UPDATES IN STRUCTURAL HEART

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FINANCIAL DISCLOSURES

- Speaker for Boston Scientific (Watchman)

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- Overview of aortic stenosis
- Overview of mitral valve disease
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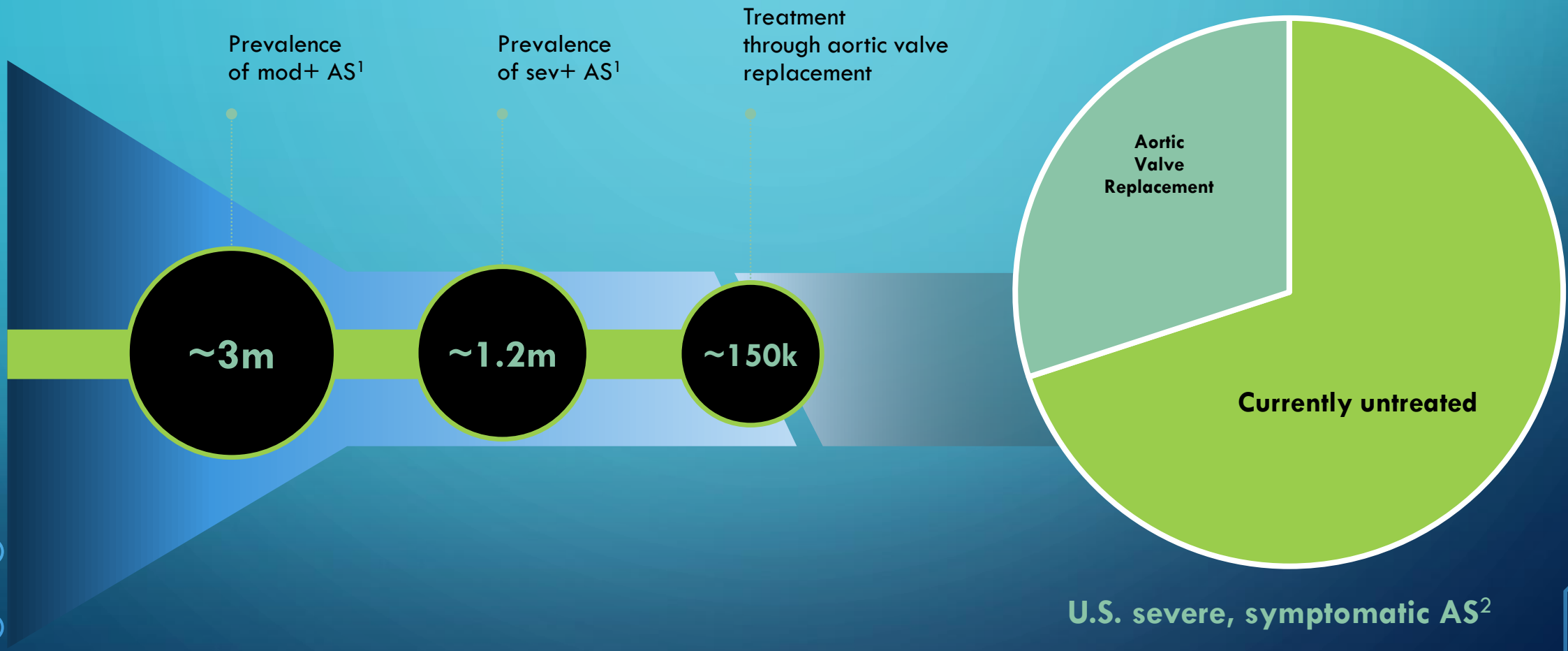
- ACC/AHA Guideline for patient selection evaluation for left atrial appendage closure (Watchman procedure)
- ACC/ AHA for patient selection and evaluation for PFO closure

HIGH NUMBER OF SEVERE AS PATIENTS REMAIN UNDERTREATED



1. Nkomo 2006, Iivanainen 1996, Aronow 1991, Bach 2007, 2019 internal estimates
2. Goldsweig, A. The Evolving Management of Aortic Valve Disease; 2019 internal estimates

ABOUT AORTIC STENOSIS

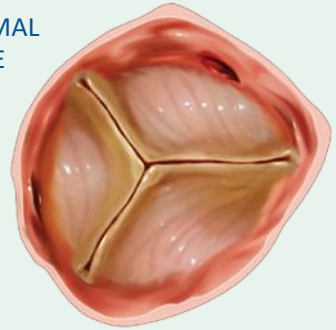
Aortic stenosis is the result of leaflet calcification or congenital stenosis with severely reduced leaflet opening.[1]

When an aortic valve becomes stenotic, it does not open properly, thus affecting the amount of oxygen-rich blood that leaves the heart with each beat.

Mechanism of stenosis is similar to atherosclerosis[3]

- Mainly solid calcium deposits within the valve cusps[2]
- Similar risk factors to coronary artery disease (CAD)[3]
- High coincidence of CAD and AS in same individual[2]
- Typically manifests itself in the sixth, seventh, and eighth decades of life[4]

NORMAL VALVE



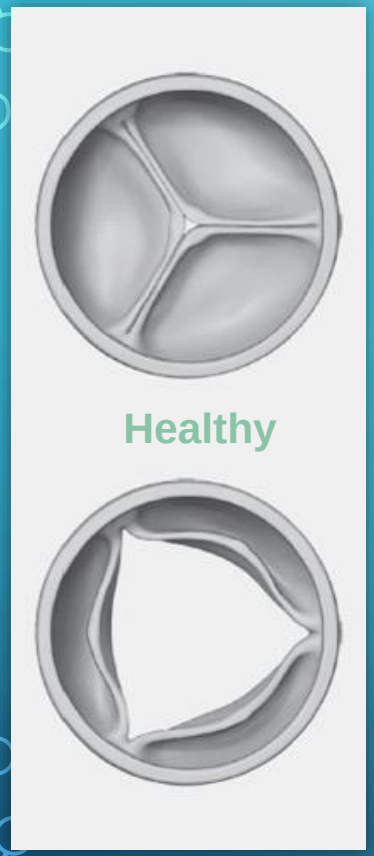
In a healthy aortic valve, three thin leaflets open and close properly.

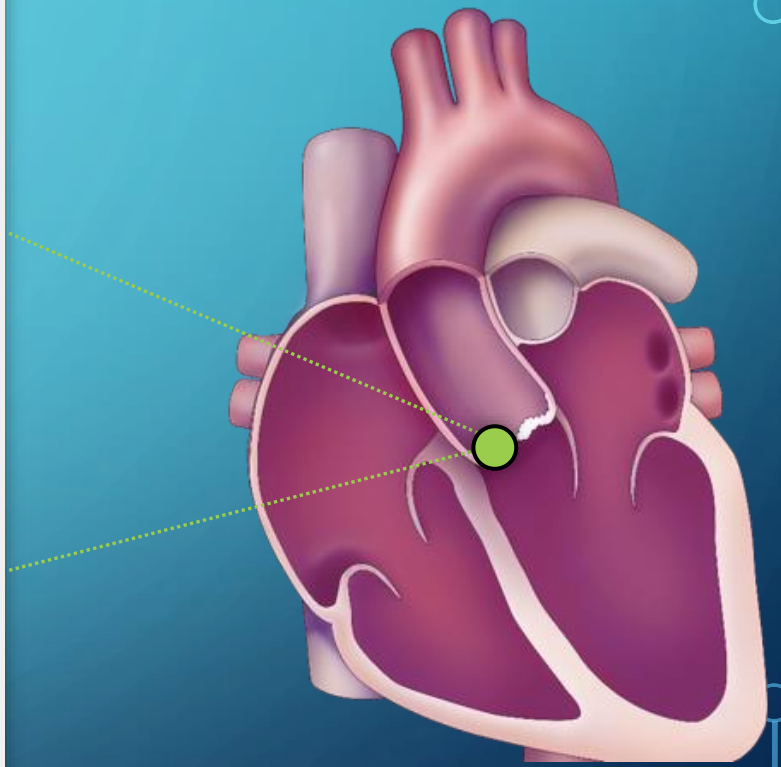
STENOTIC VALVE

In a diseased (stenotic) valve, the leaflets become stiff and thickened, making the heart work harder to pump blood to the body.

[1] Otto CM, et al. *Circulation*. 2021;43:e35-e71.
[2] Otto CM, et al. *N Engl J Med.* 1999;341:142-147.
[3] Mohler ER, et al. *Clin Cardiol.* 1991;14:995-999.
[4] Lindroos M, et al. *J Am Coll Cardiol.* 1993;21:1220-1225.

AORTIC STENOSIS IS A PROGRESSIVE DISEASE

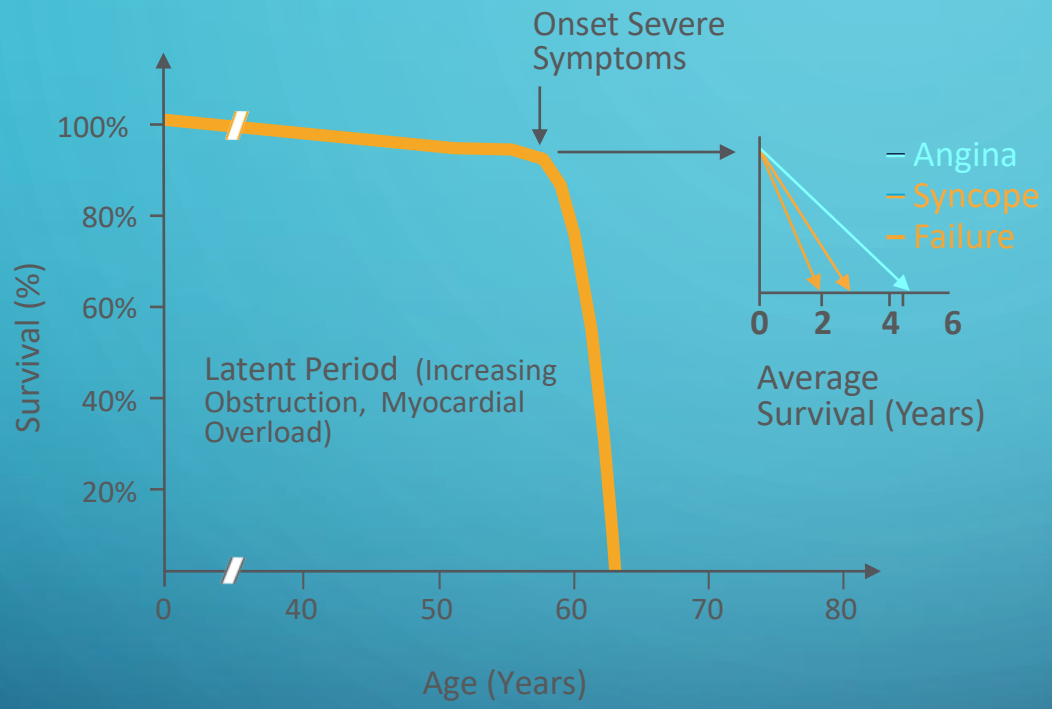




Aortic Stenosis: is a buildup of calcium deposits on the valve, which causes it to narrow and reduce blood flow to the rest of the body.

Images displayed are representative of aortic valves.

MEDICAL MANAGEMENT ISN'T ENOUGH



After developing symptomatic severe aortic stenosis, the average patient survival is two years without treatment.[1]

[1] Ross J Jr, et al. *Circulation*. 1968;38:61-67.

CRITERIA FOR AORTIC STENOSIS

ACC/AHA VHD Guidelines

Results of diagnostic tests will help determine if a patient has met the criteria for severe aortic stenosis.

ACC/AHA Guidelines Define Criteria for Severe AS[1]:

Indicator	Stage C: Asymptomatic (Severe)	Stage D: Symptomatic (Severe)
Jet velocity (m/s)	≥ 4.0	≥ 4.0
Mean gradient (mm Hg)	≥ 40	≥ 40
Valve area (cm^2)	≤ 1.0	≤ 1.0
Valve area index (cm^2/m^2)	≤ 0.6	≤ 0.6

Low-flow/low-gradient severe symptomatic AS with preserved LVEF is characterized by an aortic valve area < 1.0 cm^2, low mean gradient (< 40 mm Hg),and low flow (stroke volume index < 35 mL/m^2).

LF/LG symptomatic severe aortic stenosis (SSAS) is harder to identify but is just as important to diagnose and refer.

[1] Otto CM, et al. *Circulation*. 2021;43:e35-e71.

WITHOUT ACTION, RISK OF MORTALITY RISES

Survival after onset of symptoms for severe aortic stenosis (AS) is as low as **50% at two (2) years** and **20% at five (5) years.**[1]

Treatment is **critical** for survival.

Note: For historical series of patients before the availability of valve surgery and for a more recent series of patients who refused intervention for severe symptomatic AS

1. Otto CM. Timing of aortic valve surgery. Heart. 2000;84:211–21.

GUIDELINES SUMMARY **KEY CONSIDERATIONS**[1]

ACC/AHA VHD Guidelines

SEVERE AORTIC STENOSIS
Surgical risk stratification is no longer a factor for therapy selection.

SHARED DECISION-MAKING
between the patient and heart team will drive decisions based on lifetime risks and benefits of mechanical versus bioprosthesis and transcatheter versus surgical intervention.

"Patients with severe VHD should be evaluated by a multidisciplinary heart valve team when intervention is considered."

AGE
- 65 to 80 years of age and no anatomic contraindications to transfemoral TAVR, Class 1-A for SAVR, or transfemoral TAVR
- > 80 years of age or younger patients with life expectancy < 10 years and no anatomical contraindication to transfemoral TAVR Class 1-A

ANATOMY
- Transfemoral access is preferred for all patients considered for TAVR Class 1-A
- Coronary ostial heights, valve anatomy, and annular size should be considered

DURABILITY
- The balance between expected patient longevity and valve durability varies continuously across the age range, with a more durable valve preferred for patients with a longer life expectancy

[1] Otto CM, et al. *Circulation*. 2021;43:e35-e71.

2020 AHA/ACC GUIDELINE RECOMMENDATIONS

Today's guideline reflect the latest low-risk approval, with ***recommendations focusing on age and shared-decision making*** instead of risk.

2020 AHA/ACC guideline
on intervention recommendations by age

For symptomatic patients with severe AS and have no anatomic contraindication to transfemoral TAVR/I

Indications for TAVR/I are expanding as a result of multiple randomized trials, including the latest PARTNER trials, which are reflected in these recommendations.

Recommendations shift their focus

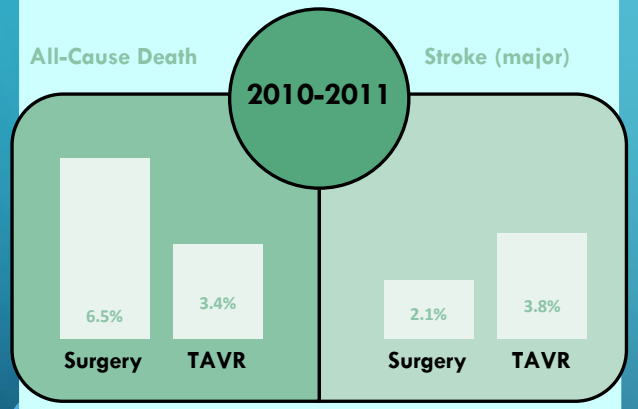
2014	2020
• Recommendations for choice of intervention were based primarily on level of surgical risk	• Only use risk score to eliminate SAVR as an option for high or prohibitive risk patients
• Prohibitive, high, intermediate, and low	• Utilize age as a key factor
	• Emphasizes a shared decision-making process that accounts for the patient's values and preferences

1. 2020 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease

PARTNER TRIALS HAVE MADE AN IMPACT ON TAVR GUIDELINES OVER THE YEARS

High
surgical risk

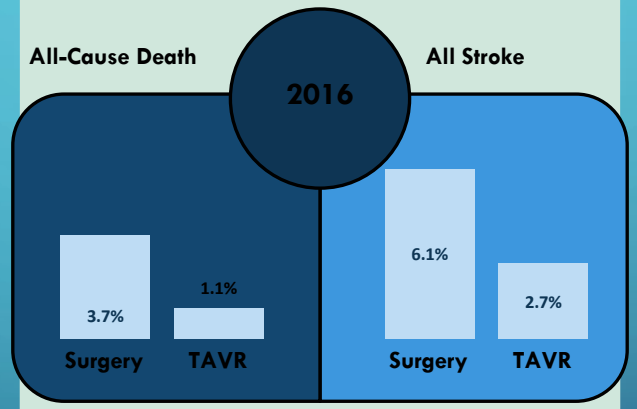
PARTNER I Trial
30-day outcomes



FDA indication
Prohibitive risk: 2011/High risk: 2012

Intermediate
surgical risk

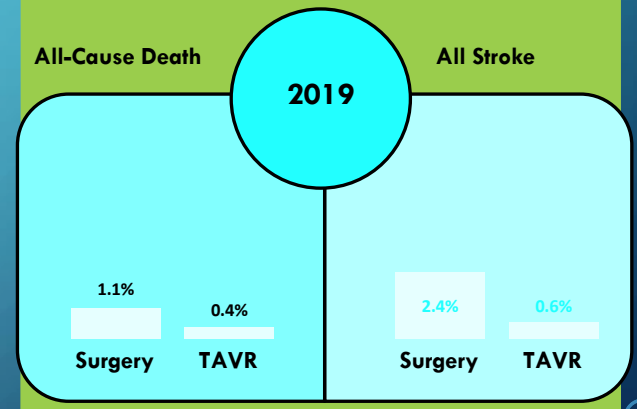
PARTNER IIA Trial
30-day outcomes



FDA indication
2016

Low
surgical risk

PARTNER 3 Trial
30-day outcomes



FDA indication
2019

DIAGNOSTICS AND TIMING OF AORTIC VALVE REPLACEMENT (AVR)[1]

ACC/AHA VHD Guidelines

Diagnostic Testing: Initial Diagnosis

Class of Recommendation (COR)	Level of Evidence (LOE)	RECOMMENDATIONS
1	A	In patients with signs or symptoms of AS or a BAV, TTE is indicated for accurate diagnosis of the cause of AS, assessment of hemodynamic severity, measurement of LV size and systolic function, and determination of prognosis and timing of valve intervention.
1	B-NR	In patients with suspected low-flow, low-gradient severe AS with normal LVEF (Stage D3), optimization of blood pressure control is recommended before measurement of AS severity by TTE, TEE, cardiac catheterization, or CMR.
2a	B-NR	In patients with suspected low-flow, low-gradient severe AS with reduced LVEF (Stage D2), low-dose dobutamine stress testing with echocardiographic or invasive hemodynamic measurements is reasonable to further define severity and assess contractile reserve.
2a	B-NR	In patients with suspected low-flow, low-gradient severe AS with normal or reduced LVEF (Stages D2 and D3), calculation of the ratio of the outflow tract to aortic velocity is reasonable to further define severity.
2a	B-NR	In patients with suspected low-flow, low-gradient severe AS with normal or reduced LVEF (Stages D2 and D3), measurement of aortic valve calcium score by CT imaging is reasonable to further define severity.

