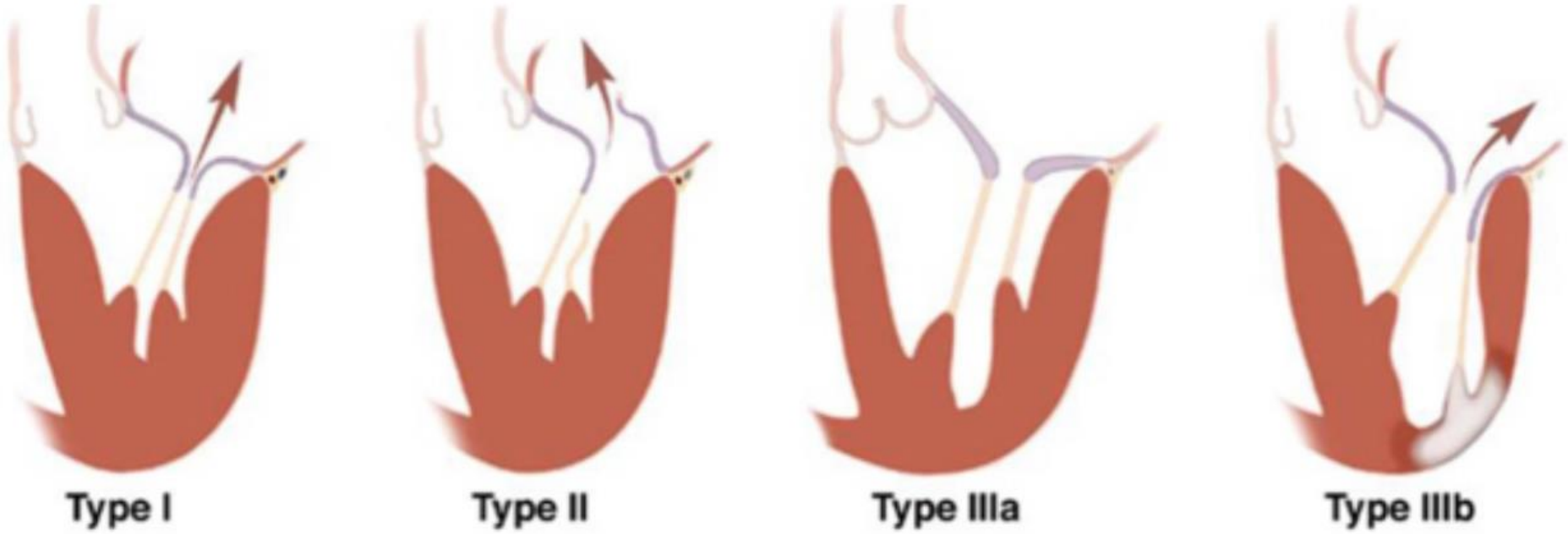
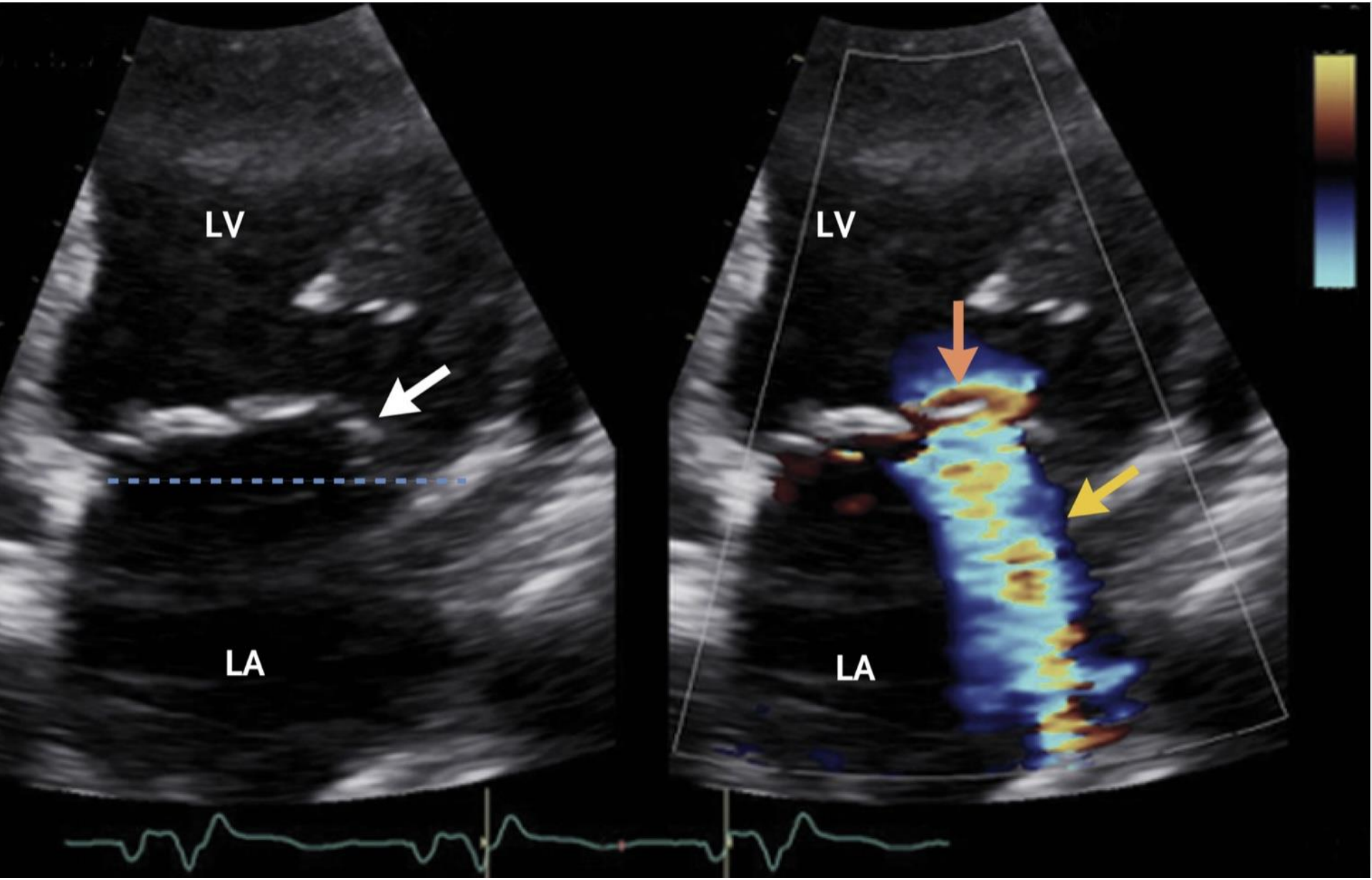
A 75-year-old man presents with dyspnea and fatigue that occur with less than moderate physical activity. He had an ST-segment elevation myocardial infarction involving the inferior and posterior segments of the left ventricle 10 years ago, and since then the left ventricular ejection fraction (LVEF) has decreased from 40% to 25%, accompanied by increasing mitral regurgitation. An implantable cardioverter–defibrillator (ICD) was placed for primary prevention 6 months ago. His medications include metoprolol succinate, spironolactone, and torsemide. How would you further evaluate and treat this patient?

