contraindications

- LAA thrombus
- Unfavorable LAA anatomy
  - Shallow, wide LAA
  - LA ostial size > 31 mm
- Absolute contraindication for OAC: Cannot take warfarin or ASA/Clopidogrel

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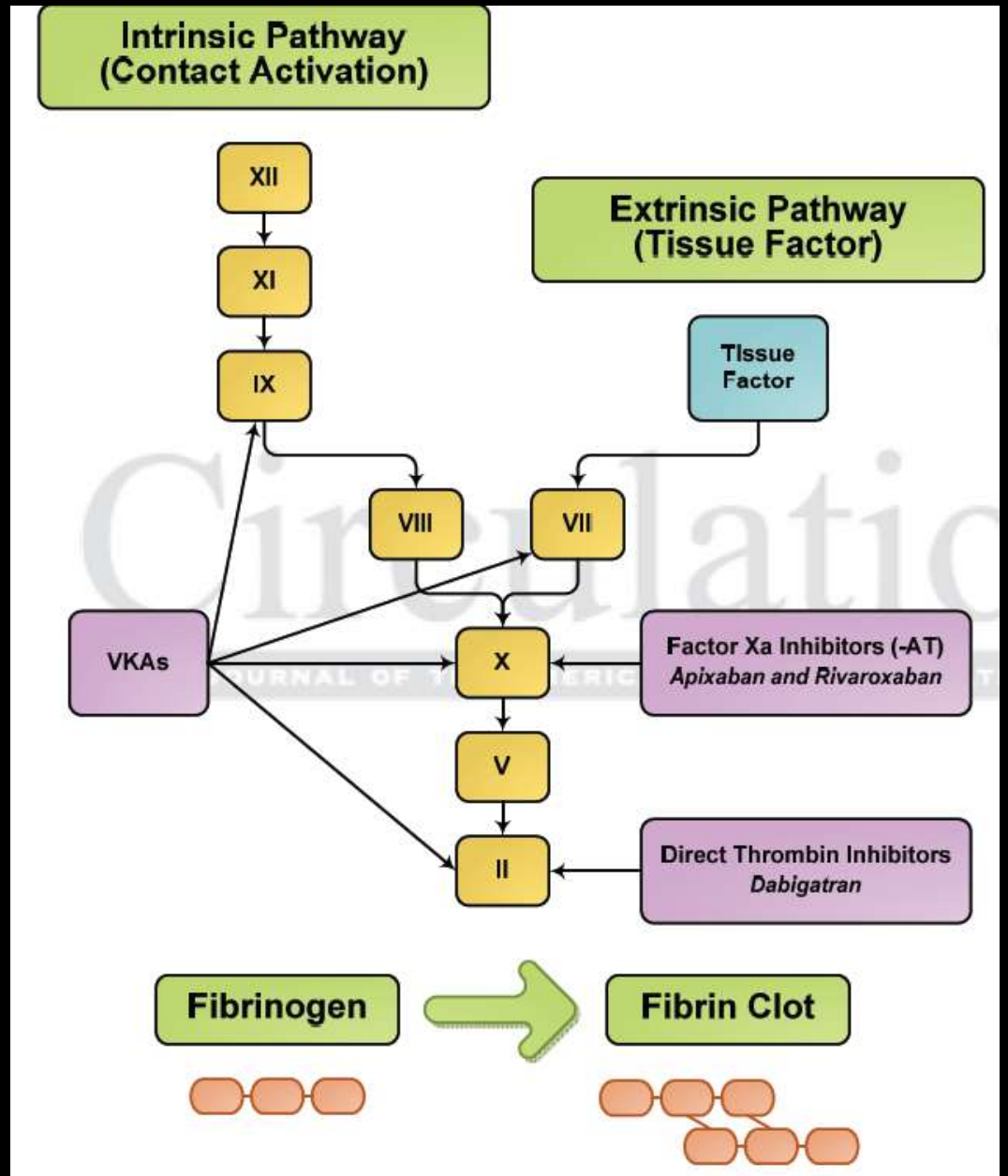
Novel Oral Anticoagulants



Better than Warfarin:

1. Dabigatran 150 mg twice daily
2. Rivaroxban 20 mg PO daily
3. Apixaban 5 mg PO twice daily

Less major bleeding than Warfarin:

1. Dabigatran 110 mg twice daily
2. Apixaban 5 mg PO twice daily

Use in ESRD/Dialysis:

Apixaban 5 mg PO twice daily

Survival Benefit:

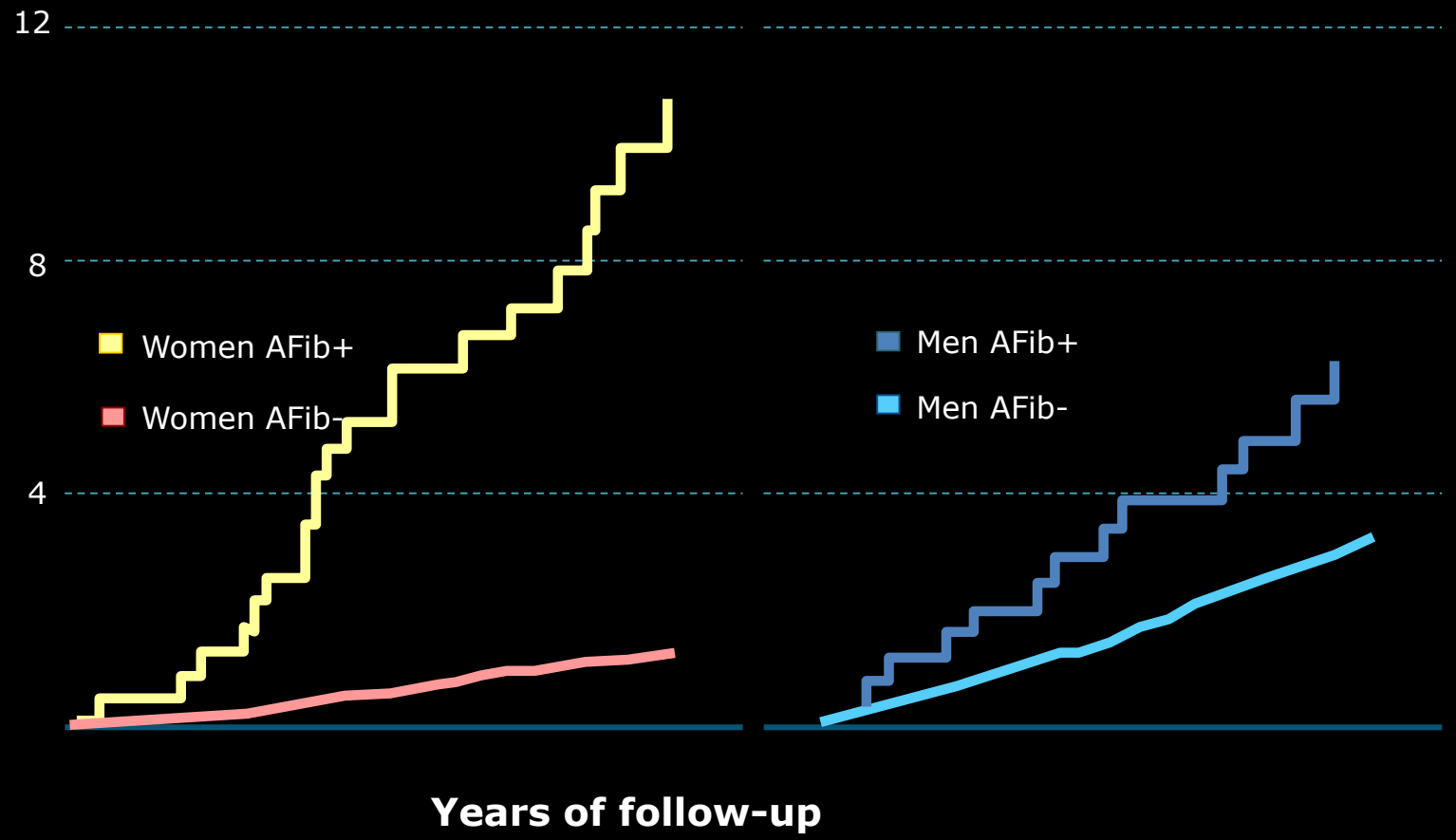
Apixaban 5 mg PO twice daily

Dialyzable:

Dabigatran

AF is Responsible for 15-20% of all Strokes

– **Non-valvular AFib is responsible for a 5-fold increase in the risk of ischemic stroke**



Wolf PA, et al. Stroke (1991) 22: 983
Go AS, et al. JAMA (2001) 285: 2370
Friberg J, et al. *Am J Cardiol* (2004) 94: 889

Incidence of AFib in the General Population – Gender Differences

Olmsted County study

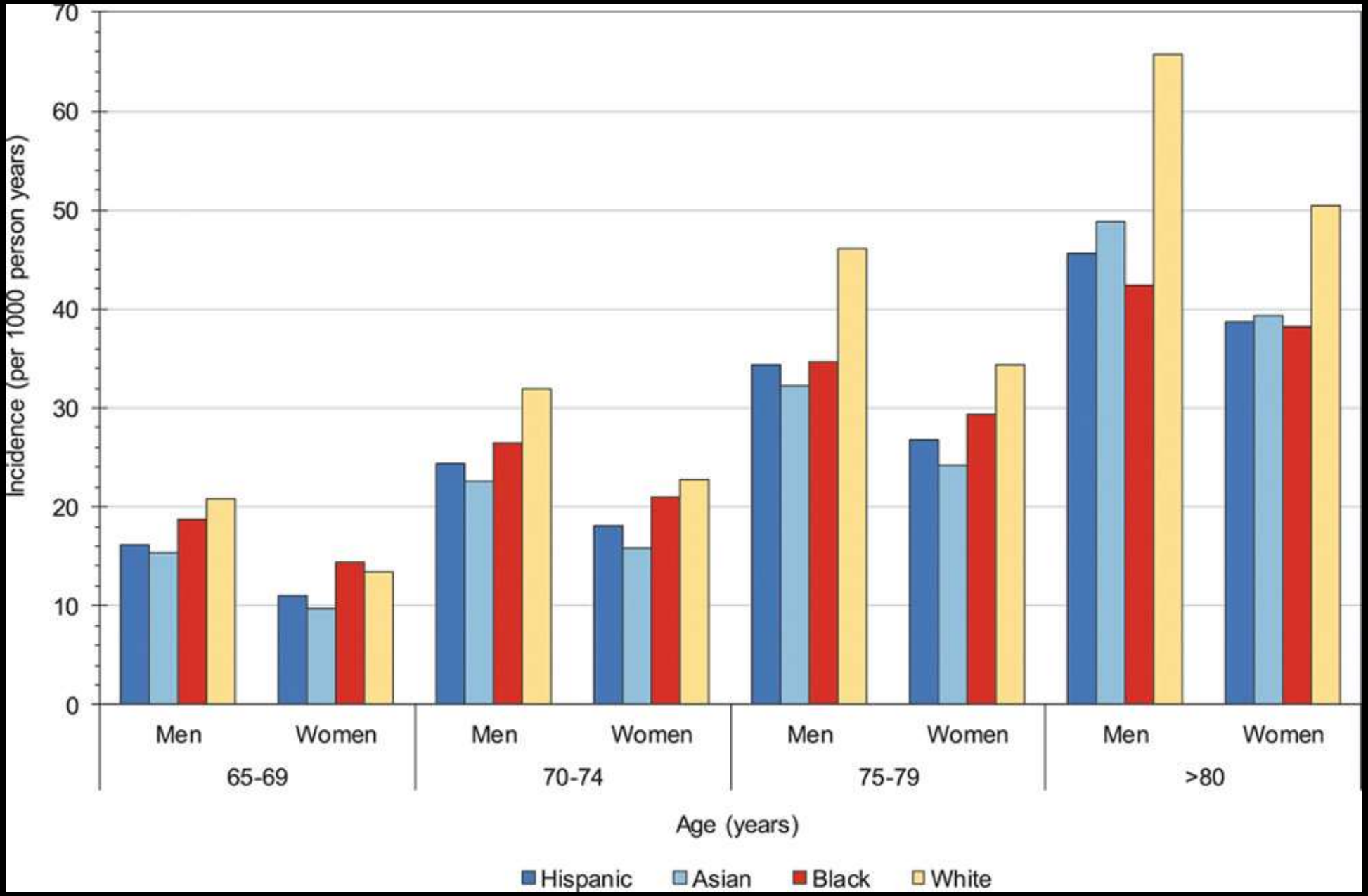
Observational period: 20 years

Men	**0.49 %**
Women	**0.28 %**

Ratio men to women = 1.86

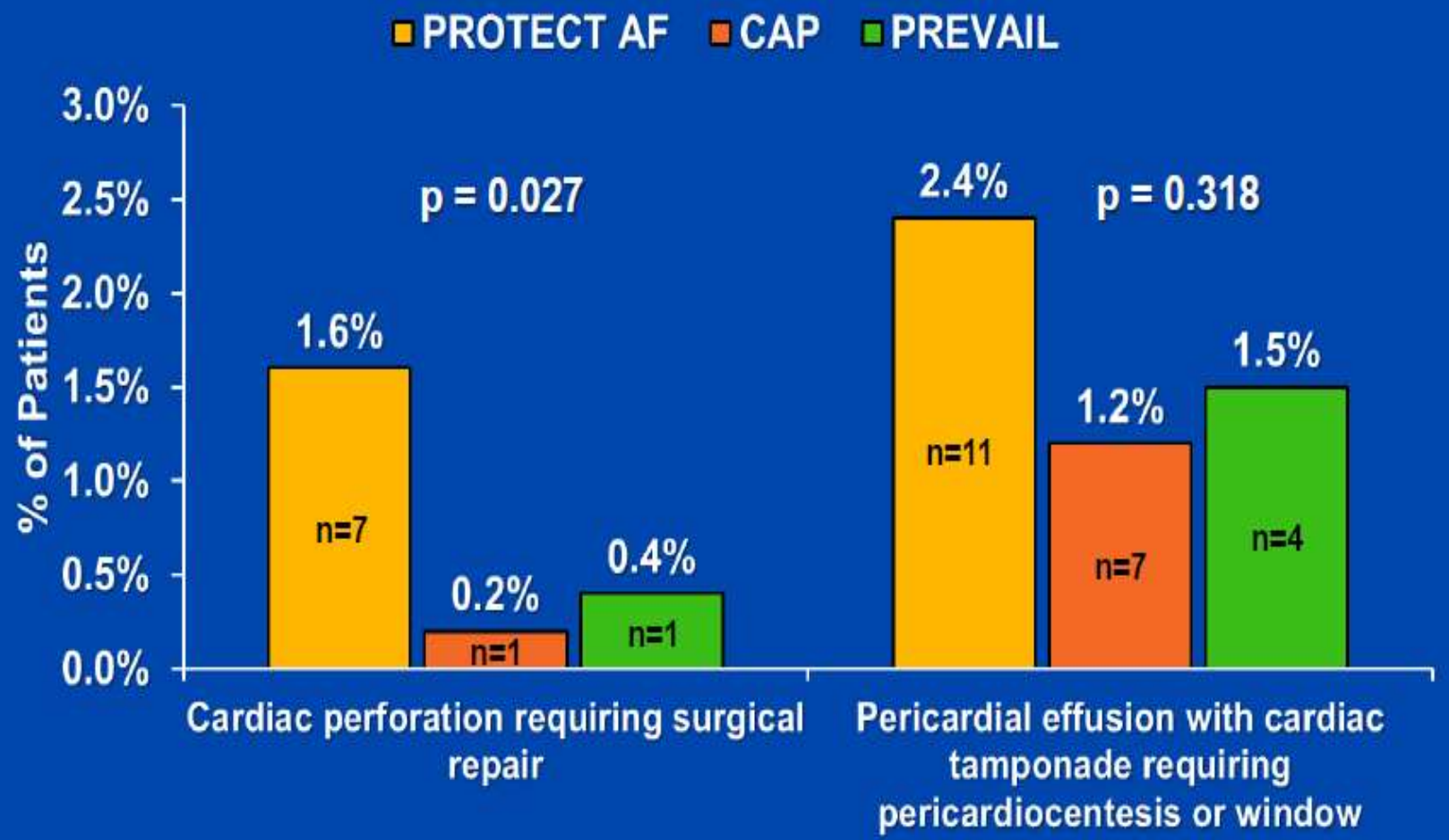
The lifetime risk of AF in men and women over 40 years of age: 1 in 4