Timing of Intervention

Class of Recommendation (COR)	Level of Evidence (LOE)	RECOMMENDATIONS
1	A	In adults with severe high-gradient AS (Stage D1) and symptoms of exertional dyspnea, HF, angina, syncope, or presyncope by history or on exercise testing, AVR is indicated.
1	B-NR	In asymptomatic patients with severe AS and an LVEF < 50% (Stage C2), AVR is indicated.
1	B-NR	In asymptomatic patients with severe AS (Stage C1) who are undergoing cardiac surgery for other indications, AVR is indicated.
1	B-NR	In symptomatic patients with low-flow, low-gradient severe AS with reduced LVEF (Stage D2), AVR is recommended.
1	B-NR	In symptomatic patients with low-flow, low-gradient severe AS with normal LVEF (Stage D3), AVR is recommended if AS is the most likely cause of symptoms.

AVR = aortic valve replacement by either surgical or transcatheter approach; VKA = vitamin k antagonists; C-EO = Expert Opinion; B-R = Randomized; B-NR = Nonrandomized

Note: The chart corresponds to the Class of Recommendation on Page 18-19 of Guidelines.

See the full tables in section 3.0 of the 2020 ACC/AHA Guidelines.

[1] Otto CM, et al. *Circulation*. 2021;43:e35-e71.

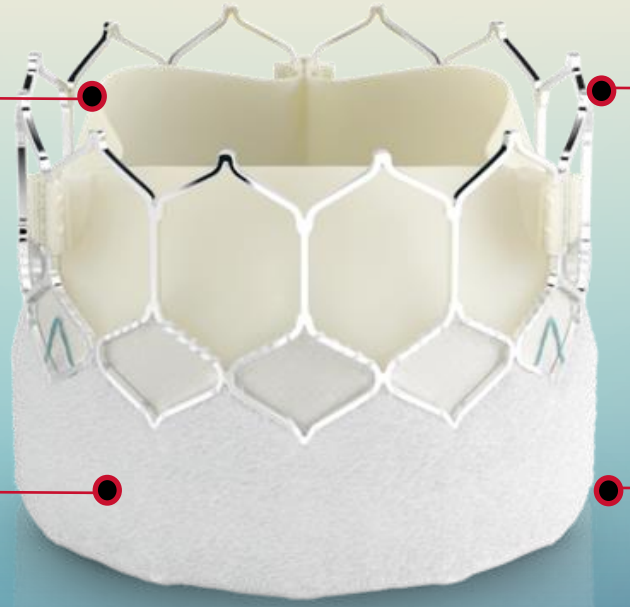
THE VALVE YOU TRUST FOR ALL RISK LEVELS

Bovine pericardial tissue

Utilizes the same bovine pericardial tissue and processes as the Edwards surgical valves

Accommodate patient anatomy

Range in valve sizes accommodates multiple patient anatomies. Available in 20, 23, 26 and 29 mm.



Edwards SAPIEN 3 Ultra valve

Future coronary access

Low frame height facilitates coronary access should your patients need a future procedure

Minimize PVL with larger skirt

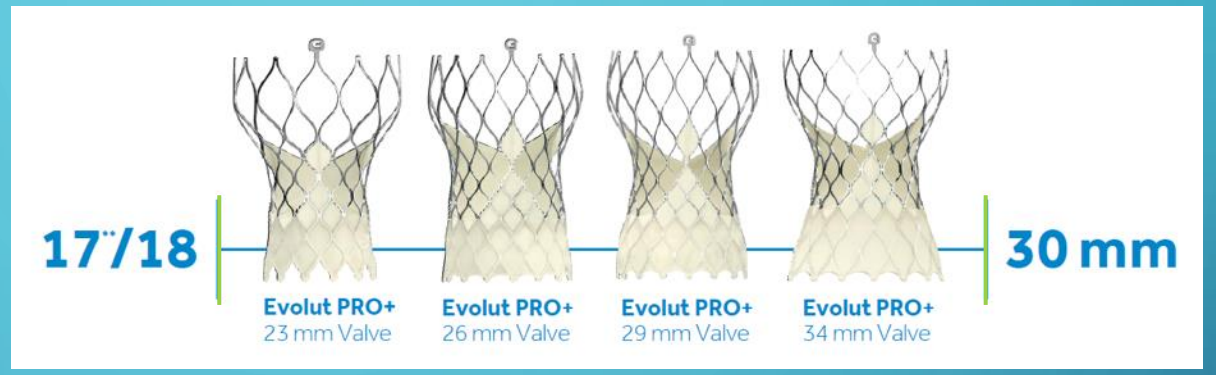
Large skirt made with textured PET material designed to minimize PVL

With TAVR, your guidance considers their needs today and tomorrow

ACCESS MORE PATIENTS

Treat More Patients

The Evolut™ PRO+ system is the only TAVR platform indicated to treat annulus ranges up to 30 mm diameter and has the ability to treat the broadest annulus range† of any commercially available TAVR system.



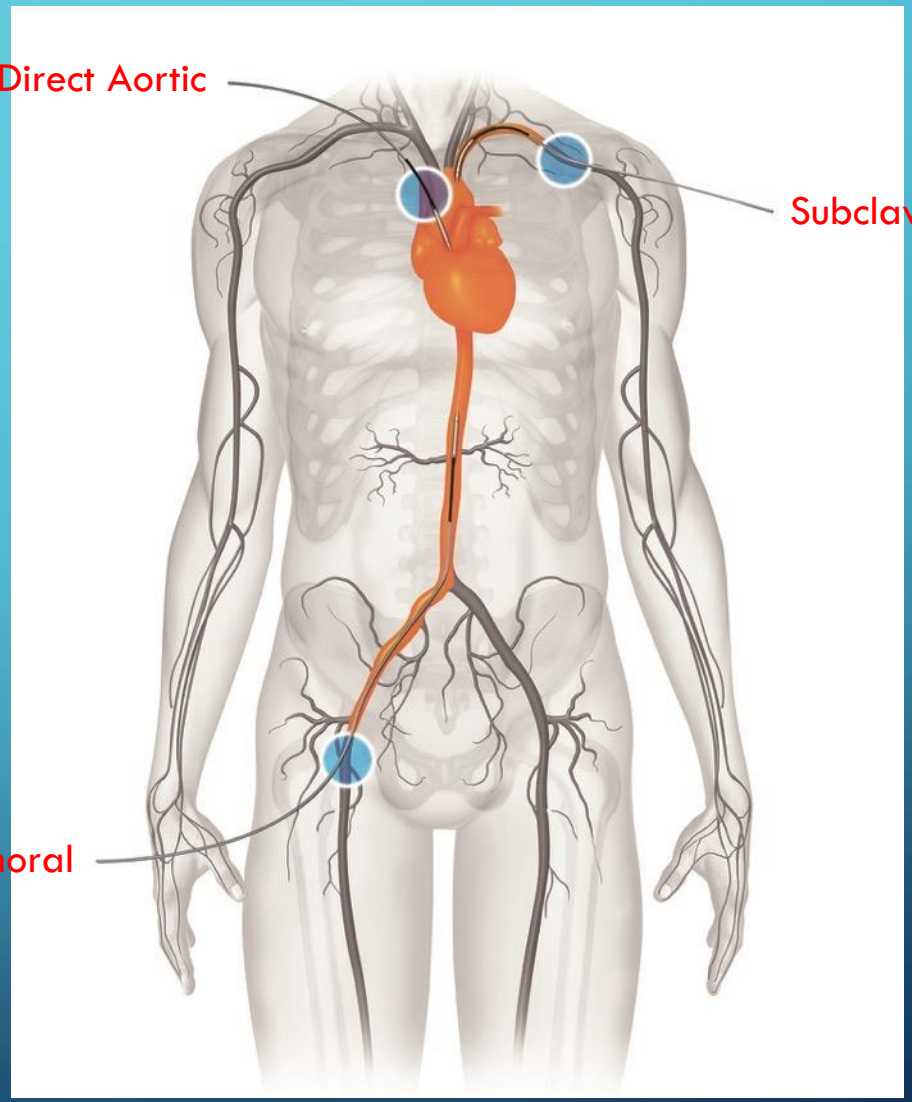
Lowest Delivery Profile

The Evolut system retains its outer diameter as it enters the vessel and remains at this diameter as it is advanced to the annulus.

Evolut PRO+ 23/26/29 mm TAV	Evolut PRO+ 34 mm TAV
≥ 5.0 mm Treatable Access Vessel Diameter	≥ 6.0 mm Treatable Access Vessel Diameter
6.0 mm Outer Diameter Capsule	7.33 mm Outer Diameter Capsule

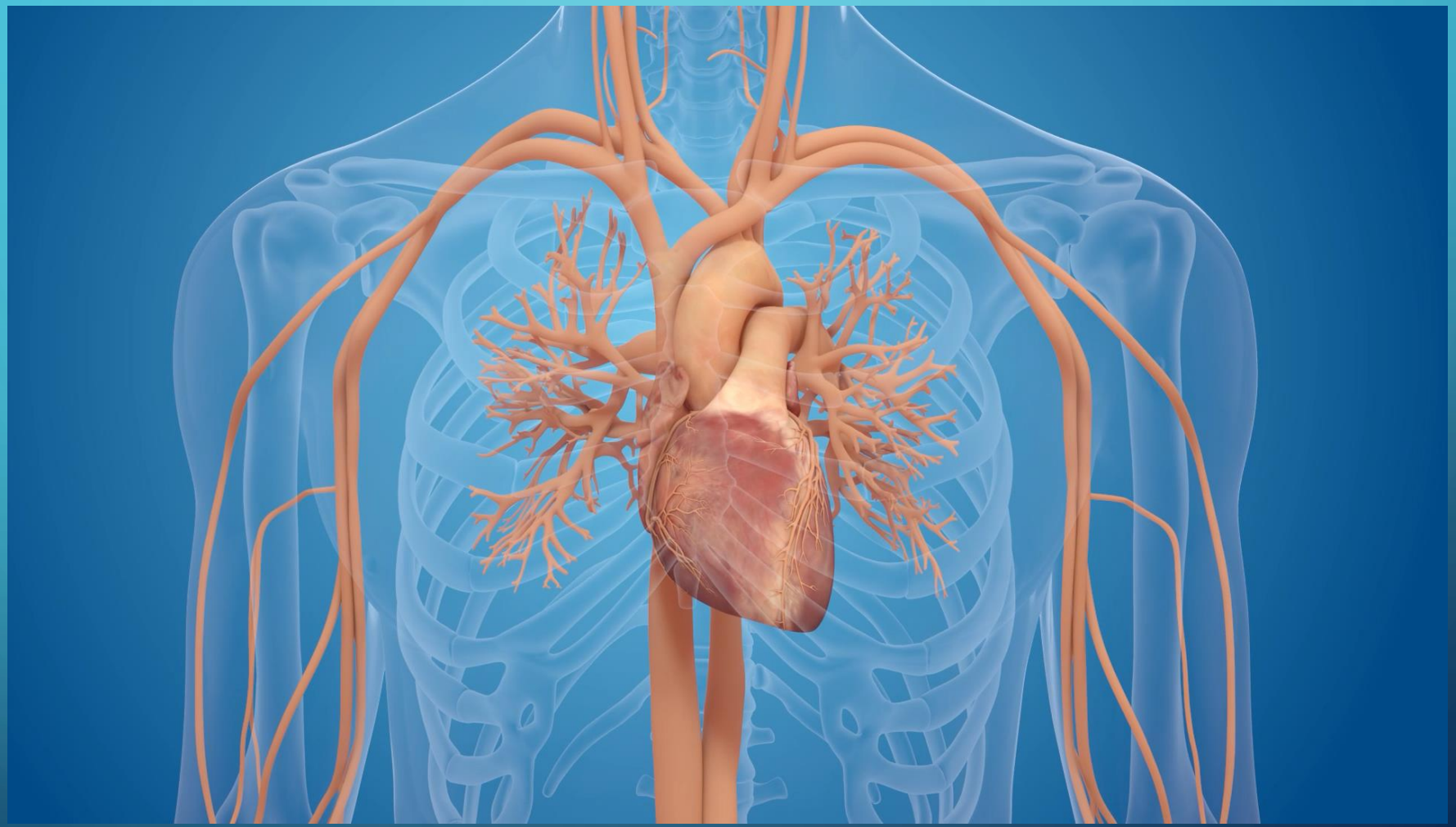
†Broadest annulus range based on CT-derived diameters.
¨Measurement for TAV-in-SAV only.

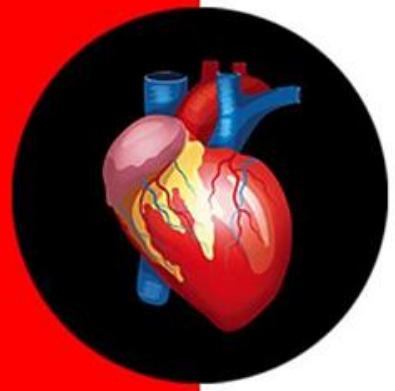
MEDTRONIC TAVR MOST COMMON ACCESS OPTIONS



To view the complete Evolut™ TAVR Instructions for Use, visit: manuals.medtronic.com.

A CLOSER LOOK AT TAVR PROCEDURE





TAVR:

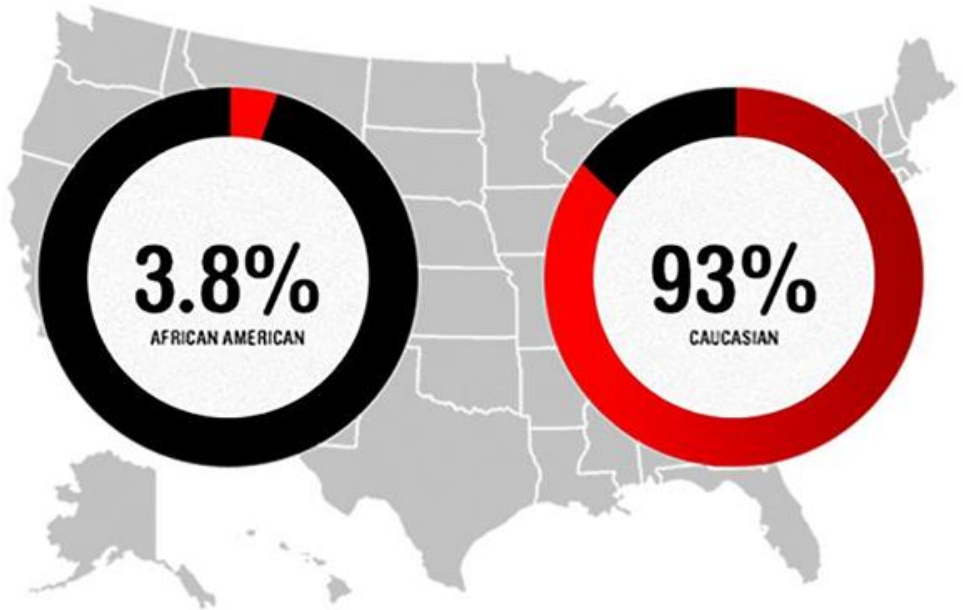
HEALTH CARE DISPARITIES

ATM ANNALS OF TRANSLATIONAL MEDICINE
AN OPEN ACCESS JOURNAL COVERING ALL SUBSPECIALTIES OF TRANSLATIONAL MEDICINE

EVOLUTION OF TAVR

TAVR continues to be an expanding and improving alternative to open heart surgery with over 58,000 patients in the US getting this procedure as of 2016.

The number of TAVR procedures performed has **DOUBLED** annually from 2012-2014 and increased by 8,000 from 2014 to nearly 25,000 in 2015. However...



RACIAL DISPARITIES IN TAVR IMPLANTATION

The percentage of African-American patients who received this therapy from 2012-2015 remained at 3.8% compared to 93% in Caucasians.

This disparity in implantation of TAVRs in non-Caucasian, especially the AA population has been attributed to several factors, including:

- **LACK OF PHYSICIAN TRUST AMONG MINORITIES**
- **LOWER LIKELIHOOD TO BE REFERRED FOR SPECIALIZED PROCEDURES**
- **LOWER INSURANCE RATES AND POORER SOCIOECONOMIC STATUS**

The previous listed percentages were not solely due to an increased geographical density of Caucasians in centers that offer this therapy: a single center study done in a large urban area in the US with a relatively large AA population (37%) showed only 10% of those who received TAVRs were AA's compared to 90% Caucasians.

EXPLAINING THE DISPARITIES

INSURANCE COMPANIES

Due to the private and often "for-profit" nature of the American health care industry, insurance companies are not willing to cover expensive procedures regardless of the benefits previously explained.