left ventricle, papillary muscles, chordae tendineae, leaflets, and annulus.[1] The two broad categories of mitral regurgitation are primary (or degenerative) mitral regurgitation, which is most commonly caused by leaflet prolapse or flail, and secondary (or functional) mitral regurgitation. Primary mitral regurgitation is a disease of the valve (or chordae), and secondary mitral regurgitation is a disease of the left ventricle or left atrium.

Secondary Mitral Regurgitation

- Mitral regurgitation can be broadly classified into two different categories — primary and secondary mitral regurgitation. The evaluation, treatment, and prognosis in patients with these conditions differ. Primary mitral regurgitation is usually caused by leaflet abnormalities (prolapse), whereas secondary mitral regurgitation results from abnormal left ventricular size, shape, or function.
- Transthoracic echocardiography is the most frequently used test to determine the cause, mechanism, and severity of mitral regurgitation.
- Guideline-directed medical therapy is the first-line approach in the treatment of patients who have heart failure with secondary mitral regurgitation and a reduced left ventricular ejection fraction (LVEF). Surgical or transcatheter intervention should be undertaken only after the patient has received the maximal dose of medical therapy without adverse effects.
- Surgical treatment of secondary mitral regurgitation consists of downsized annuloplasty repair or replacement. Surgery has not been shown to improve long-term survival among these patients.
- In one of two randomized trials of transcatheter edge-to-edge repair (TEER) involving patients with secondary mitral regurgitation and a reduced LVEF, guideline-directed medical therapy plus TEER significantly decreased the incidence of hospitalization for heart failure or death from any cause at 2 years.
- The concept of differentiating mitral regurgitation as proportionate or disproportionate has been proposed to explain the benefit of TEER for secondary mitral regurgitation. Prospective validation of this concept is needed.