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



Dewland TA et al. Circulation. 2013;128:2470–2477

Pericardial Effusions Requiring Intervention



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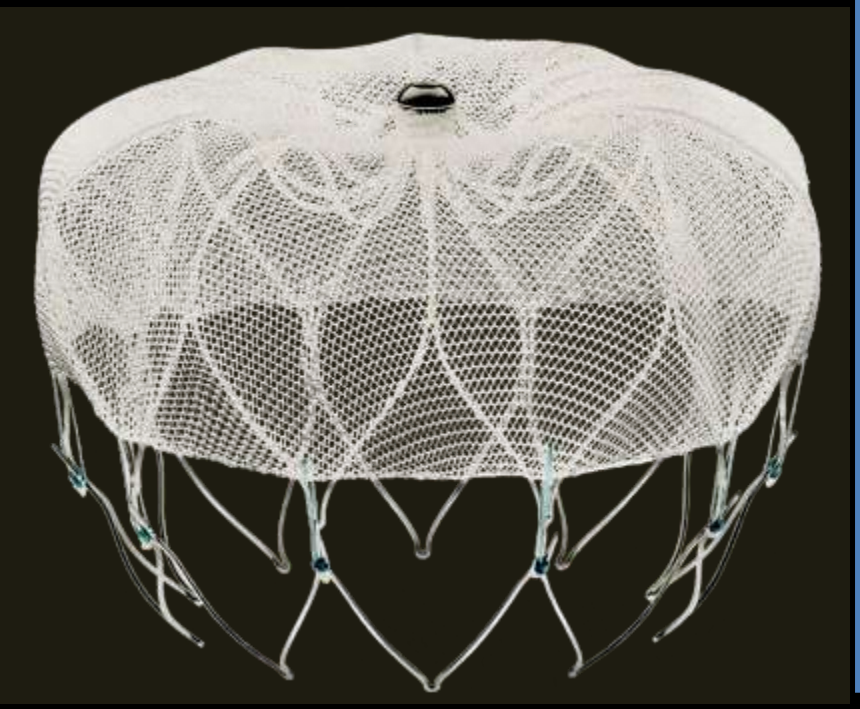
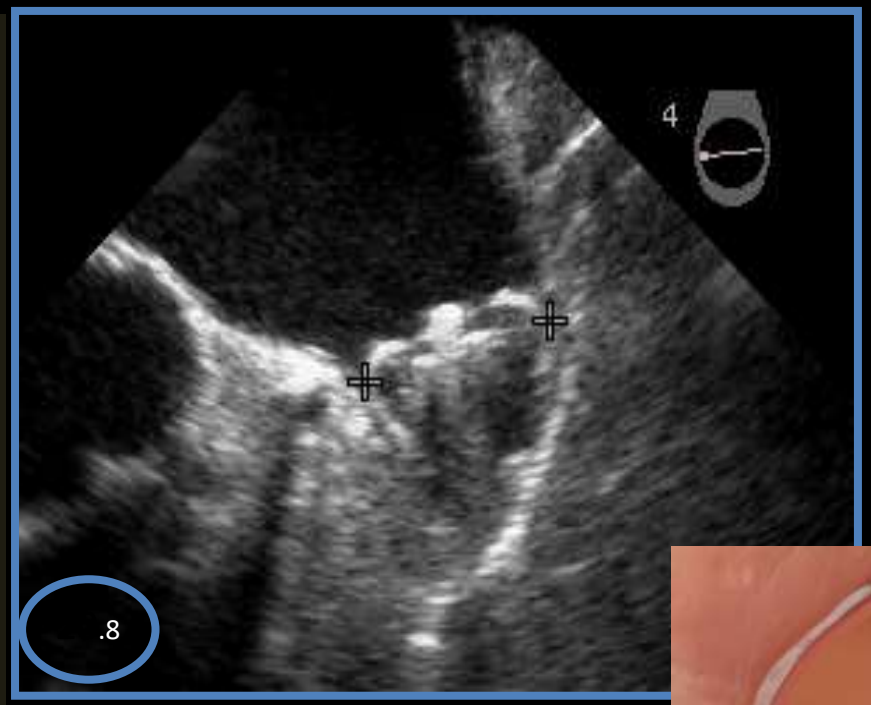
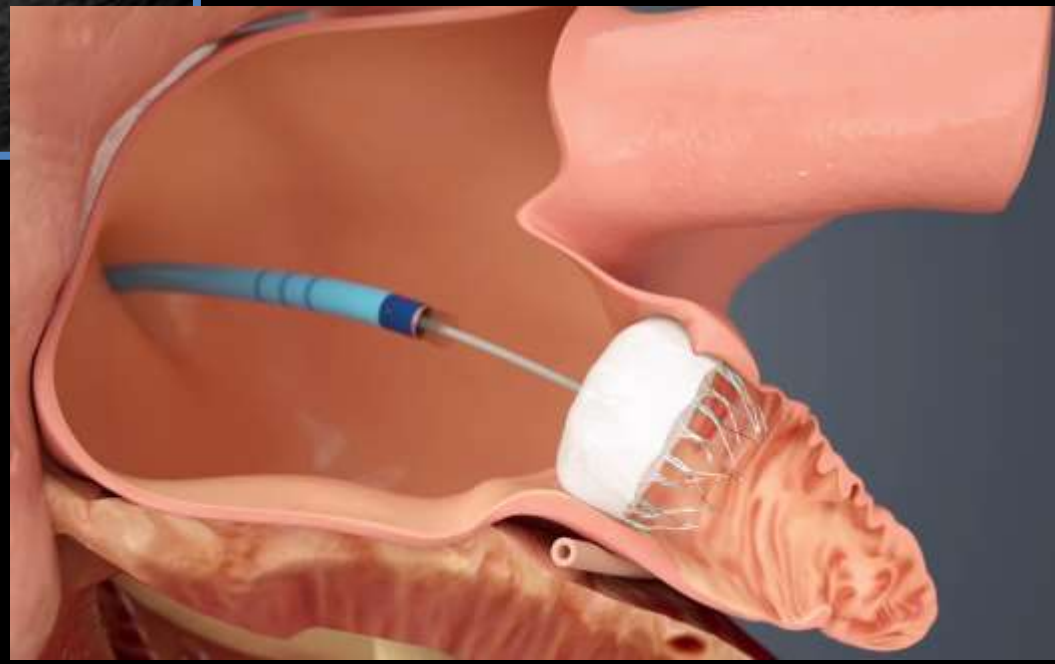
Holmes DR et al. J Am Coll Cardiol 2014;64:1–12