LANGUAGE BARRIERS

Many uninsured minorities less than 65 with severe AS, may be unaware of their eligibility for government support programs such as Medicaid.

Almost 70-80% of uninsured Hispanic and African American children are eligible for Medicaid and other programs.

SPECIALIST REFERRALS

African American patients with severe AS were less likely to be referred to Cardiology, more likely to decline intervention, or be lost to follow-up.

African Americans are at INCREASED risk for earlier onset of AS, making it even more important to seek care.

CULTURE & KNOWLEDGE

Manifestation of these cultural differences include the following:

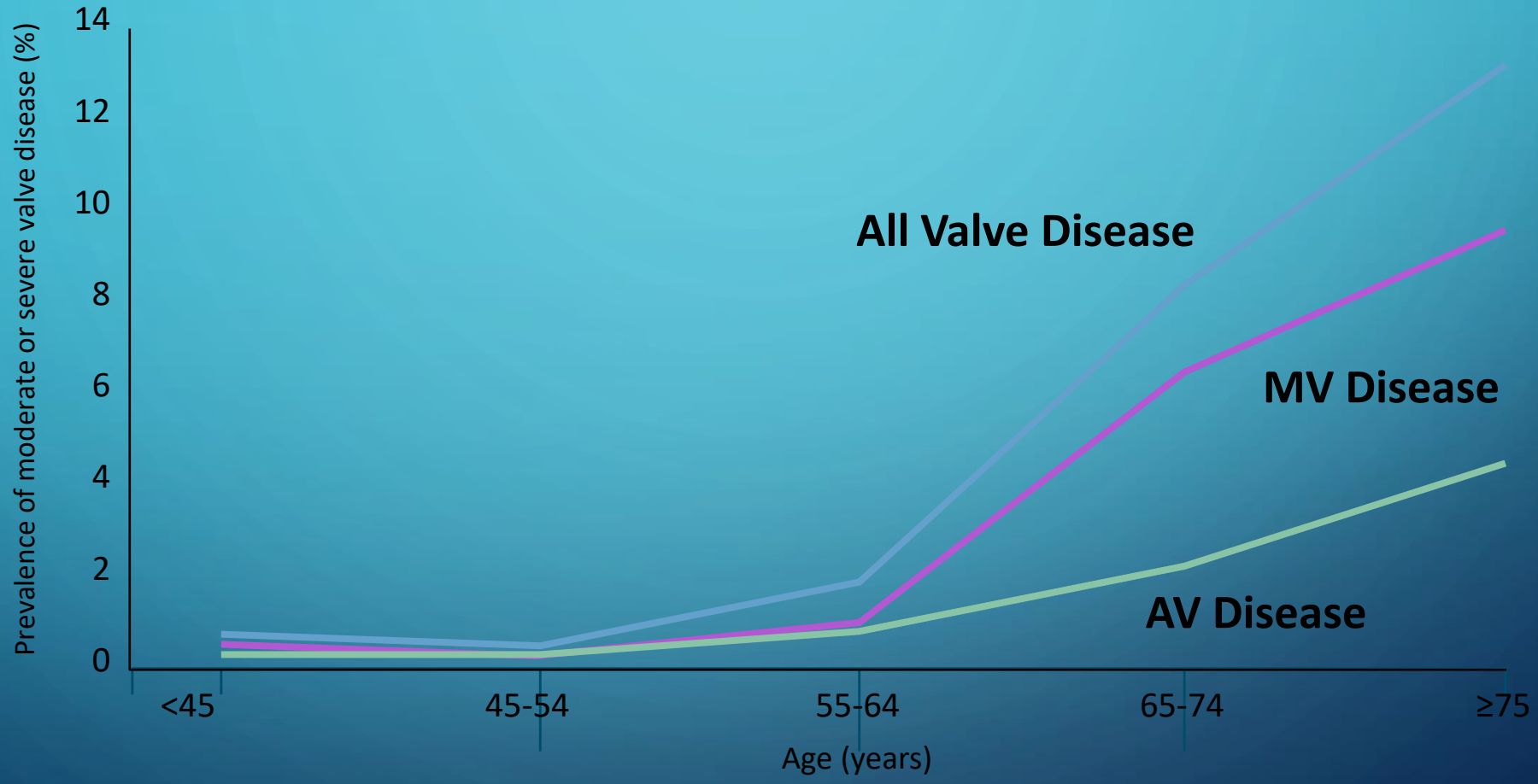
- SEEKING CARE LATE
- LATE SYMPTOM RECOGNITION AND INTERVENTION
- PERCEPTION OF BEING "TOO OLD" FOR TAVR
- FAMILY DECISION MAKING

HOW CAN WE REDUCE DISPARITIES IN TAVR?

- Advocate widespread outreach in multilingual pamphlets and programs encouraging health insurance and health seeking behaviors among minorities.
- Encourage early specialty referrals for minorities, recommend minority patients to get health insurance or be covered by support programs and lobby for the acceptance of these patients into specialist practices.
- Increase the education of minority patients and their extended family members about the procedure and potential benefits and risks.
- Intentionally increase the numbers of minorities involved in clinical trials.

PREVALENCE OF MITRAL VALVE DISEASE

MITRAL VALVE DISEASE IS 2-3X AORTIC VALVE DISEASE



Nkomo, et al. Lancet. 2006; 368: 1007

MITRAL REGURGITATION IS CLASSIFIED INTO 2 TYPES

MR occurs when the mitral valve fails to close completely, causing blood flow to move backward into the left atrium[1]

PRIMARY VALVE ABNORMALITY

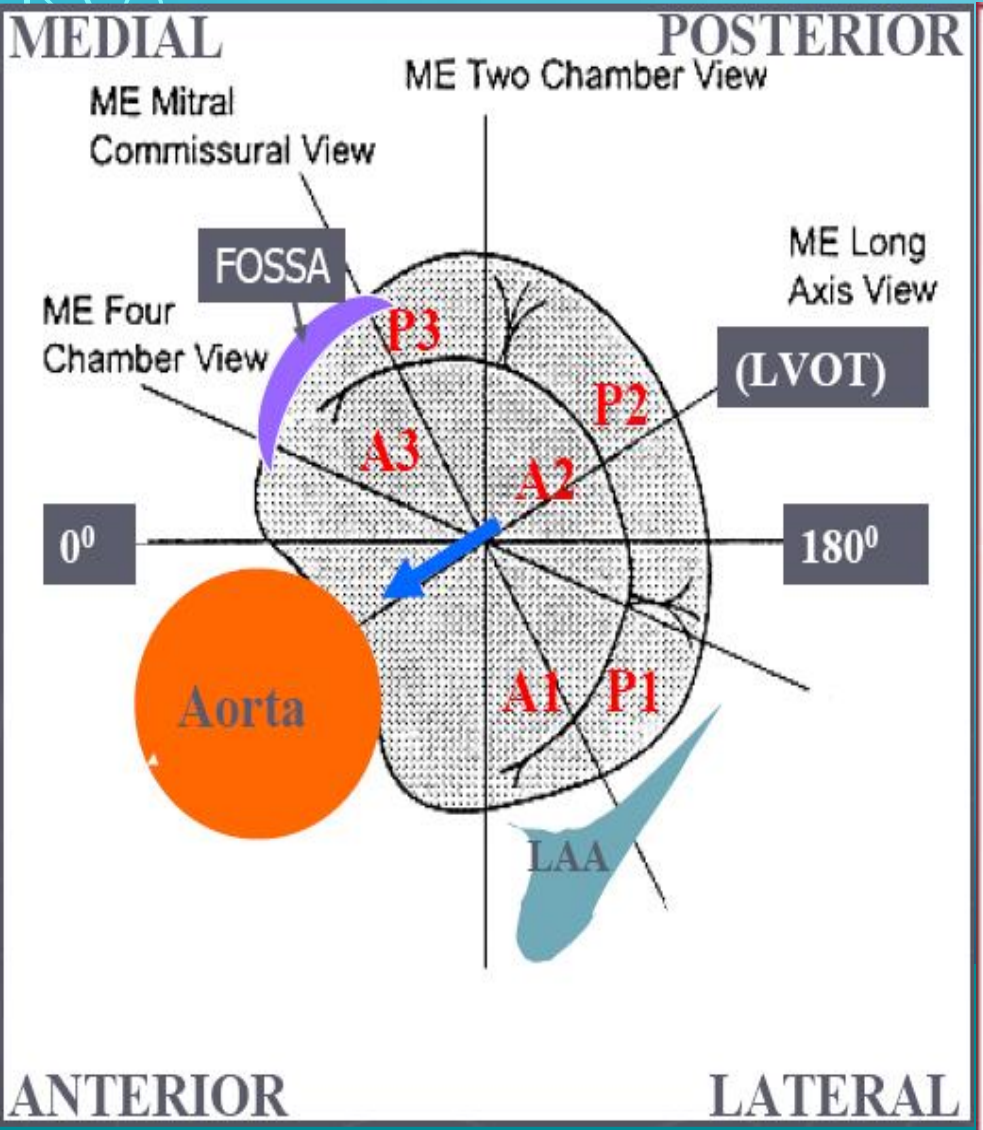
- Leaflets
- Subvalvular apparatus
- Chordae and papillary muscles

SECONDARY - LEFT VENTRICLE DILATION

- Leaflet tethering
- Mitral annular dilation
- Incomplete coaptation of the mitral valve

1. Mayo Clinic Staff. Mitral valve regurgitation: symptoms and causes. The Mayo Clinic. http://www.mayoclinic.org/diseases-conditions/mitral-valve-regurgitation/symptoms-causes/dxc-20121850. Published March 22, 2016. Accessed July 28, 2016

Etiology of Chronic MR
Carpentier Classification System



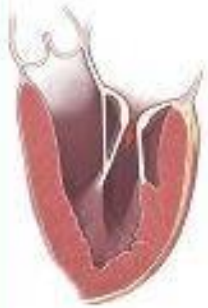
Type I

Normal motion

Annular dilatation
Annular deformation
Perforation of leaflets
Clefts in leaflets

Type IIIA

Restricted motion
(Retraction)



Thickening of leaflets
Retraction of leaflets
Thickening of chordae
Retraction of chordae
Fusion of chordae
Calcification
Fusion of commissures
Ventricular fibrosis

Type II — **Primary Degenerative**

Excess motion

Myxamotous degeneration
Elongation of chordae
Rupture of chordae
Elongation of papillary muscle
Rupture of papillary muscle

Type IIIB — **Secondary Functional Systole Only**

Restricted motion
(Apical displacement)

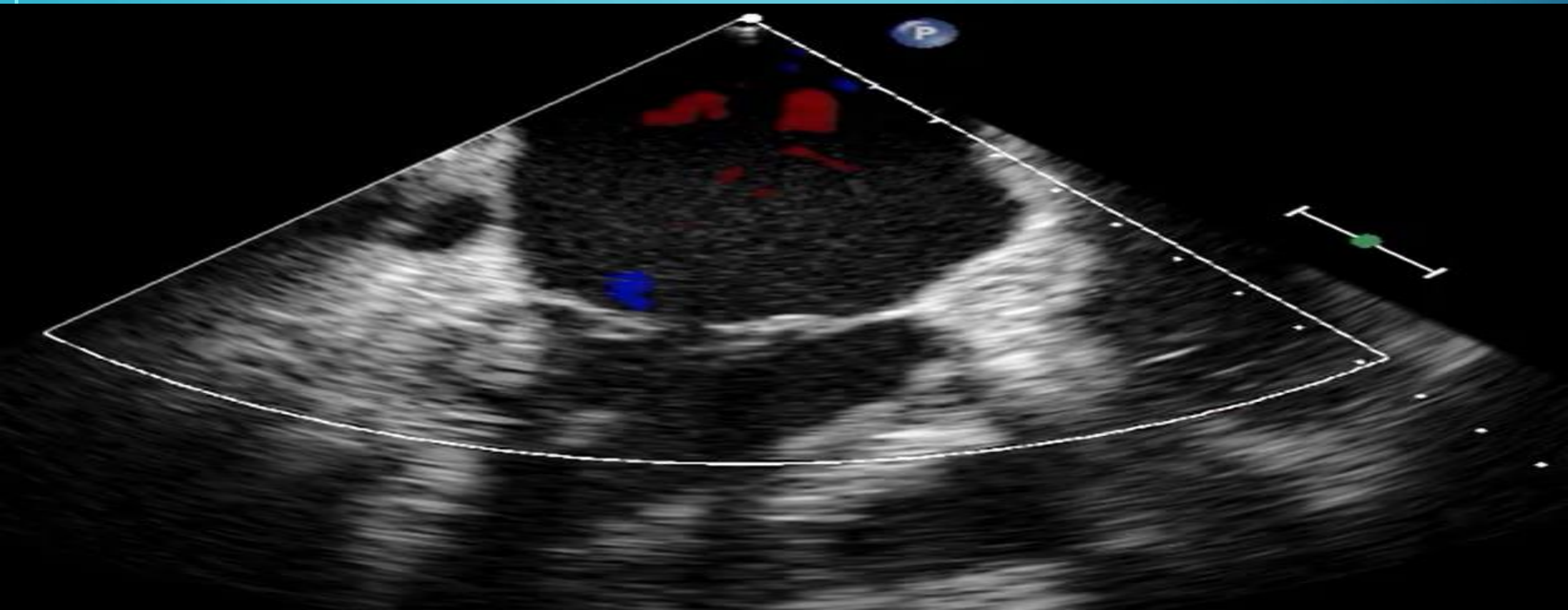
Tethering of leaflets
Papillary displacement
Ventricular dilatation
Ventricular aneurysm
Ventricular fibrosis