Type I
Type II
Type IIIa
Type IIIb


LV
LA
LV
LA

The severity of secondary mitral regurgitation may vary dynamically as a function of left ventricular loading conditions, heart rhythm, conduction system disease, and myocardial ischemia. Ischemic mitral regurgitation is a type of secondary mitral regurgitation that occurs after myocardial infarction. Several studies have shown

	MR Severity*		
	Mild	Moderate	Severe
Structural			
MV morphology	None or mild leaflet tenting	Moderate tenting	Severe tenting, poor leaflet coaptation
LV and LA size^	See legend below	See legend below	See legend below

Qualitative Doppler

Color flow jet area	Small, narrow, brief	Variable	Large central jet (>50% LA) or eccentric jet of variable size
Flow convergence	Not visible, transient or small	Intermediate in size and duration	Large throughout systole

Semi-quantitative

VCW (cm)	<0.3cm	Intermediate	≥0.7cm
Pulmonary vein flow	Systolic dominance (may be blunted in LV dysfunction or AF)	Normal or systolic blunting	Minimal to no systolic flow/ systolic flow reversal
Mitral inflow	A-wave dominant	Variable	E-wave dominant

Quantitative[+]

EROA, 2D PISA (cm^2)	<0.20	0.20-0.29	0.30-0.39	≥0.40 (may be lower in secondary MR with elliptical ROA)
RVol (mL)	<30	0-44	44-59	≥60 (may be lower in low flow conditions)
RF (%)	<30	30-39	40-49	≥50

Table 1 **Echocardiographic parameters for the grading of MR severity**

Parameter	Mild	Moderate	Severe
Qualitative			
Mitral valve morphology	Normal /abnormal	Normal /abnormal	Significant prolapse of a leaflet or leaflets, flail leaflet or ruptured papillary muscle, severe leaflet(s) restriction
MR colour jet	Small central jet $<4\ cm^2$ or $<20\%$ of LA volume	Signs of MR >mild but no criteria for severe MR	Large central jet >40% of LA volume/ eccentric jet swirling in LA (any size)
Flow convergence	No or minimal flow convergence	Signs of MR >mild but no criteria for severe MR	Large flow convergence
CW-Doppler signal of MR jet	Soft density/parabolic	Dense/parabolic	Dense/triangular
Semi-quantitative			
Vena contracta width (cm)	<0.3 cm	Signs of MR >mild but no criteria for severe MR	≥0.7 cm (> 0.8 cm biplane)
Pulmonary vein flow	Systolic dominant flow	Intermediate signs	Systolic flow reversal
Mitral inflow	A-wave dominant	Intermediate signs	E-wave dominant (>1.5 m/s)
LA/LV size	Normal LV size	Intermediate signs	Enlarged LA and LV
Quantitative			
Regurgitant volume (R Vol) (mL/beat)[a]	<30	Mild–moderate: 30–44, moderate–severe: 45–59	≥60
Regurgitant fraction (RF) (%)	<30	Mild–moderate:30–39, moderate–severe: 40–49	>50
Effective regurgitant orifice area (EROA) (cm^2)[a]	<0.2	Mild–moderate: 0.2–0.29, moderate–severe: 0.3–0.39	≥0.4

categorization and surgical planning (Fig. S1). In Carpentier type IIIB disease, which is the main focus of this article, mitral regurgitation is attributable to restricted mitral-valve leaflet motion during systole in patients with an ischemic or nonischemic (dilated) cardiomyopathy. In patients with ischemic mitral regurgitation, the mitral-valve leaflets are also thickened and fibrotic, with reduced lengthening.[11] Mitral regurgitation occurs most often as a consequence of adverse left ventricular remodeling with papillary muscle displacement, leaflet tethering, reduced mitral-valve closing forces, annular dilation, and failure of leaflet coaptation. In some patients with ischemic mitral regurgitation, however, the left

ventricle is not substantially remodeled. With atrial functional mitral regurgitation (Carpentier type I), mitral-valve leaflet motion is normal and the mitral regurgitation is due to left atrium and annular enlargement with insufficient leaflet lengthening, as occurs in some patients with chronic persistent atrial fibrillation.[12]

regurgitation. The American College of Cardiology–American Heart Association (ACC–AHA) guidelines define severe secondary mitral regurgitation on the basis of an effective regurgitant orifice area of at least 0.4 cm^2 and a regurgitant volume of 60 ml or more (the same thresholds as those applied to primary mitral regurgitation).[15,16] In contrast, the guidelines of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery use lower cutoff points (effective regurgitant orifice area ≥0.2 cm^2 and regurgitant volume ≥30 ml)[17]; these cutoff points are based on data on the natural history of this condition that link these lower values with poor outcomes. The American Society of Echocardiography guidelines[14] caution that secondary mitral regurgitation may be severe even with an effective regurgitant orifice area of 0.3 cm^2 or more because of limitations in the technique used to measure it. One echocardiographic finding in isolation cannot define the severity of mitral regurgitation, and thus an integrative approach is needed.