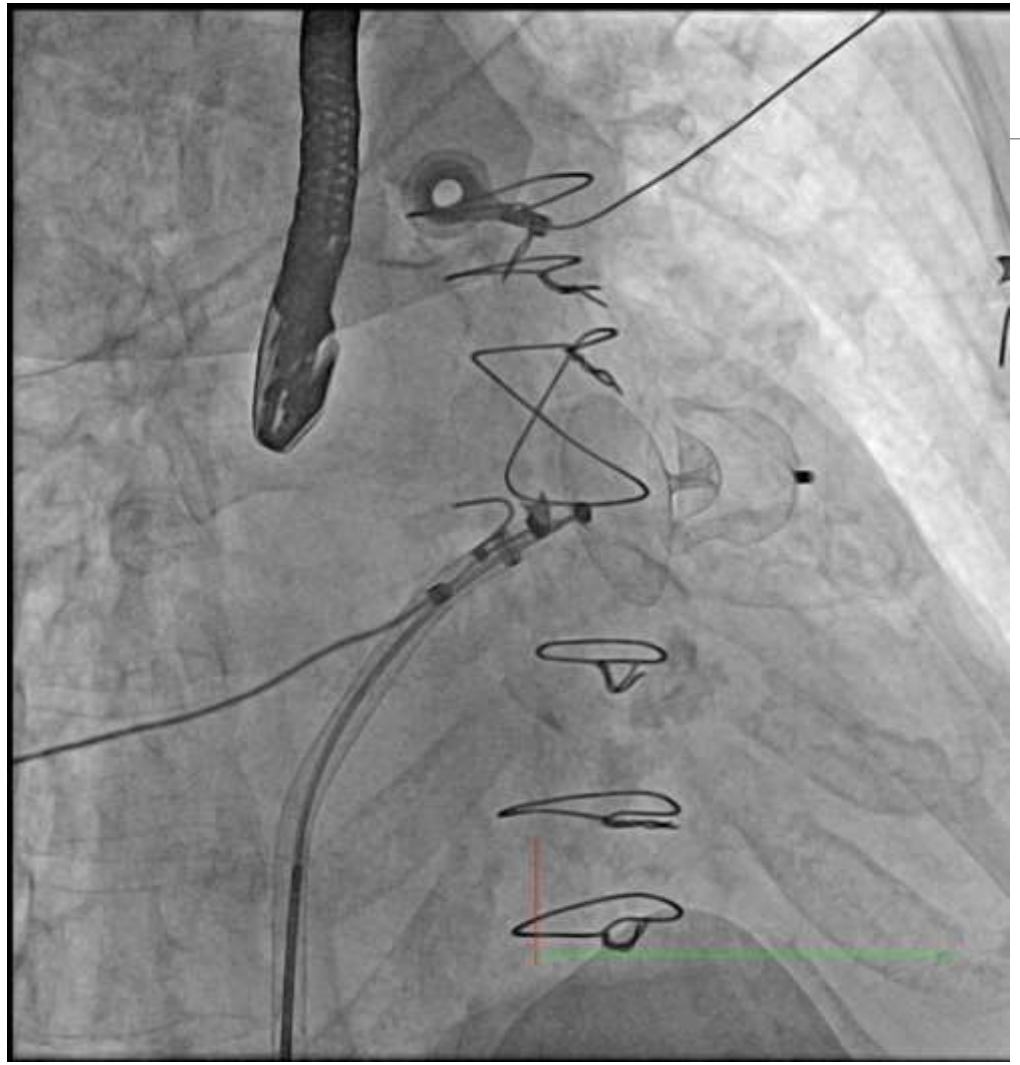
Left Atrial Appendage closure for Stroke Prevention