CARPENTIER I

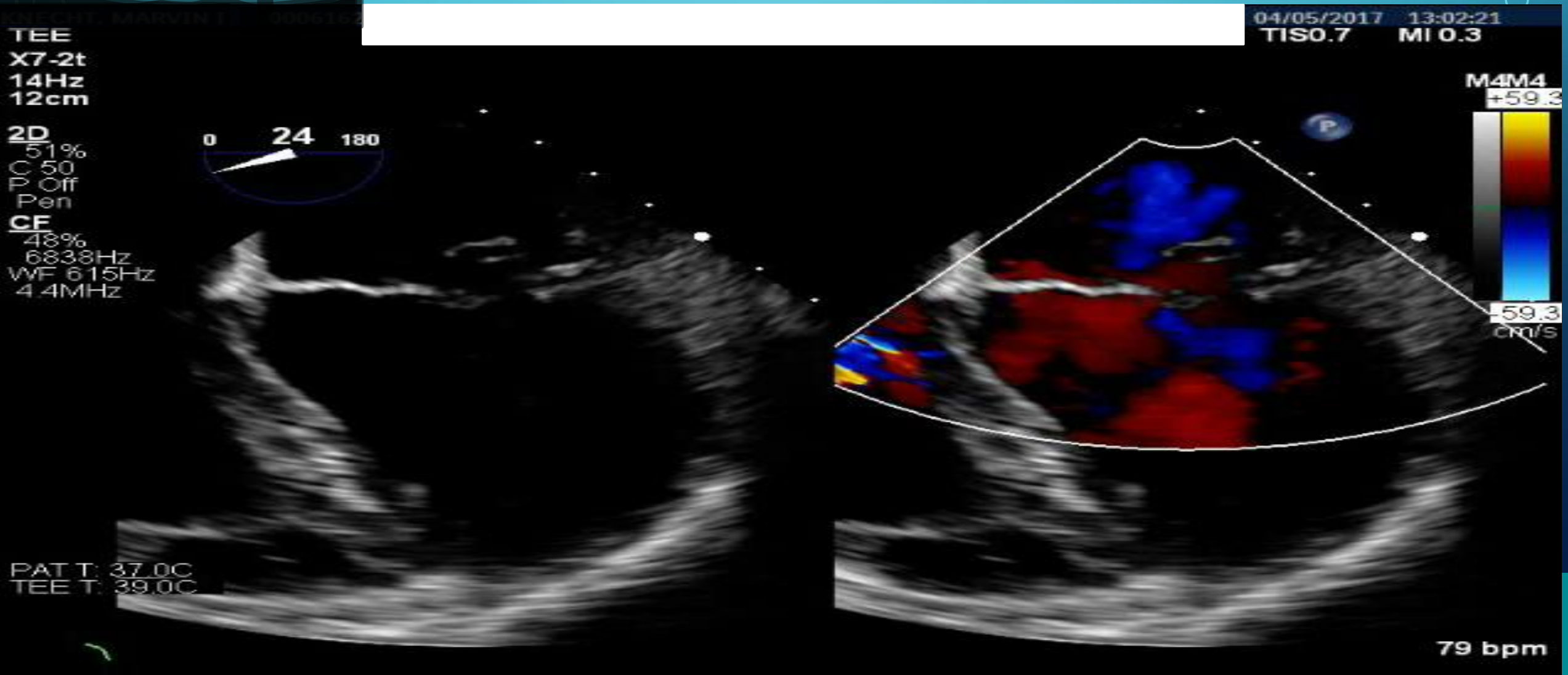
ANNULAR DILATION FROM LA ENLARGEMENT

SECONDARY ETIOLOGY THOUGH LESS RESPONSIVE TO MEDICAL THERAPY

IF FAILS DIURETICS THEN REPAIR/REPLACE



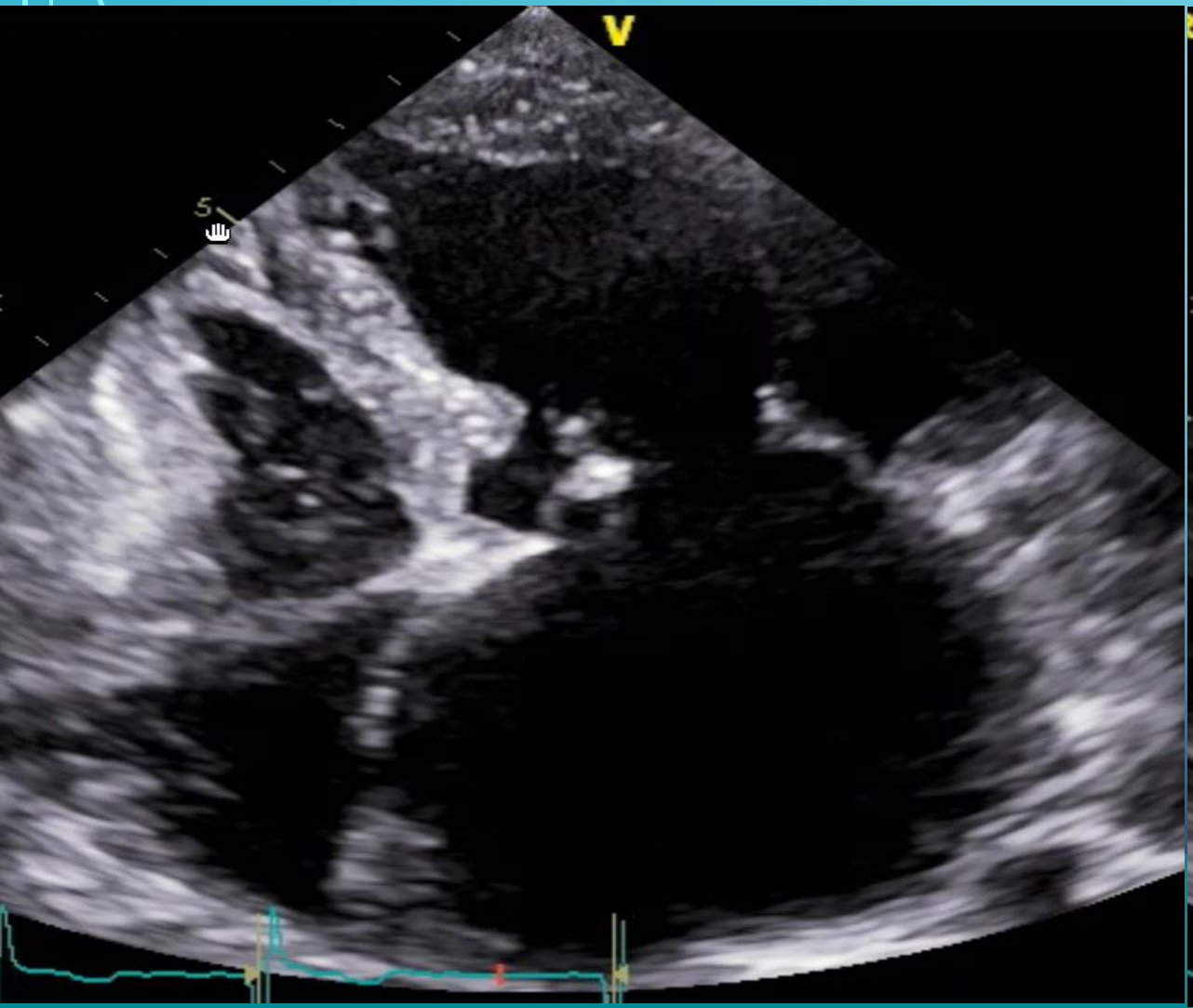
CARPENTIER II
POSTERIOR LEAFLET PROLAPSE / FLAIL
PRIMARY ETIOLOGY -REPAIR FIRST LINE THERAPY

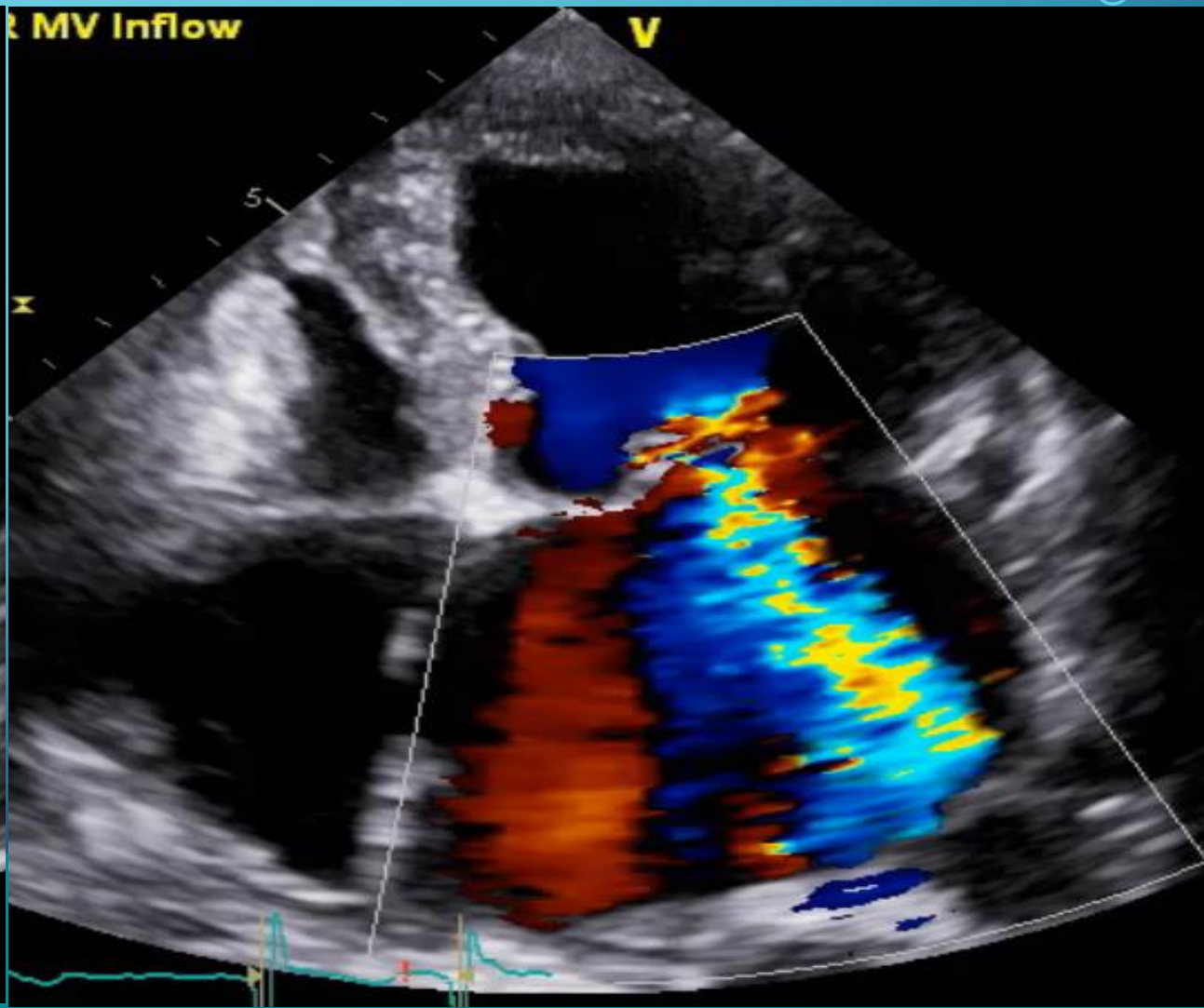


CARPENTIER IIIA

RHEUMATIC DISEASE

PRIMARY ETIOLOGY BUT ONLY THERAPY IS REPLACEMENT

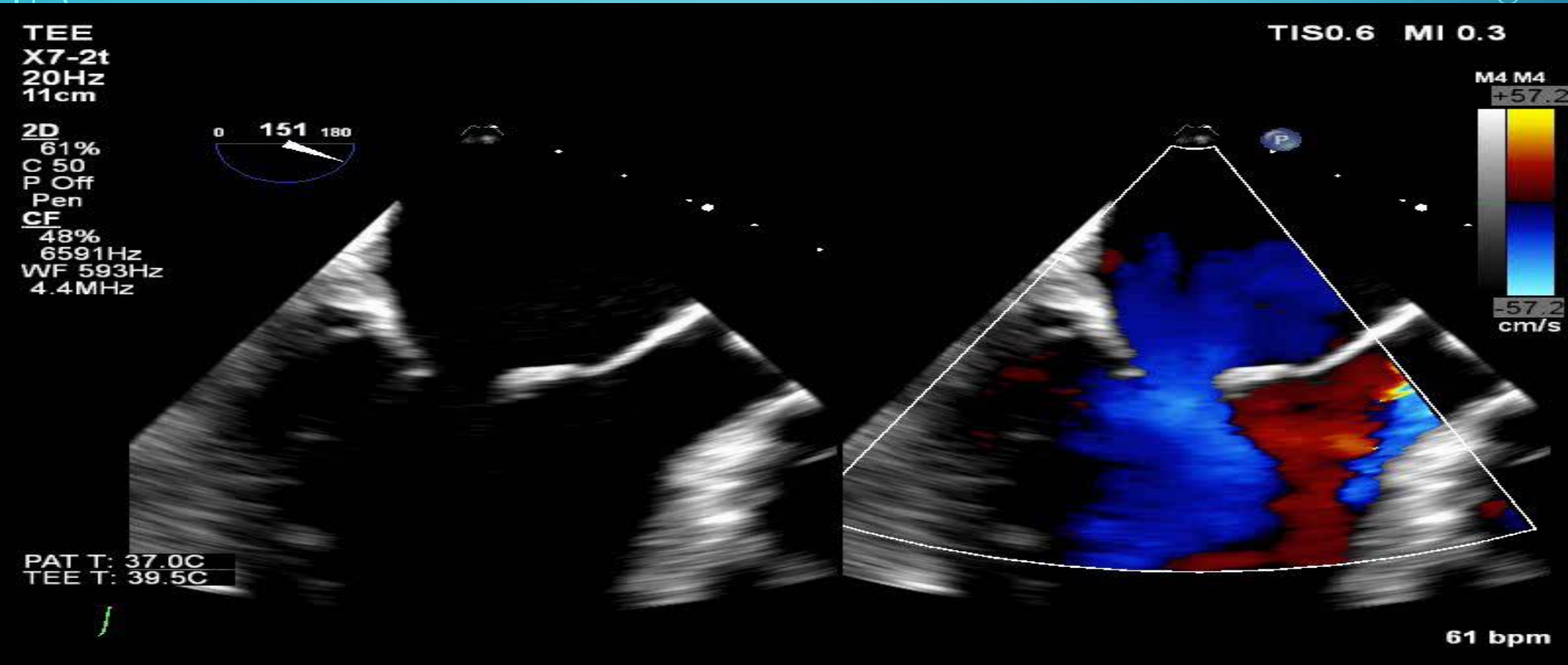




CARPENTIER IIIB

TETHERED POSTERIOR LEAFLET

GDMT FOR HFrEF IS FIRST LINE



PREVALENCE OF SMR IS 2-3X LARGER THAN PMR

6.5M Patients

Heart Failure Prevalence[1]

50% **HFpEF: EF >50%[2]**

50% **HFrEF: EF ≤ 50%[2]**

3% **NYHA I[3]**

32% **NYHA II[3]**

50-70% **NYHA III/IV[3]**

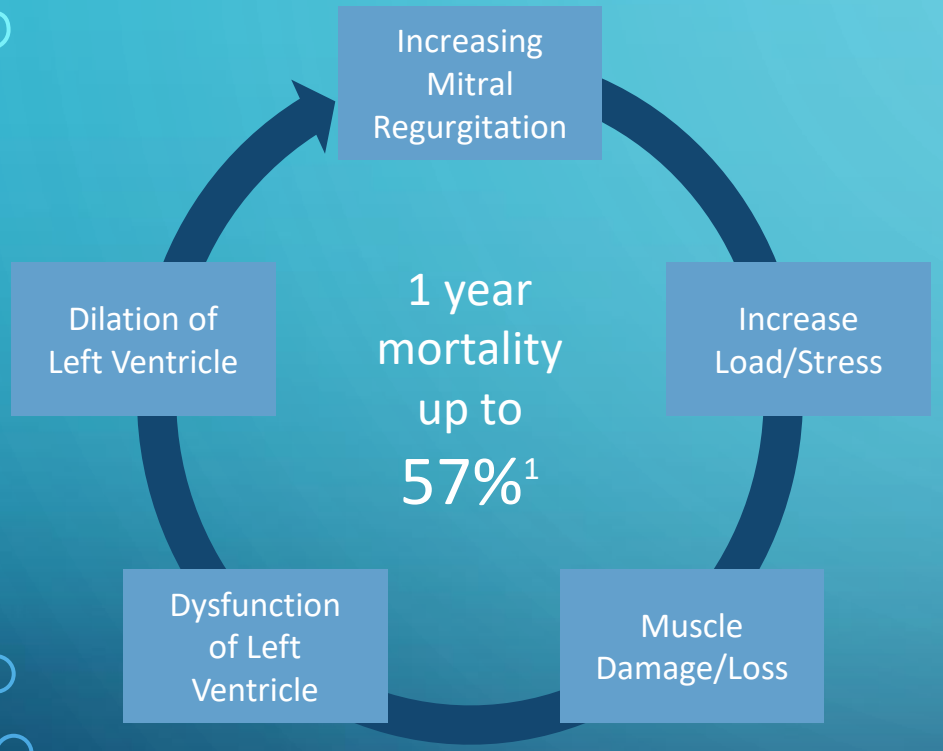
~40% **Moderate to Severe MR[4,5]**

1 in 5 of HF patients have moderate-to-severe and severe secondary MR.[1-6*]

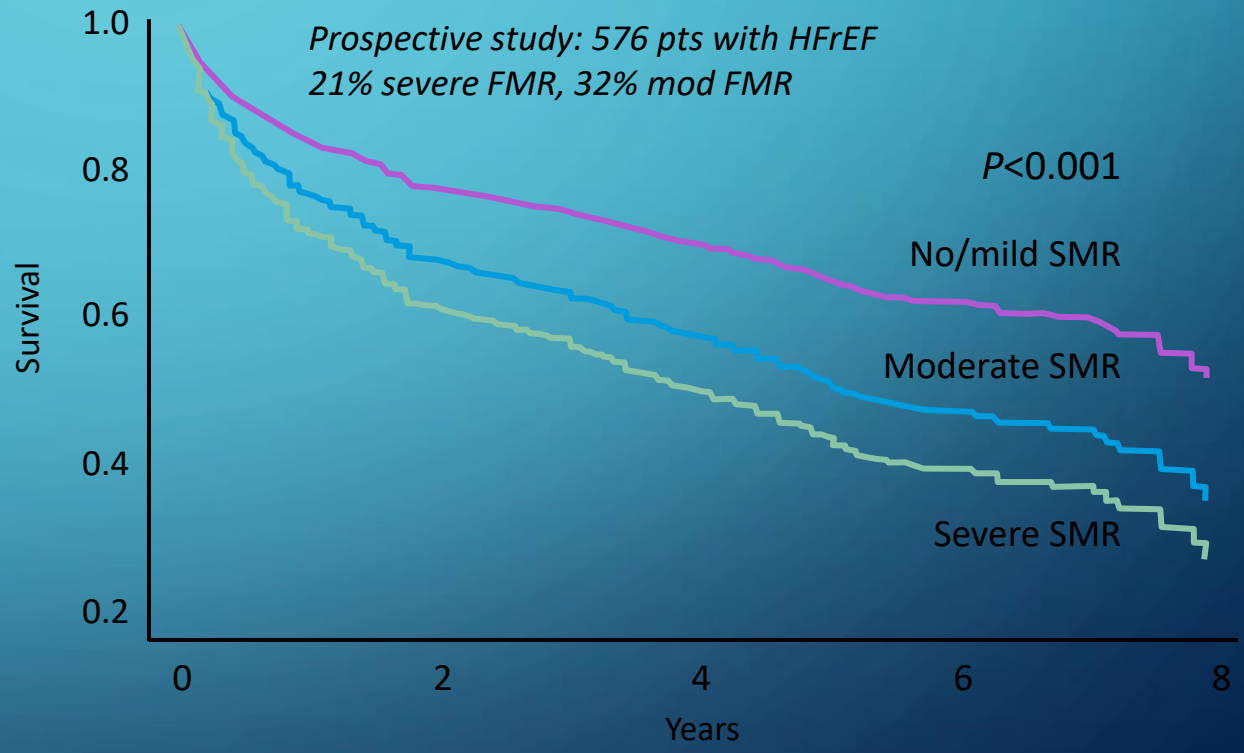
* Heart Failure patients with reduced EF and with moderate to severe and severe secondary MR

1. AHA Heart Disease and Stroke Statistics Update, Circulation 2017
2. Yancy CW et al, JACC 2013
3. Pecini et al EHJ 2011
4. Asgar et al, JACC 2015
5. Nieminen et al, EHJ 2006
6. Patel et al, Journal of Cardiac Failure 2004.

SECONDARY MR IS A PREDICTOR OF MORTALITY



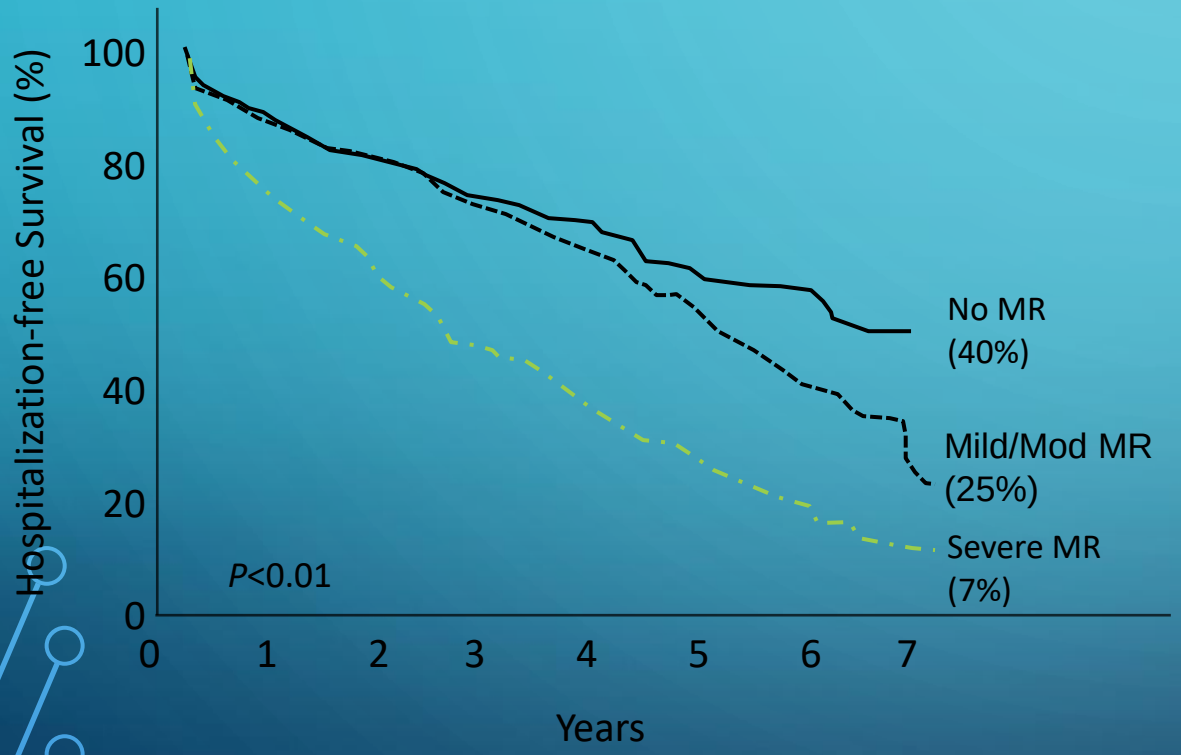
SEVERE SECONDARY MR IS AN INDEPENDENT PREDICTOR OF MORTALITY[2]



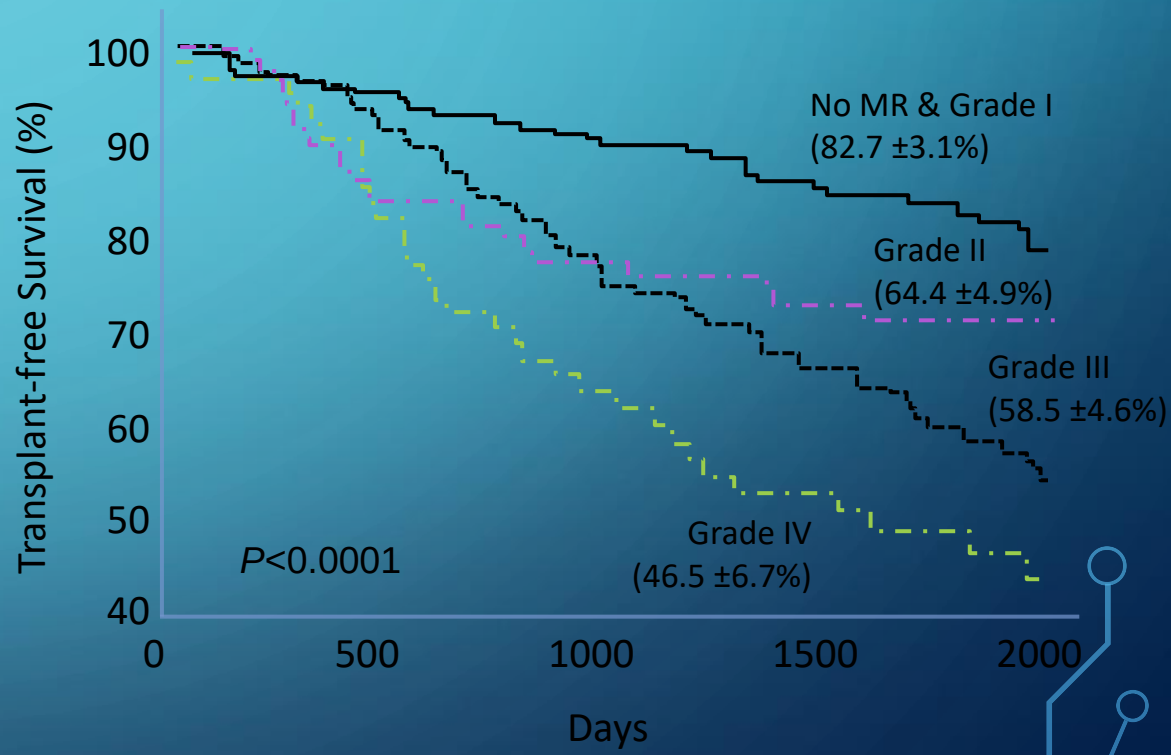
1. Cioffi G, et al. European Journal of Heart Failure 2005 Dec;7(7):1112-7
2. Goliasch G et al. EHJ 2018;39:39-46. Graph courtesy of Dr. G Stone

SECONDARY MR WORSENS HEART FAILURE OUTCOMES

HOSPITALIZATION-FREE SURVIVAL DECREASED WITH INCREASED MR SEVERITY[1]



TRANSPLANT-FREE SURVIVAL DECREASED WITH INCREASED MR SEVERITY[2]

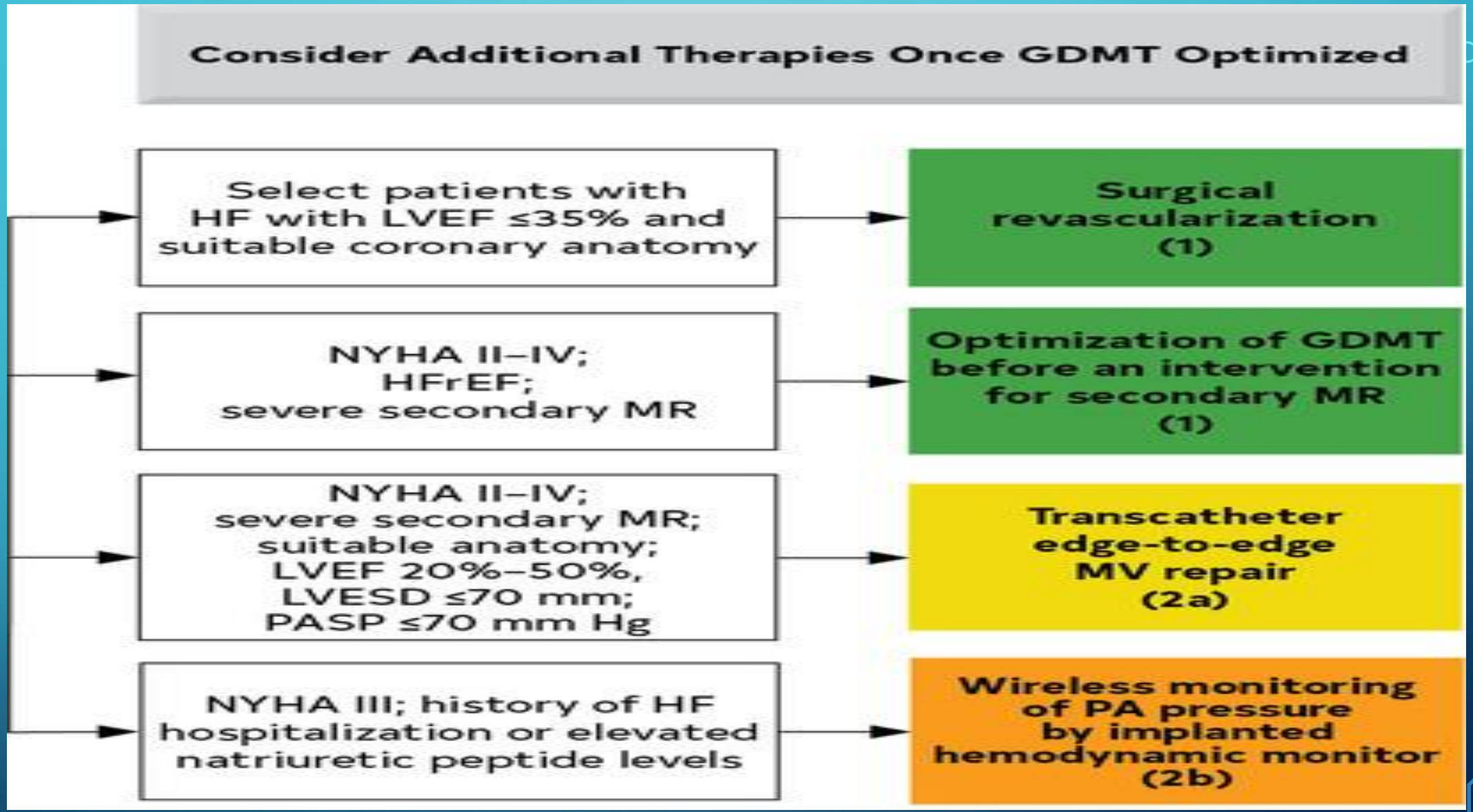


1. Rossi A, et al. Heart 2011; 97:1675-1680
2. Bursi F, et al. Eur J Heart Fail 2010; 12:382-388

2022 GUIDELINE FOR THE MANAGEMENT OF PATIENTS WITH HEART FAILURE (HF) TAKE-AWAY MESSAGES

The HF guideline have now been upgraded to show Transcatheter edge-to-edge repair (TEER) as a Class 2a recommendation for COAPT-like* Secondary Mitral Regurgitation (SMR) patients based solely on MitraClip data. “

VHD is a significant cause of HF. In patients with HF, management of VHD should be performed by a multidisciplinary team with expertise in HF and VHD, in accordance with the VHD guidelines.



Paul A. Heidenreich. Circulation. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, Volume: 145, Issue: 18, Pages: e895-e1032, DOI: (10.1161/CIR.0000000000001063)

Guideline Directed Therapy for Severe MR

Primary (non-rheumatic)

No Medical Therapy
(Diuretics palliative)

Surgery for symptoms or LV dysfunction (I)

(Repair > Replacement) (I)

Consider prophylactic repair for low risk with long term survival (younger healthy with favorable anatomy) (IIa)

TEER for symptomatic high/prohibitive risk patients (IIa)

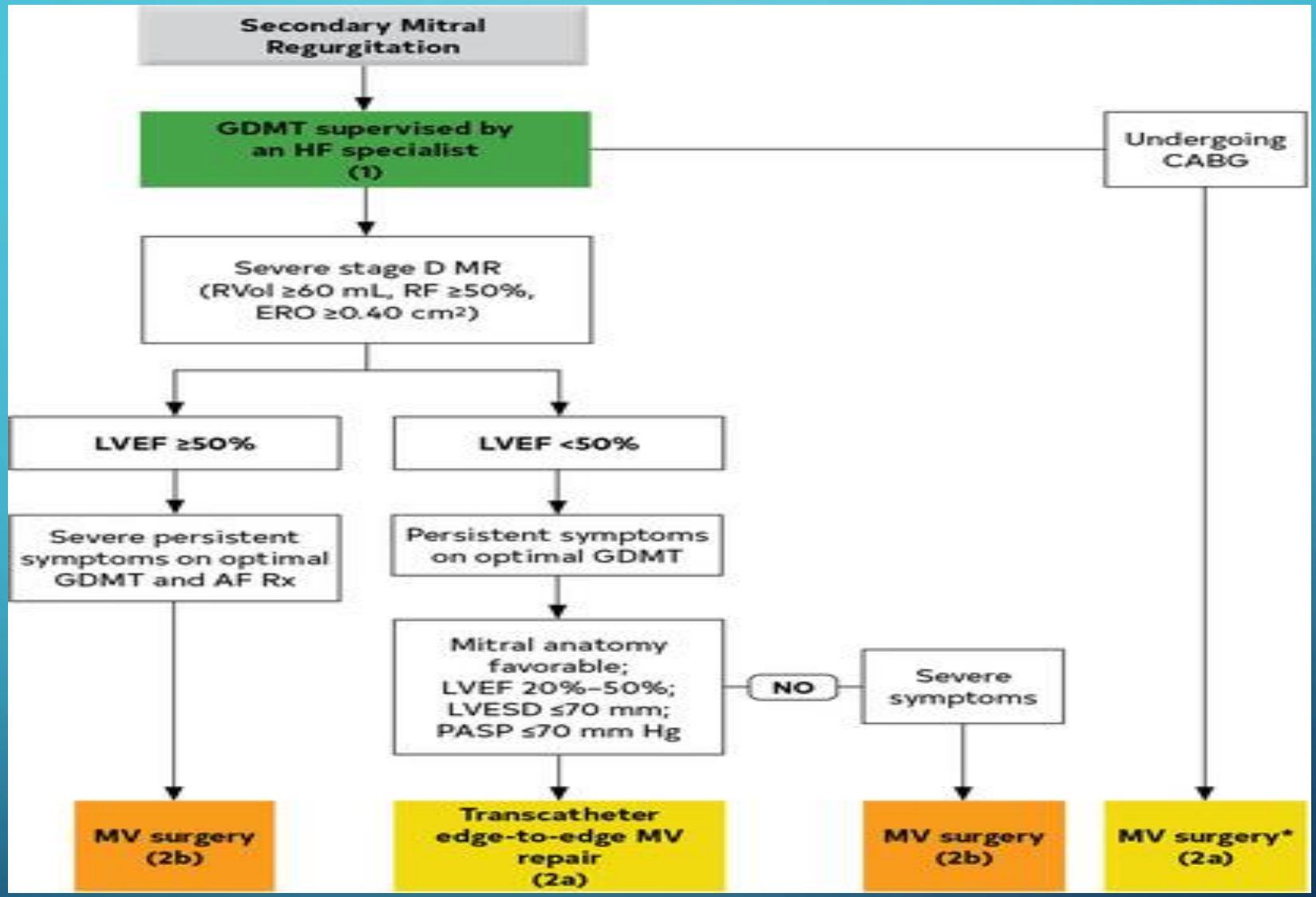
Secondary

Medical therapy first (I)
(BB,ACE/ARB/ARNI, hydralazine/nitrates, ARA, Diuretics, SLGT2)

CRT (I)
(EF≤35, LBBB)

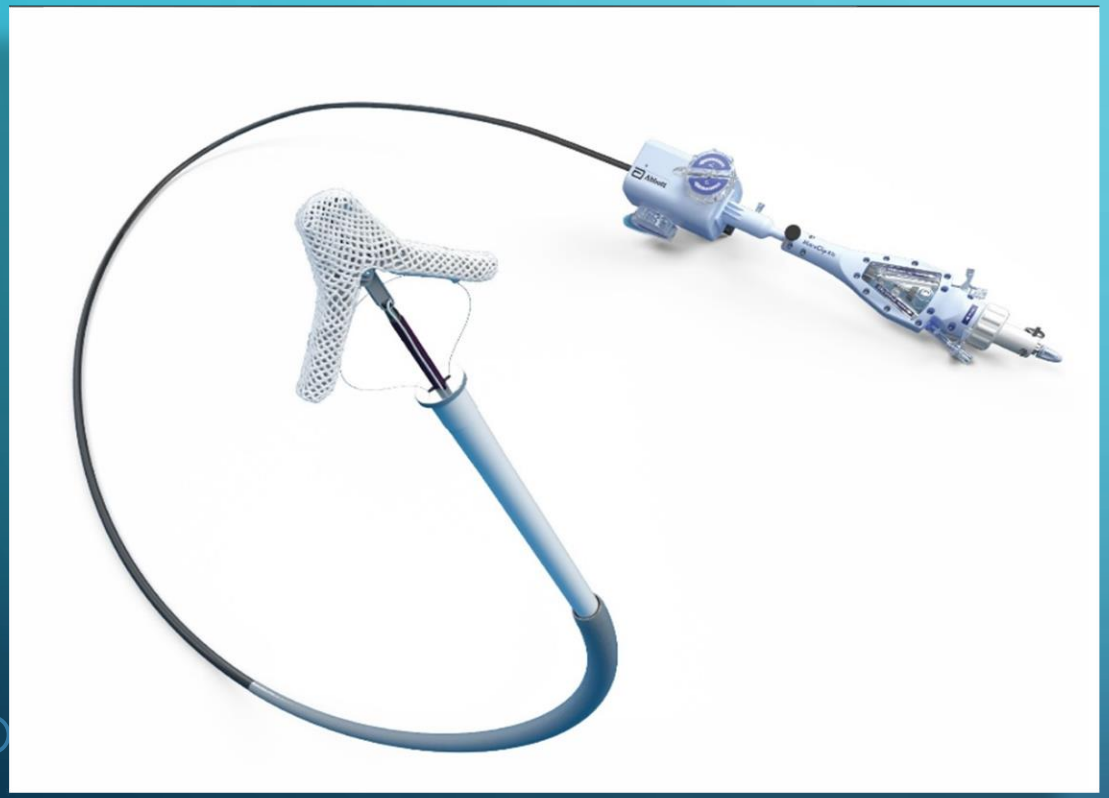
TEER for symptomatic despite GDMT in "COAPT-like" patients (IIa)
(any surgical risk)

Surgery in selected Class 3/4 pts (Replacement or Repair)(IIb)



Paul A. Heidenreich. Circulation. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines, Volume: 145, Issue: 18, Pages: e895-e1032, DOI: (10.1161/CIR.0000000000001063)