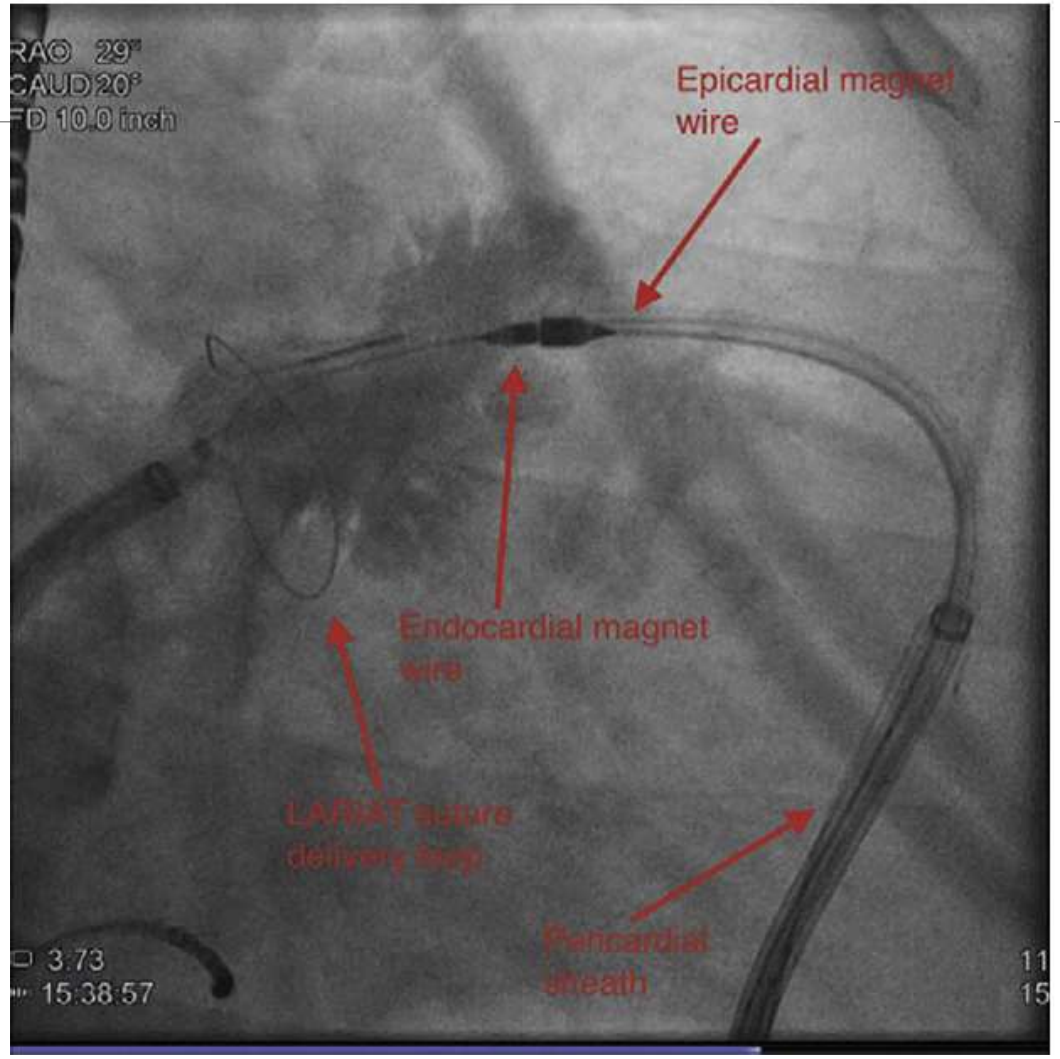






Left Atrial Appendage closure for Stroke Prevention





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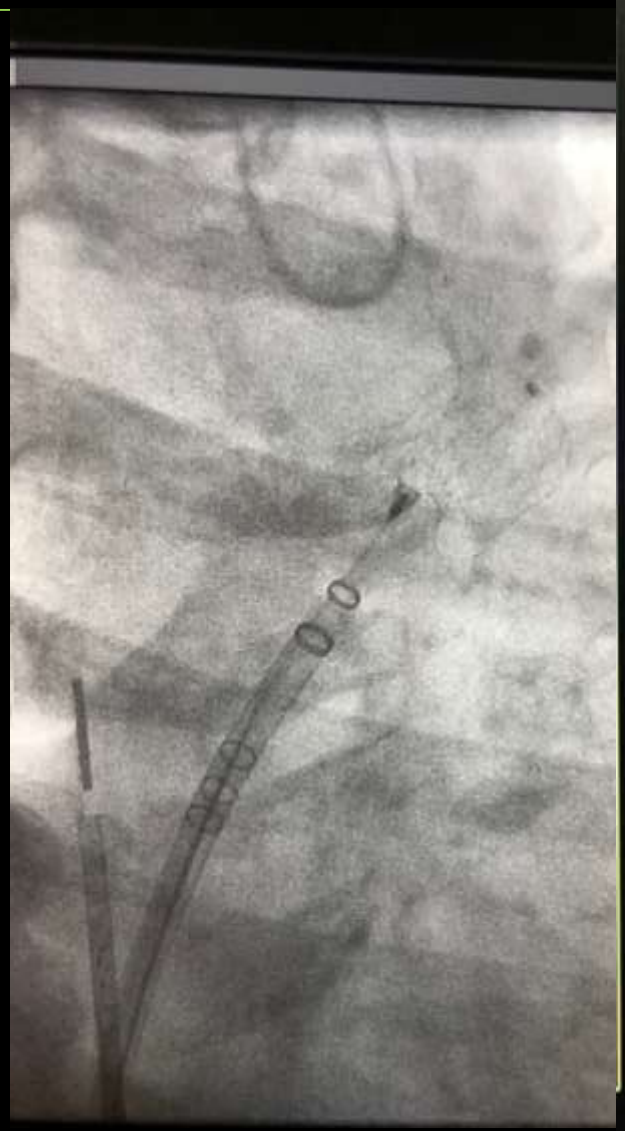