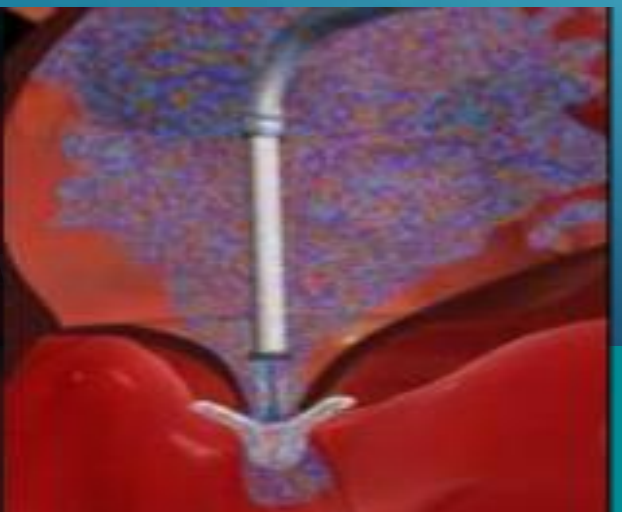
MITRACLIP™: FDA APPROVAL OCTOBER 2013 FOR PROHIBITIVE RISK PRIMARY MR

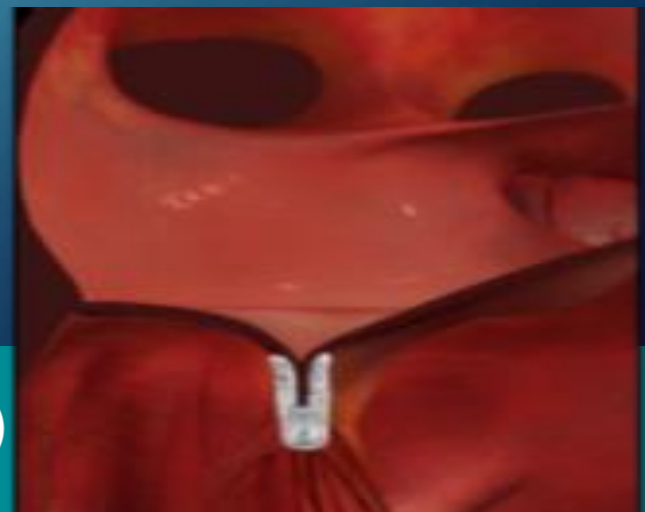


- Based on a surgical approach wherein the anterior leaflet and posterior leaflet are mechanically coapted
- Transseptal access via right transfemoral venous approach

Commercially available Transcatheter MV Therapies

Transcatheter Edge to Edge Repair (TEER) with MitraClip

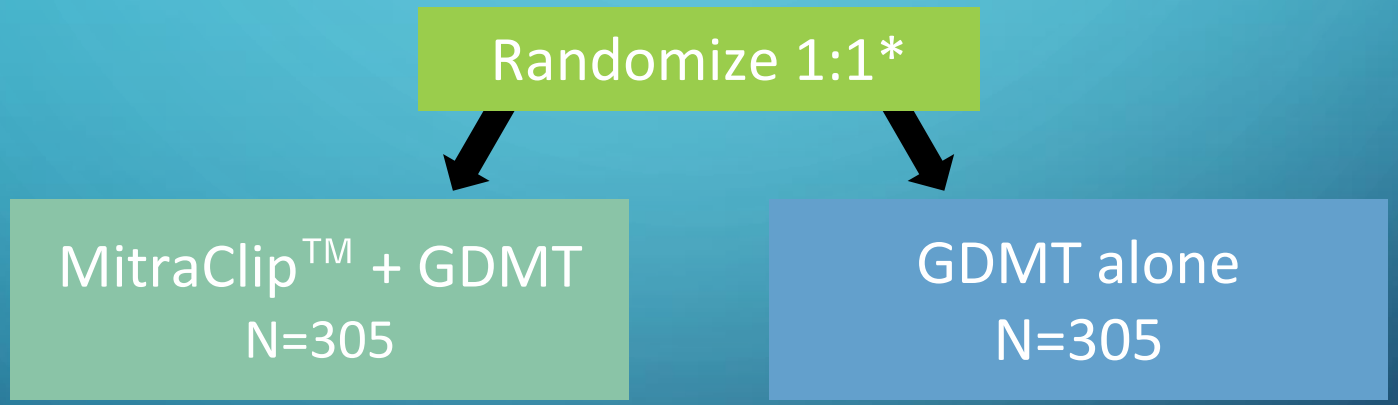




CARDIOVASCULAR OUTCOMES ASSESSMENT OF THE MITRACLIP PERCUTANEOUS THERAPY FOR HEART FAILURE PATIENTS WITH FUNCTIONAL MITRAL REGURGITATION

THE COAPT™ TRIAL

A parallel-controlled, open-label, multicenter trial in ~610 patients with heart failure and moderate-to-severe (3+) or severe (4+) secondary MR who remained symptomatic despite maximally-tolerated GDMT



INDICATION FOR USE

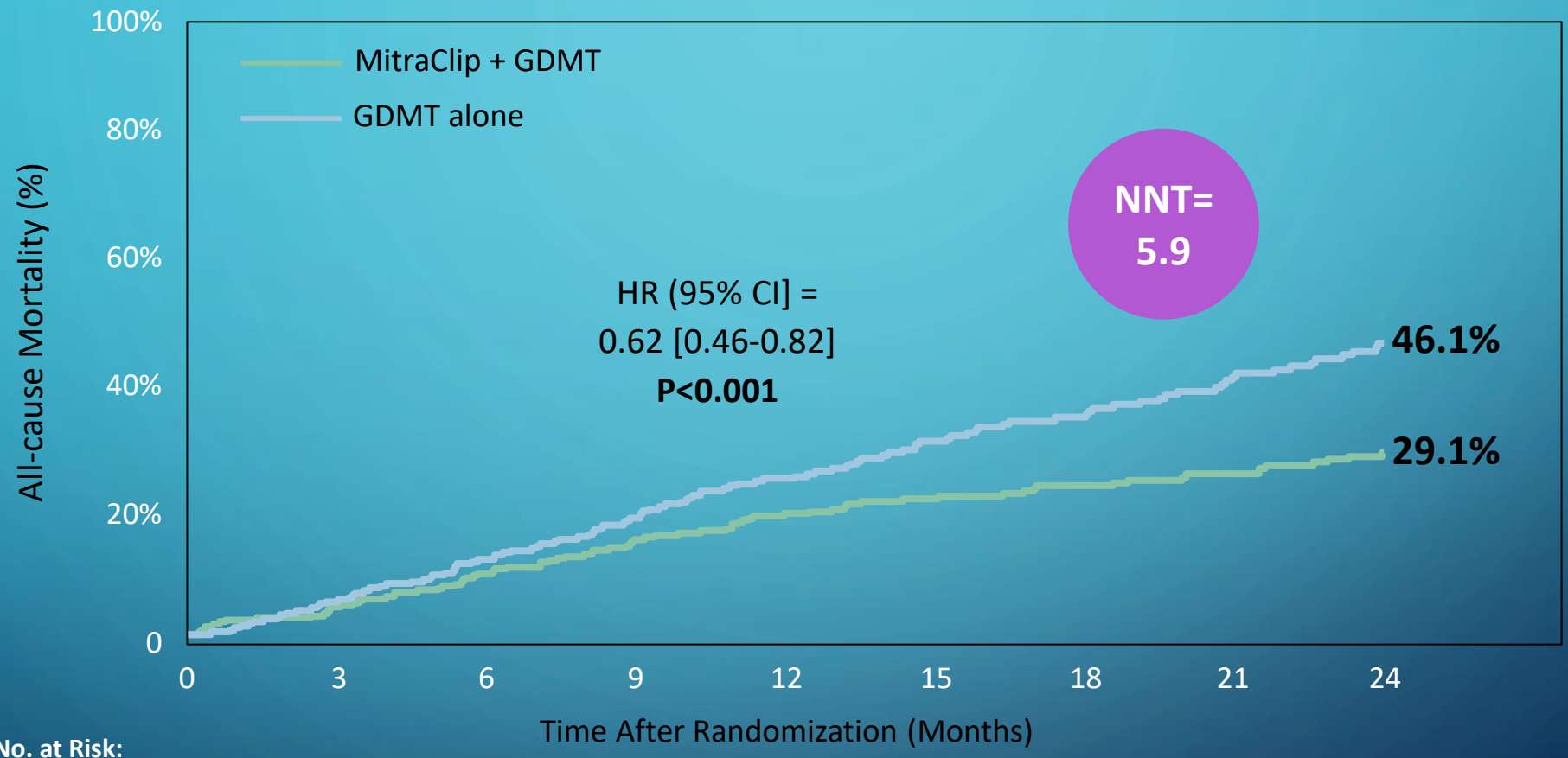
The MitraClipTM NTR/XTR Clip Delivery System is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR ≥ 3+) due to primary abnormality of the mitral apparatus [degenerative MR] in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation.

The MitraClipTM NTR/XTR Clip Delivery System, when used with maximally tolerated guideline-directed medical therapy (GDMT), is indicated for the treatment of symptomatic, moderate-to-severe or severe secondary (or functional) mitral regurgitation (MR; MR ≥ Grade III per American Society of Echocardiography criteria) in patients with a left ventricular ejection fraction (LVEF) ≥ 20% and ≤ 50%, and a left ventricular end systolic dimension (LVESD) ≤ 70 mm whose symptoms and MR severity persist despite maximally tolerated GDMT as determined by a multidisciplinary heart team experienced in the evaluation and treatment of heart failure and mitral valve disease.

*Stratified by cardiomyopathy etiology (ischemic vs. non-ischemic) and site

Stone GW et al. NEJM 2018

MITRACLIP™ + GMDT IMPROVES SURVIVAL VS. GDMT ALONE



No. at Risk:									
MitraClip + GDMT	302	286	269	253	236	191	178	161	124
GDMT Alone	312	294	271	245	219	176	145	121	88

Stone GW et al. NEJM 2018

CONCLUSIONS

Mitral Regurgitation in the heart failure patient has been associated with worsening outcomes in multiple studies

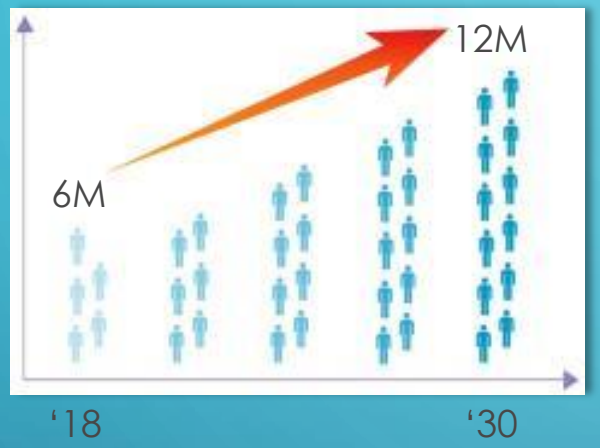
GDMT has been shown to be effective in reducing HF hospitalizations and improving mortality

The COAPT™ trial, randomizing MitraClip + GDMT vs. GDMT alone, is a landmark clinical trial demonstrating a reduction in mitral regurgitation, reduction in HF hospitalizations (NNT= 3.1) and improvement in mortality (NNT=5.9) in HFrEF patients

Early identification and referral to a multi-disciplinary team specializing in heart failure and mitral valve transcatheter repair, with MitraClip™, is an important next step to improve the prognosis of these patients

PROVEN
SAFE
EFFECTIVE

Atrial Fibrillation is a Prevalent and Growing Condition and a Leading Cause of Stroke



~6M

people with AF in U.S., estimated to double by 2030[1]

AF

5X increased risk of stroke for AF patients[2]

1 in 6 strokes occur in patients with AF[3]

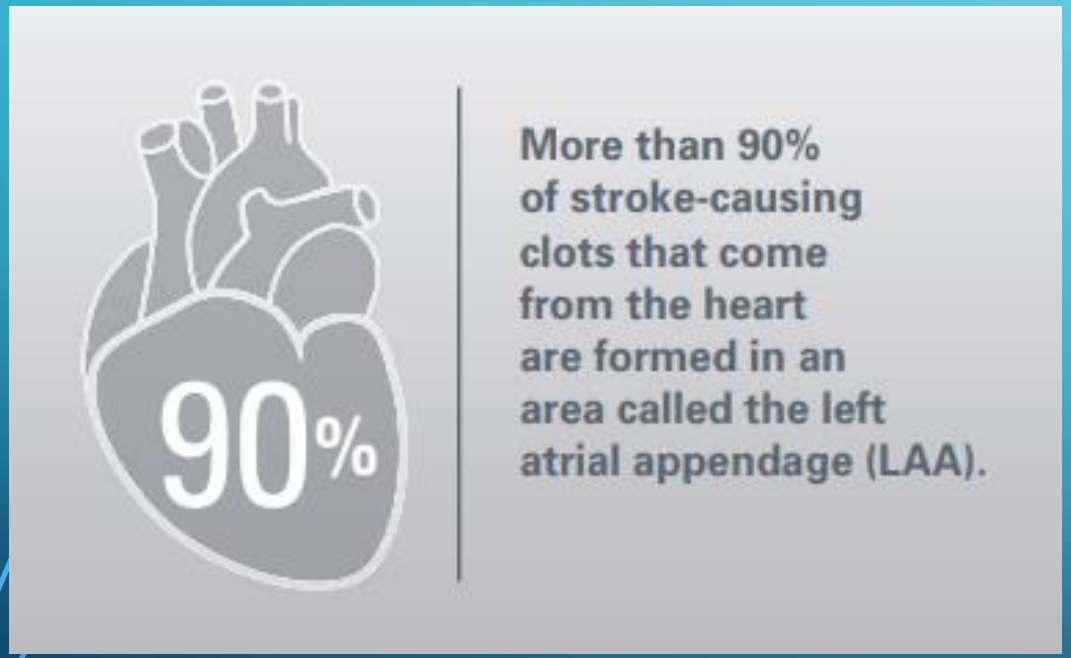
47% of AF patients experiencing a stroke will **suffer a second stroke** within 6 months[4]

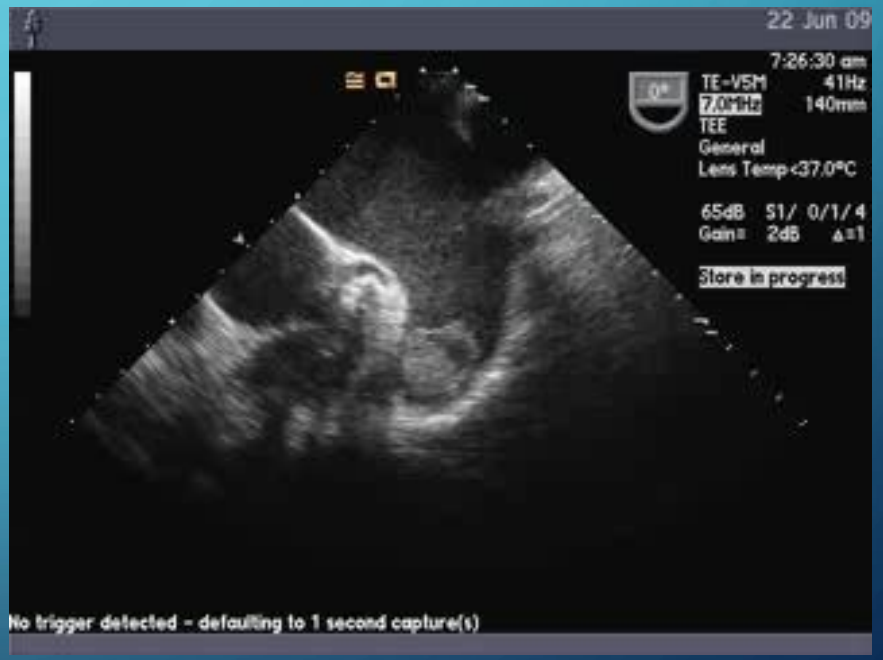
~2X greater likelihood of stroke recurrence in AF patients (within 6 months)[4]

1. Benjamin, EJ et al., Heart Disease and Stroke Statistics—2018 Update: A Report From the American Heart Association. Circulation. 2018; 137: e67-e492.
2. Holmes DR, Atrial Fibrillation and Stroke Management: Present and Future, Seminars in Neurology 2010;30:528–536
3. Hart RG, Halperin JL. Atrial fibrillation and thromboembolism: a decade of progress in stroke prevention. *Ann Intern Med.* 1999.
4. Wolf PA et al, Duration of Atrial Fibrillation and the Imminence of Stroke: The Framingham Study, Stroke 1983; 14:664-667

AF Creates Environment for Thrombus Formation in Left Atrium

The WATCHMAN Implant is an innovative one-time procedure designed to reduce the risk of strokes that originate in the left atrial appendage (LAA)





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)

Atrial Fibrillation Guidelines

2014 ACC/AHA/HRS Treatment Guidelines to Prevent Thromboembolism in Patients with AF & 2019 Focused Update

Balance stroke risk reduction benefit vs. bleeding risk

CHA_2DS_2-VASc Score in Men	CHA_2DS_2-VASc Score In Women	Recommendation
0	0	No anticoagulant
1	2	Aspirin (81-325 mg daily) or oral anticoagulants may be considered*
≥ 2	≥ 3	Oral anticoagulants are recommended**

** WATCHMAN and WATCHMAN FLX labeling updated to 81-100 mg ASA in 2020.*

***DOACS (dabigatran, rivaroxaban, apixaban, and edoxaban) recommended over warfarin in DOAC-eligible patients.*

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

Long-Term Oral Anticoagulation is Not Ideal for All NVAF Patients

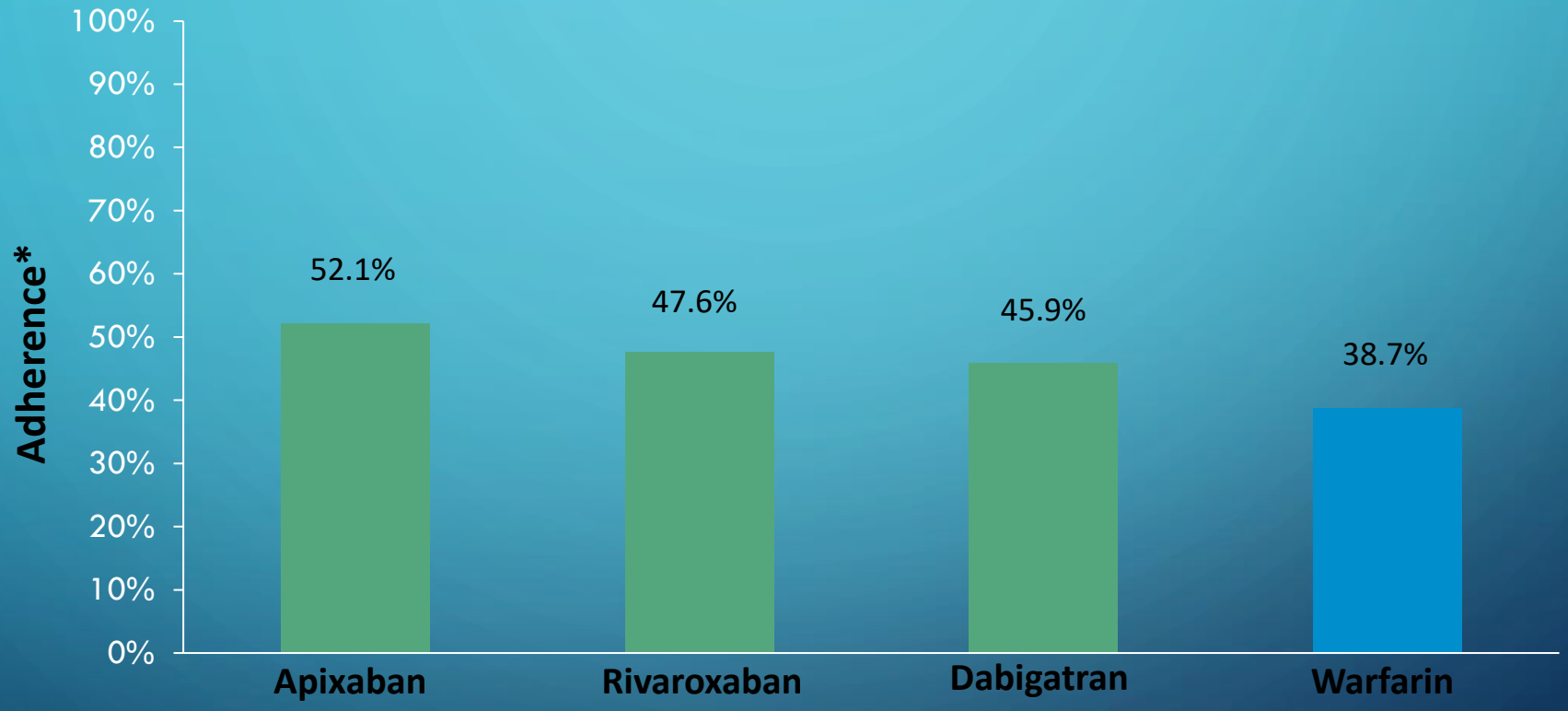
- Warfarin and Direct Oral Anticoagulants come with risk factors for many NVAF patients.

Examples of those risk factors include:

Warfarin	Direct Oral Anticoagulants
Bleeding Risk	Bleeding Risk
Daily Regimen	Daily Regimen
High Non-Adherence Rates	High Non-Adherence Rates
Regular INR Monitoring	Complicate Surgical Procedures
Food & Drug Interaction Issues	Drug Interaction Issues
Complicate Surgical Procedures	High Cost

Less than Half of Patients on DOACS are Adherent

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



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

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

PROVEN
SAFE
EFFECTIVE

WATCHMAN is a One-Time Procedure that Provides a Lifetime of Stroke Risk Reduction

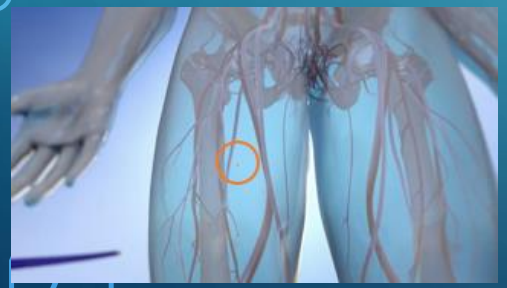
Minimally Invasive
Permanent Procedure

1 Hour
Typical Procedure Takes
Less than an Hour

24 Hour
Average Hospital Stay

1

Using a standard percutaneous technique, a guidewire and vessel dilator are inserted into the femoral vein

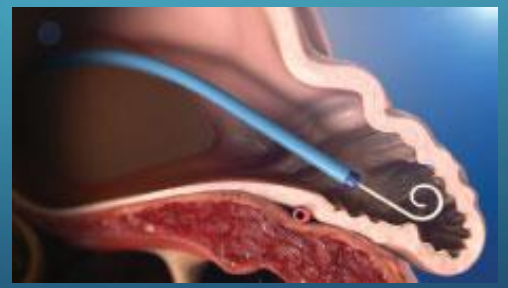


2

The implant procedure is performed with fluoroscopy and transesophageal echocardiography (TEE). The interatrial septum is crossed using a standard transseptal access system.

3

The access sheath is advanced over the guidewire into the left atrium and then navigated into the distal portion of the LAA over a pigtail catheter.

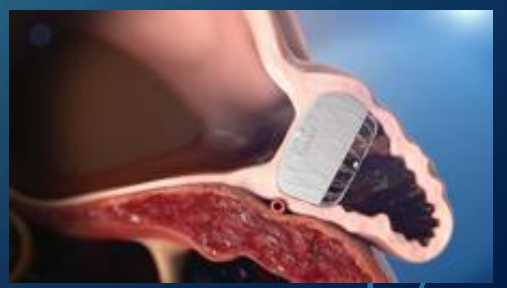


4

WATCHMAN is then deployed and released in the LAA.

5

Heart tissue grows over the WATCHMAN Implant, and the LAA is permanently sealed. Patients remain on OAC for at least 45 days post-procedure. TEE is used to confirm seal.



The WATCHMAN Difference

Long-term results demonstrated WATCHMAN reduced risk of disabling stroke, post-procedure bleeding, and mortality vs. warfarin

72%
MAJOR BLEEDING
(95% CI: 0.16 – 0.49, p=0.001)[6]

>6 MONTHS
POST-PROCEDURE

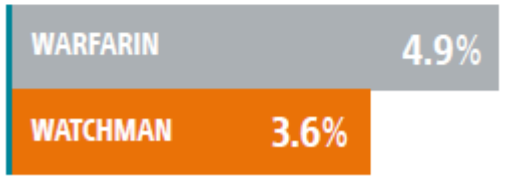
After discontinuation of concomitant antithrombotic therapy
Note: Data are from five-year results from PROTECT AF and 2 year results from PREVAIL.

55%
RELATIVE RISK REDUCTION OF DISABLING AND FATAL STROKES[7]

REDUCED
RISK OF DISABLING AND FATAL STROKE

27%
ALL CAUSE MORTALITY[7]

5 YEARS
POST-PROCEDURE



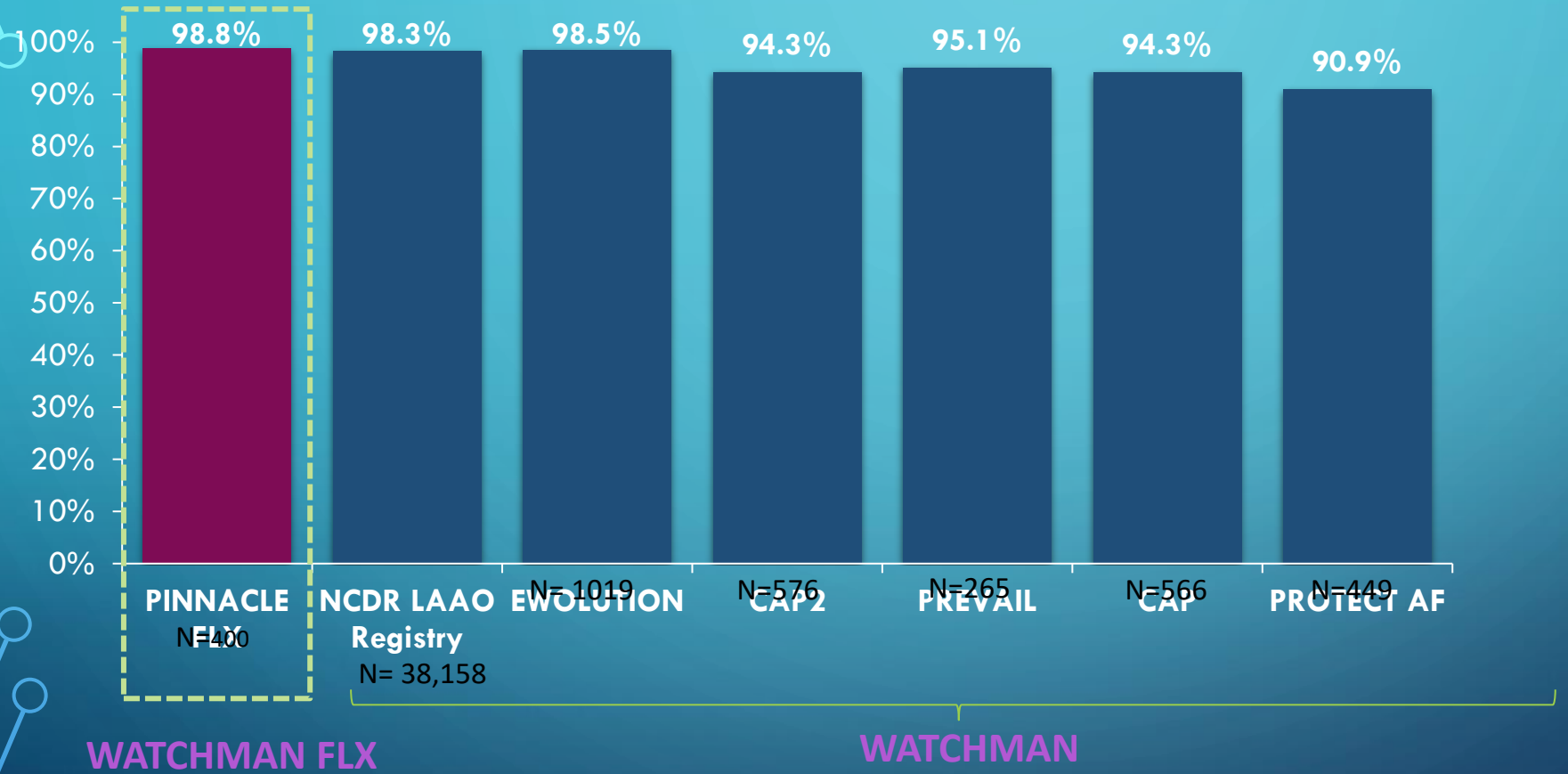
- Bleed Reduction Findings from PROTECT AF & PREVAIL Meta Analysis (3 Year)
- Disabling Stroke & All Cause Mortality Finding from PROTECT AF & PREVAIL Meta Analysis (5 Year)

*Major bleeding defined as adverse event that was assigned one of several bleeding codes and was adjudicated by an independent Clinical Events Committee as significant (life-threatening or resulting in hospitalization, prolongation of hospitalization, substantial disability, or death).

1. Reddy VY, et al. JACC 2017; 70(24): 2964-2975.
2. Price, MJ, et al. JACC: CV Interv 2015; 8(15): 1925-1932

WATCHMAN has a High Procedural Success Rate

WATCHMAN maintains favorable safety outcomes from clinical studies to real-world experience



98.8%

PATIENTS SUCCESSFULLY IMPLANTED*[2]

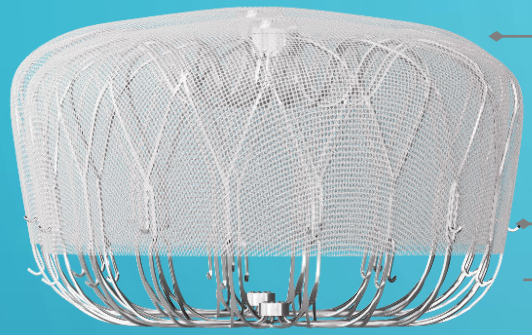
0.5%

EVENT RATE†[2]

Implant success defined as deployment and release of the device into the LAA
Reported N values on this slide are those of attempted implants. All cancelled procedures are excluded from this analysis

[1]Boersma, L.et al. EHJ. 2016. 37(31): 2465-2474 [2]Reddy VY, et al. JACC 2017; 69(3): 253-261 [3]Holmes DR et al. JACC 2019; 74(23): 2878-2889. [4]Doshi, SK. Presented at HRS 2020 .
[2] PINNACLE FLX. Doshi, SK. Results Presented at HRS 2020.

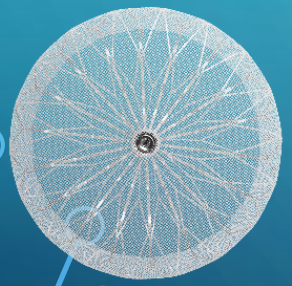
WATCHMAN FLX



Full recapture & redeployment
For precise device placement

Dual-row precision anchors
Designed to provide optimal device engagement with LAA tissue for long-term stability

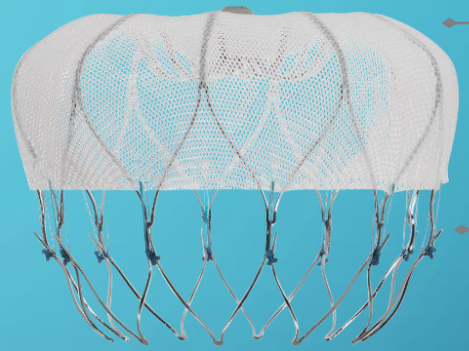
Closed end



18 strut frame
Designed for conformability to appendage and improved sealing

Fully-Rounded WATCHMAN FLX Ball
Designed to safely advance & maneuver within the LAA

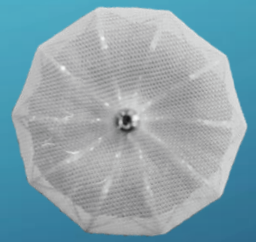
WATCHMAN



Partial recapture only

Single-row anchors

Open end



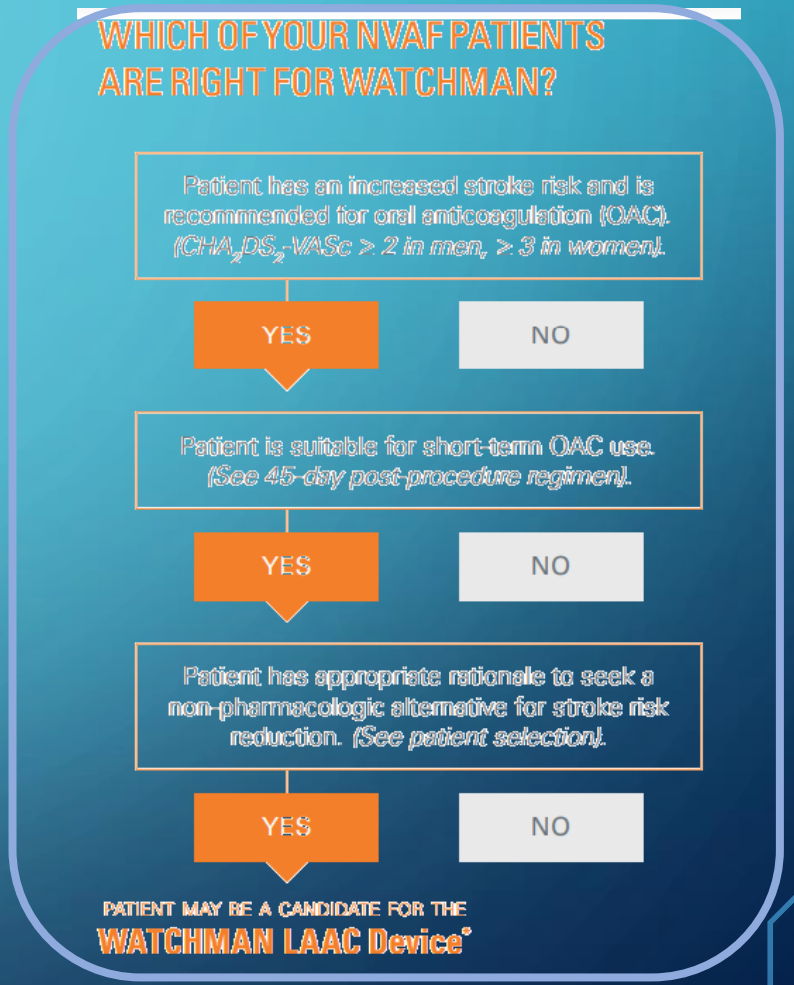
10 strut frame

WATCHMAN Patient Selection

US Indications for Use

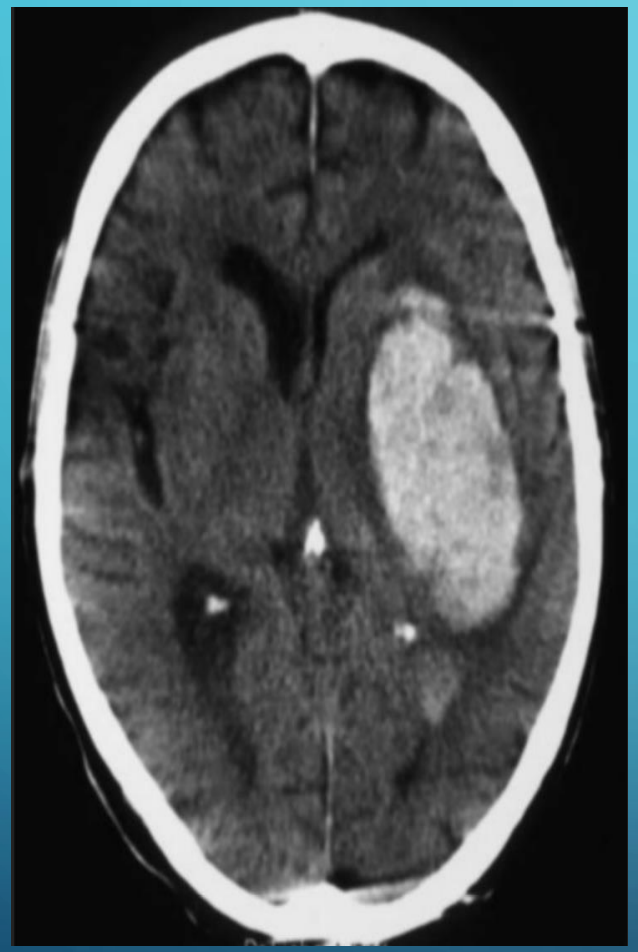
The WATCHMAN Device is indicated to reduce the risk of thromboembolism from the left atrial appendage in patients with non-valvular atrial fibrillation who:

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

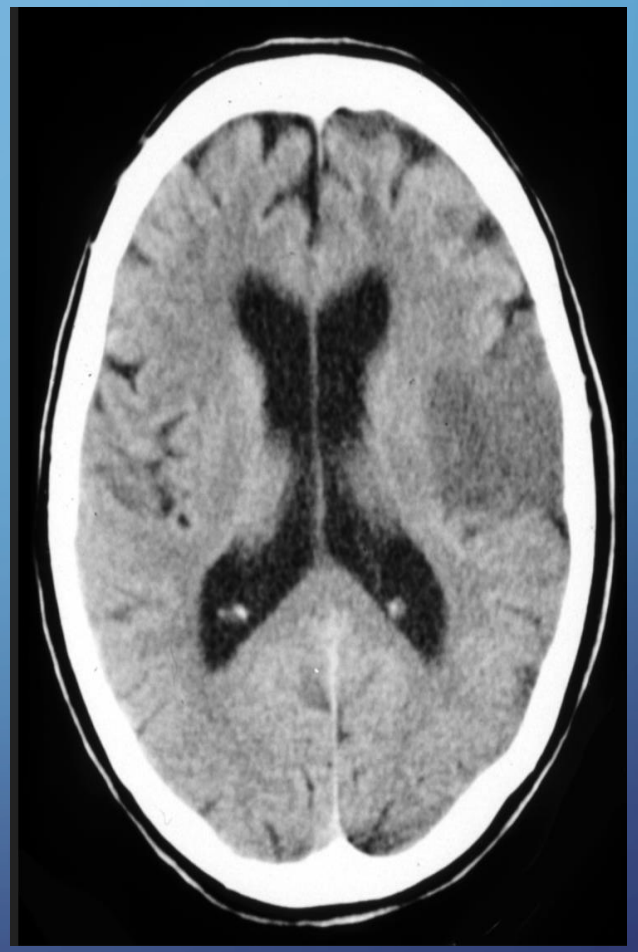


Over Eighty Percent of Strokes are Ischemic

HEMORRHAGIC STROKE



ISCHEMIC STROKE INFARCT

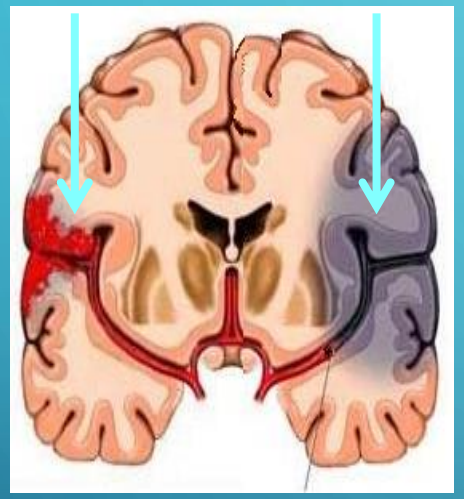


Images Courtesy of Dr. Hans-Christoph Diener

Types of Stroke[1,2]

VESSEL RUPTURE
15%

ARTERY OCCLUSION
85%



15-20% Atherothrombotic
Stenotic artery feeding area of infarction

25-30% Cardioembolic
A thrombus or other material dislodges from the heart of aortic arch

15-20% Lacunar/Small Vessel

25-30% Cryptogenic
Unknown cause

5-10% "Other"

1. Petty, et al Ischemic Stroke Subtypes: A population-based study of incide3nce and risk factors. Stroke 1999 ;30:2513–2516
2. AHA Understanding Diagnosis and Treatment of Cryptogenic Stroke: A Healthcare Professional Guide, 2015.

STROKE IN YOUNGER PATIENTS (< 60)

795,000 strokes annually[1]

34% of all strokes occur in patients younger than 65 (270,300)[2] (18-60)

25% of all ischemic strokes are Cryptogenic

PFO Present in 40-50% of cryptogenic stroke patients

Treatments frequently unproven – lack of clinical trials

Mozzafarian, D, et al. *Circulation* 2105: 131:e29-e33
https://www.cdc.gov/stroke/facts.htm
AHA Heart Disease and Stroke Statistics – 2016 Update

Definitions of Cryptogenic Stroke

- **TOAST DEFINES CRYPTOGENIC STROKE** (stroke of undetermined etiology) as brain infarction that is not attributable to a definite cardioembolism, large artery atherosclerosis, or small artery disease despite extensive vascular, cardiac and serologic evaluation.

CLASSIFICATION SCHEME	REQUIRED WORKUP
TOAST[1]	Not specified
Embolic strokes of undetermined source[2]	Brain CT/MR, 12-lead ECG, precordial echocardiogram, extra/intravascular imaging, cardiac monitoring for ≥ 24 hours

EMBOLIC STROKE OF UNDETERMINED SOURCE (ESUS) IS THE SAME AS A THOROUGHLY EVALUATED CRYPTOGENIC STROKE

1. Adams HP, et al. *Stroke*. 1993;24:35-41.
2. Hart RG, et al. *Lancet Neurol*. 2014;13:429-438

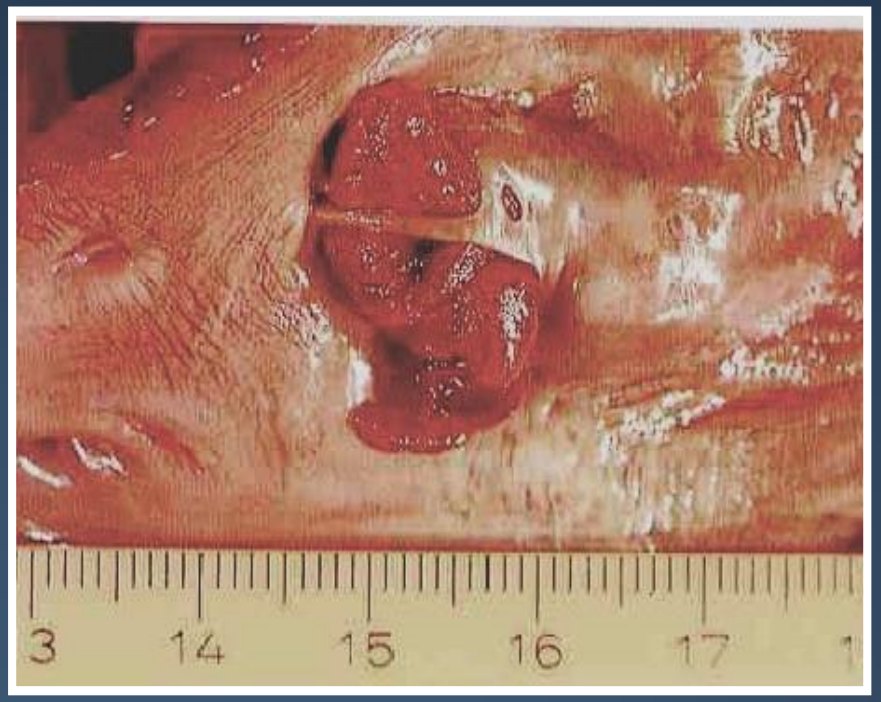
Cryptogenic Stroke and PFO[1]

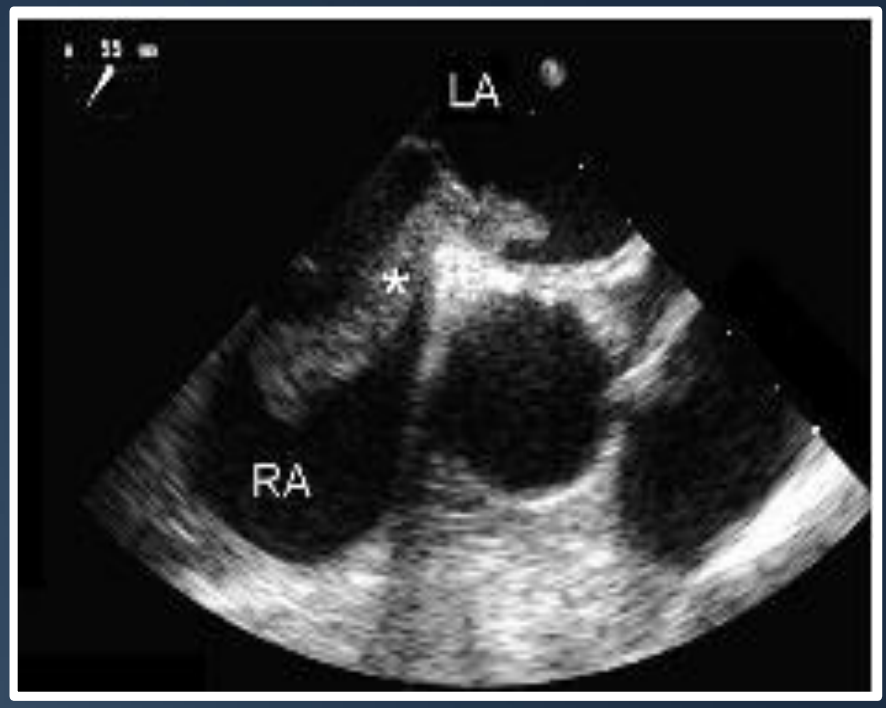
- Some patients with PFO experience a stroke at a young age.
- PFO can allow clots to go from the right side of the heart to the left, travel to the brain and cause a stroke.
- Mechanism is **presumed to be** paradoxical embolism.
  - Venous thrombus crosses the PFO and then occludes a systemic artery.

1. American Heart Association, Understanding Diagnosis and Treatment of Cryptogenic Stroke. A Healthcare Professional Guide. www.strokeassociation.org

1990's CASE REPORTS

- ✓ Proving that thrombus <u>can</u> form in a PFO





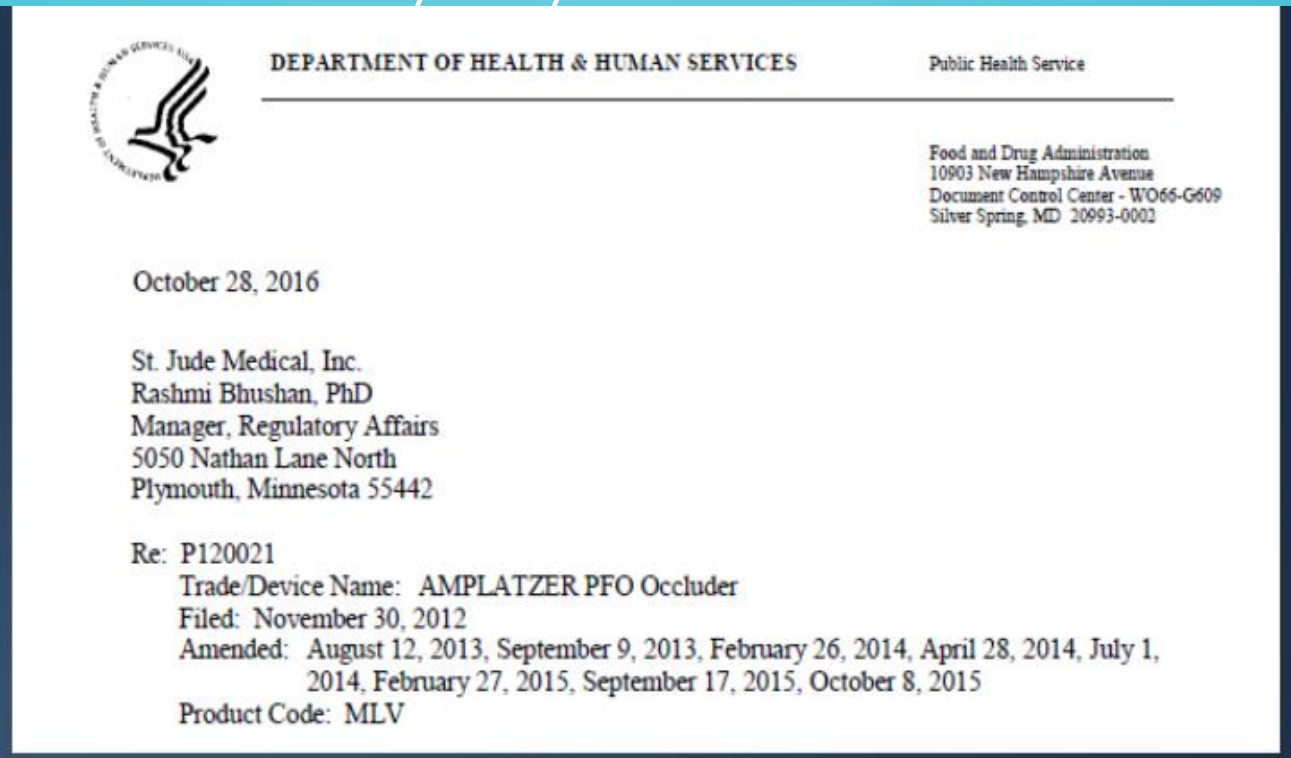
- ✓ Rare, documented echo images of actual thrombo-embolic transit

Comprehensive Evaluation for Stroke Mechanism

- **WHAT DEFINES A CRYPTOGENIC STROKE/EMBOLIC STROKE OF UNKNOWN SOURCE?**
  - Ischemic stroke detected by CT or MRI that is not lacunar
  - Absence of extracranial or intracranial atherosclerosis causing ≥ 50% luminal stenosis in arteries supplying the area of ischemia
  - No major risk cardioembolic source of embolism
    - Requires minimum diagnostic evaluation that includes cardiac rhythm monitoring for > 24 hours with automated rhythm detection
    - Permanent or paroxysmal AFIB, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumors, mitral stenosis, recent (< 4 weeks) MI, LVEF < 30%, valvular vegetations or infective endocarditis
  - No other specific cause of stroke identified (eg, arteritis, dissection, migraine/vasospasm and drug abuse)

Hart et al, Embolic Stroke of Undetermined Source: A Systematic Review and Clinical Update Stroke, 2017 Apr;48(4):867-872.

FDA APPROVAL 10/28/16



DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center - WO66-G609
Silver Spring, MD 20993-0002

October 28, 2016

St. Jude Medical, Inc.
Rashmi Bhushan, PhD
Manager, Regulatory Affairs
5050 Nathan Lane North
Plymouth, Minnesota 55442

Re: P120021
Trade/Device Name: AMPLATZER PFO Occluder
Filed: November 30, 2012
Amended: August 12, 2013, September 9, 2013, February 26, 2014, April 28, 2014, July 1, 2014, February 27, 2015, September 17, 2015, October 8, 2015
Product Code: MLV

The AMPLATZER™ PFO Occluder is indicated for percutaneous transcatheter closure of a patent foramen ovale (PFO) to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an

FDA REQUIREMENTS FOR PFO CLOSURE

- Ages 18-60 years
- *Cryptogenic stroke* determined by neurologist and cardiologist
- Amplatzer PFO Occluder device

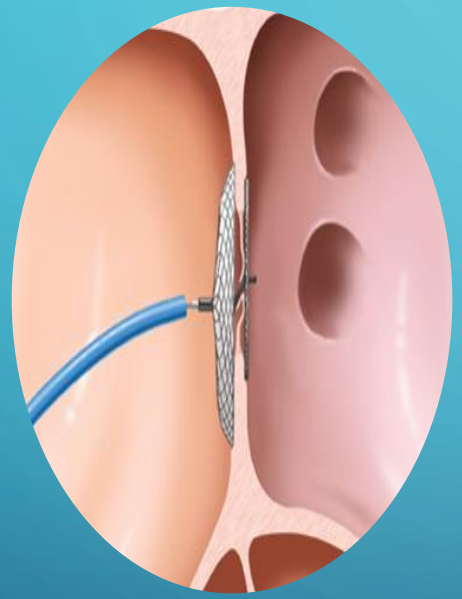
AMPLATZER™ PFO OCCLUDER

- DEVICE DESIGN
  - Percutaneous, transcatheter device
  - Self-expanding, double-disc design
  - Nitinol wire mesh with polyester fabric/thread
  - Recapturable and repositionable
  - FDA approval 2016; CE mark 1998

FIRST HUMAN USE OF THE AMPLATZER™ PFO OCCLUDER WAS 1997. TWO DECADES LATER, OVER 100,000 DEVICES HAVE BEEN IMPLANTED WORLDWIDE.[1]

1 Abbott, Data on File.

RESPECT PROCEDURAL RESULTS



TECHNICAL SUCCESS —
Device delivery and release

99.1 %

PROCEDURAL SUCCESS —
Implantation without in-hospital SAE

96.1 %

Carroll et al. Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke. *N Engl J Med*. 2013;368;12.1092 org.

CONCLUSION

- FDA mandates age, neurology and cardiology assessment of stroke etiology, and device
- Recommendation for shared decision making in IFU
- Controversial: is PFO closure in cryptogenic stroke a preference-sensitive decision?

QUESTIONS?????