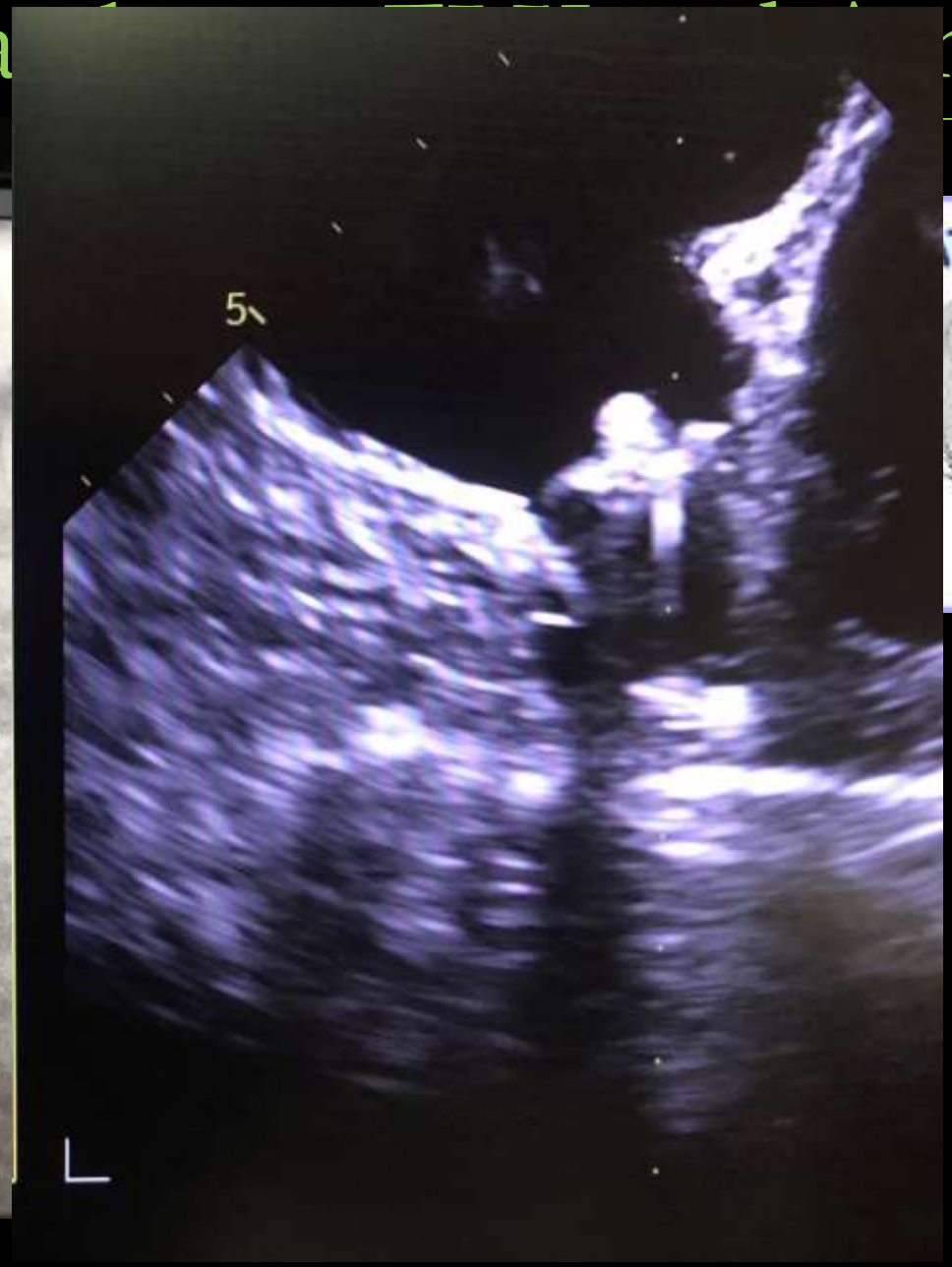

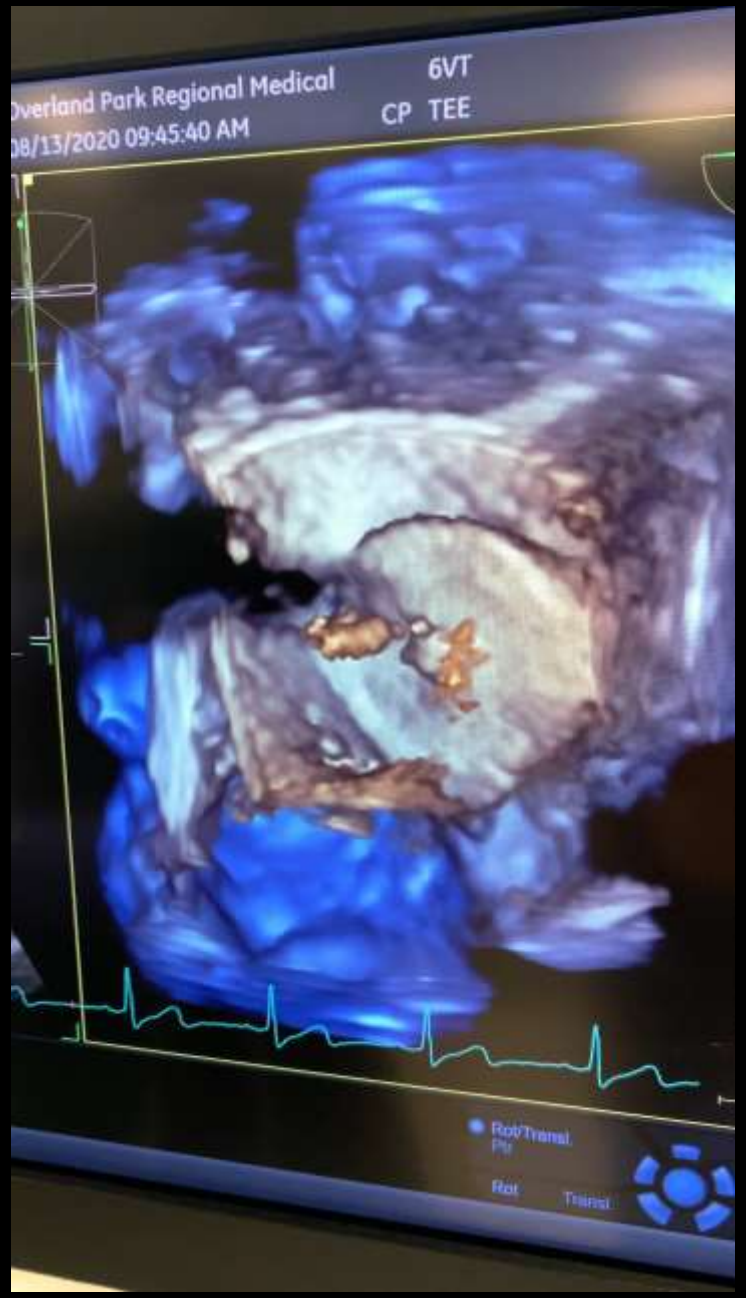
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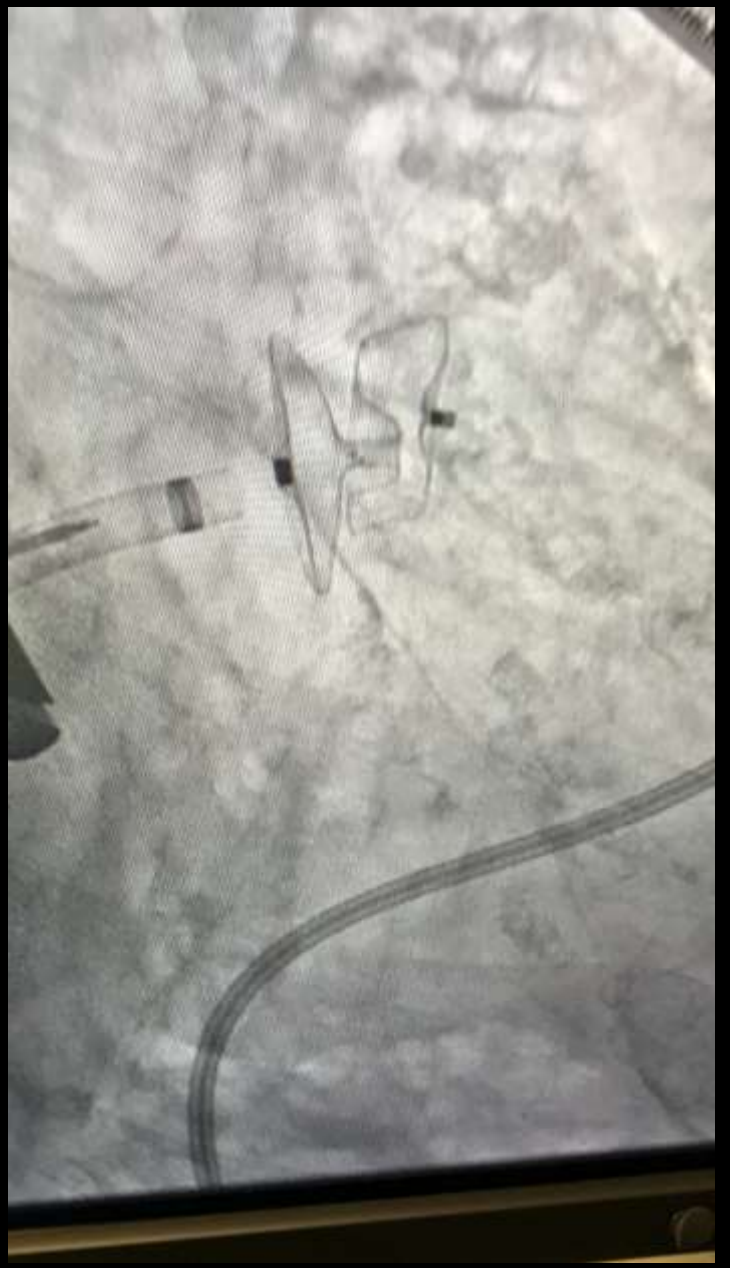
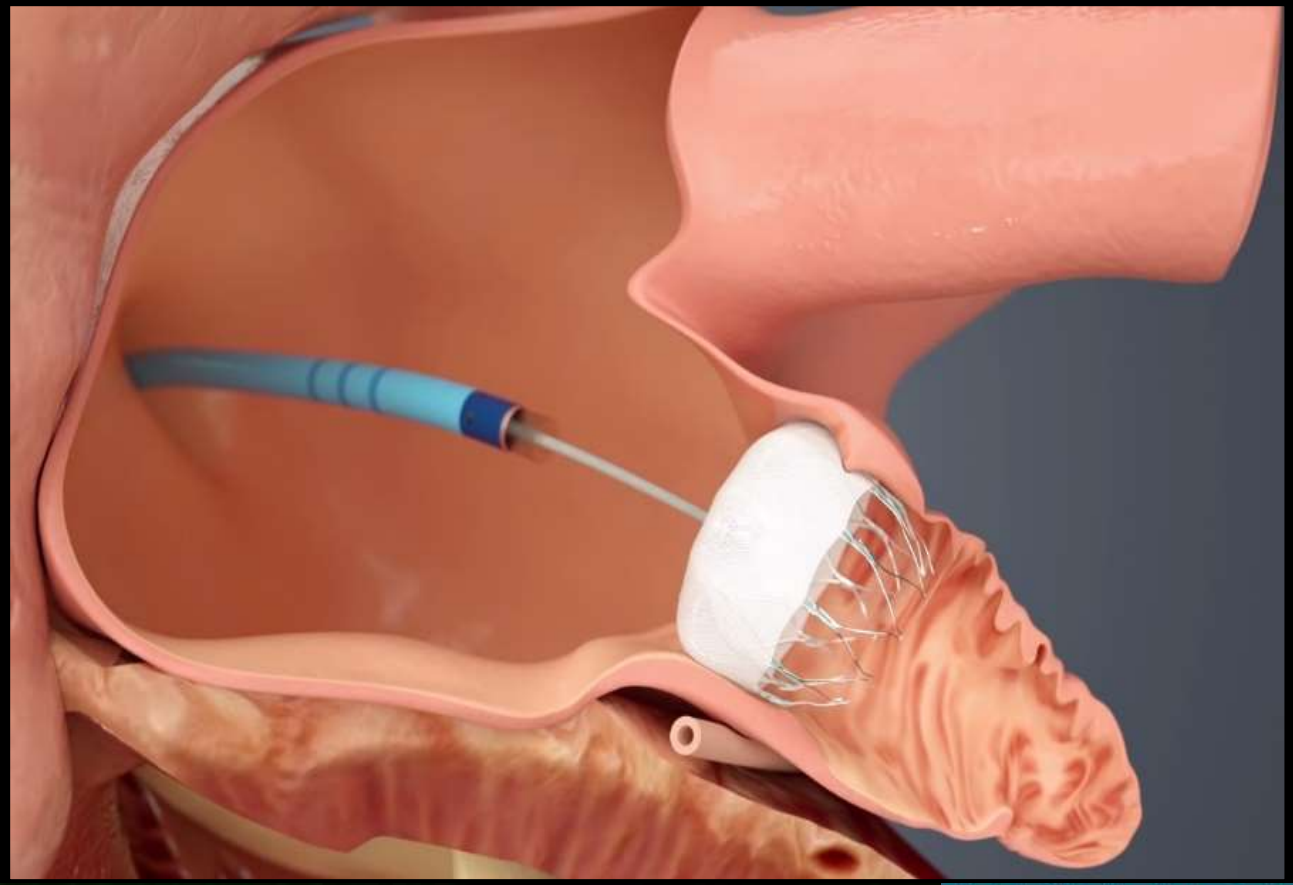


WATCHMAN™ Procedure

- One-time implant
- Performed in a cardiac EP Lab
- Performed by a heart team
  - EP or IC with transseptal and structural experience, 1 expert echocardiographer, general anesthesia, surgical back up, WATCHMAN Clinical Specialist
- Transfemoral Access: 14 F WATCHMAN Sheath advanced to the LAA via the femoral vein
- 1 hour procedure | 1 day hospital stay



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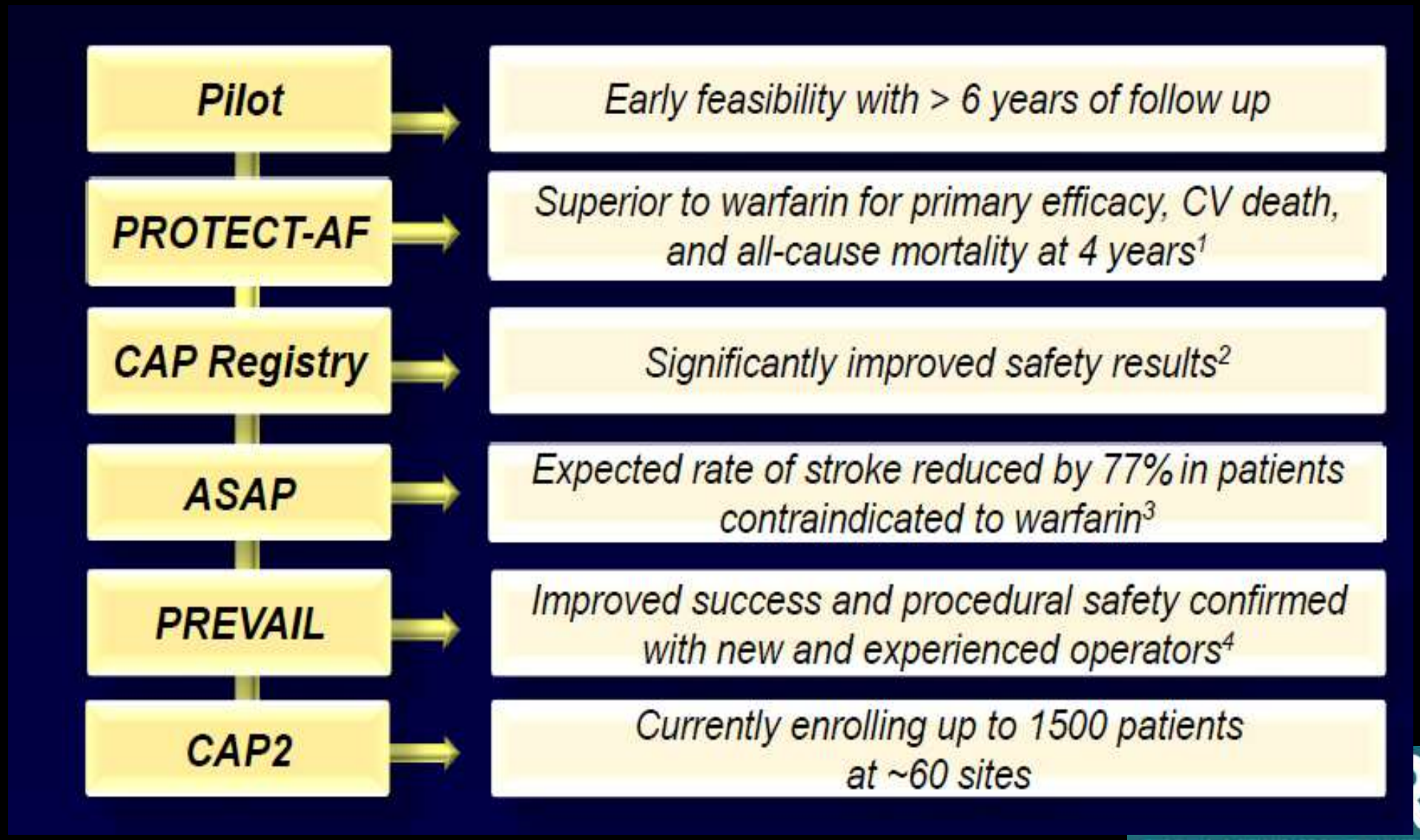
Watchman Clinical Studies

Over 2,000 patients with 4,800 patient years follow-up



Procedural Success and Risks: Commercial Experience

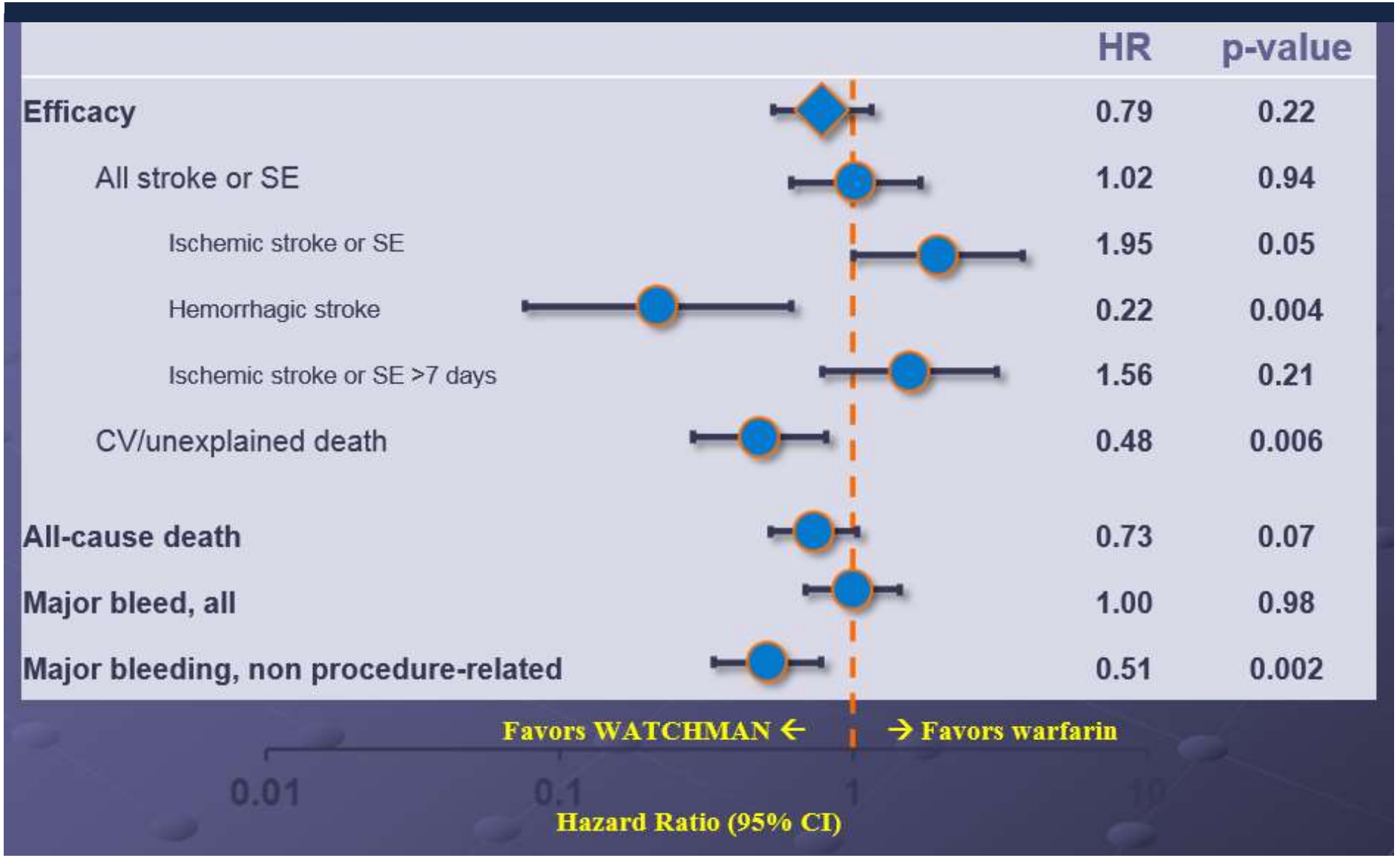
	Aggregate Clinical Data
Procedural Parameters	
No. of Procedures	6,720
Implantation Success, %	94.9%

	Aggregate Clinical Data
Complication Rates	
Periodical Tamponade	1.28%
Procedure-Related Stroke	0.18%
Device Embolization	0.25%
Procedure-Related Death	0.06%

Shah RU, Freeman JV, et al. JACC. 2012;59(2):143-149.
Reddy VY, Gibson DN, et al. JACC. 2016

Patient-Level Meta-analysis of PROTECT AF, PREVAIL, and CAP Registries

2,406 patients with 5,931 patient years of follow up. (Mean follow up 2.69 years)

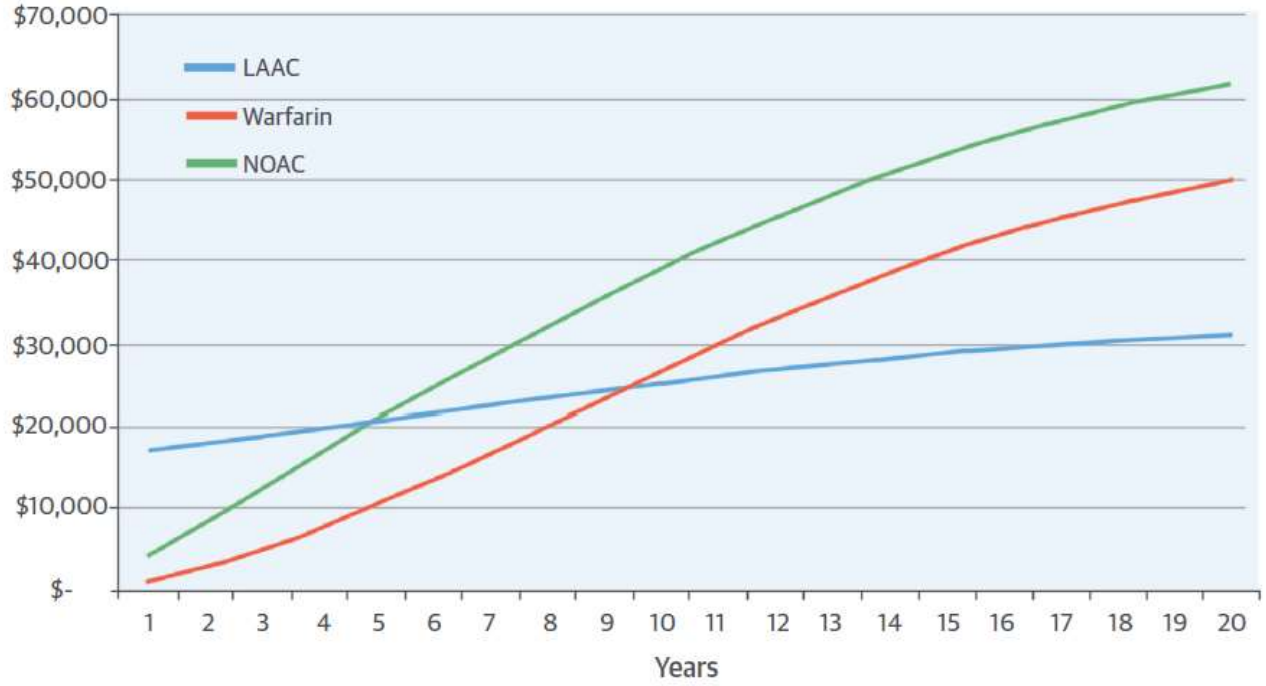


Holmes DR et al. J Am Coll Cardiol 2015;65:2614–23

Cost Effectiveness

- Both NOACs and LAAC with the Watchman device were cost-effective relative to warfarin
- Only LAAC demonstrated cost savings by year 10 relative to warfarin, and by year 5 relative to NOACs

CENTRAL ILLUSTRATION **Warfarin Versus NOACs Versus LAAC: Cumulative Cost and Time to Cost-Effectiveness Following Treatment Initiation**



	Time to Clinical Effectiveness (Incremental QALYs)	Time to Cost-Effectiveness (Cost per QALY)	Time to Dominance (More Effective, Less Costly)
LAAC vs. warfarin	Year 3 (0.015)	Year 7 ($42,994/QALY)	Year 10
NOACs vs. warfarin	Year 1 (0.008)	Year 16 ($48,446/QALY)	N/A
LAAC vs. NOACs	Year 5 (0.007)	Year 5 (Dominant)	Year 5

Reddy VY et al. J Am Coll Card 2015, 66(24), 2728-39

LAAC – Market Capture & Growth Opportunities

- At present, LAAC with WATCHMAN captures only 1% of the market in which it is indicated
- Tremendous room to improve patient care in this population
- Several new devices in horizon
- Expansion of indications with more data

LAAC – Summary

- A significant proportion of NVAF patients who need OAC are either not on it or cannot take it long-term
- LAA is primary source for NVAF-related thromboembolism
- Percutaneous LAAC is a promising alternative to anticoagulation in patients with NVAF at high risk for bleeding or having contraindications to OAC
- WATCHMAN: Only FDA-approved percutaneous LAAC device in the U.S. and has the most data
- Indication: **Moderate to high risk of stroke with appropriate rationale to seek alternative to long-term anticoagulation**
- Randomized trials have proved efficacy and safety of WATCHMANN compared to warfarin → Equivalent for total stroke; superior for hemorrhagic stroke and cardiovascular mortality
- Trials are underway to assess LAAC as first line therapy instead of OAC