When assessment of the anatomy and function of the mitral valve by means of transthoracic echocardiography is not adequate, transesophageal echocardiography and cardiac magnetic resonance imaging (MRI) can provide more specific anatomical and hemodynamic detail.[14] Because the patient has to be sedated during transesophageal echocardiography, the performance of this test can result in favorably altered left ventricular loading conditions and reduced severity of secondary mitral regurgitation. Thus, observations made on transthoracic echocardiography while the patient is awake should be used in clinical decision making. Cardiac MRI can provide accurate measurement of left ventricular volumes, detect areas of myocardial scarring, and assess for regional ischemia. Exercise transthoracic echocardiography may be useful when there are discrepancies between the clinical findings and data from other noninvasive testing. Cardiac catheterization with hemodynamic assessment, coronary angiography, and left ventriculography has a role in selected patients, particularly those with known or suspected coronary artery disease.[9]

MEDICAL THERAPY OR DEVICES

Recommendations regarding the treatment of secondary mitral regurgitation are based on multiple variables, including the type (ventricular or atrial), severity, and hemodynamic consequences of secondary mitral regurgitation; coexisting conditions; and the experience and expertise of the multidisciplinary team providing care. Guideline-directed medical therapy (Table S2) is the first-line

Drug Class and Agents	Initial Dose	Maximal or Target Dose	Comment
Beta-blockers Metoprolol Succinate	12.5-25 mg once daily	200 mg daily	Dose escalation should occur when the patient is in stable condition. Monitor HR, BP, ECG conduction intervals
Carvedilol	3.125 mg twice daily	25 mg twice daily (50 mg twice daily if weight >85kg)	Shown to reduce magnitude of secondary MR
Bisoprolol	1.25 mg twice daily	10 mg once daily	Less frequently used and longer-acting medication than metoprolol succinate and carvedilol
Angiotensin Receptor/Neprilysin Inhibitor: Sacubitril/Valsartan	24mg-26 mg twice daily	97mg-103 mg twice daily	Monitor blood pressure, renal function and potassium level; when transitioning from an ACE inhibitor, the ACE inhibitor should be held for at least 36 hours before first dose ofangiotensin-neprilysin inhibitor; do not administer to patients with history of angioedema with use of an ACE inhibitor.

ACE inhibitors Lisinopril	2.5-5 mg once daily	20-30 mg once daily	Cough occurs in 10-15% of patients who receive ACE inhibitors; monitor blood pressure, renal function and potassium level with use of all ACE inhibitors.
Ramipril	1.25-2.5mg once daily	10 mg once daily	
Enalapril	2.5mg twice daily	10 mg twice daily	Enalapril was the active control arm in PARADIGM-HF[20] trial showing benefit of an angiotensin-neprilysin inhibitor.
Captopril	6.25 mg thrice daily	50 mg thrice daily	Thricedaily regimen difficult to manage for outpatients.

Valsartan	40 mg twice daily	160 mg twice daily	
Candesartan	4-8 mg once daily	32 mg once daily	
Aldosterone Antagonists Spironolactone	12.5-25 mg once daily	25-50 mg once daily	Monitor potassium level; avoid use in patients with advanced chronic kidney disease.
Eplerenone	25 mg once daily	50 mg once daily	Use is associated with less frequent gynecomastia than occurs with spironolactone
Combination vasodilator: hydralazine-isosorbide dinitrate	37.5mg-20 mg twice daily	75mg-40 mg twice daily	Useful in Black patients and useful to consider in non-Black patients who cannot receive ACE inhibitors, ARBs or angiotensin-neprilysiin inhibitors; lower doses of the component medications may be necessary at initiation of therapy
I_f current inhibitor (the I_f current controls spontaneous phase 4 depolarization) ivabradine	5 mg twice	7.5mg twice	Use restricted to patients in sinus rhythm with resting heart rate > 70 beats/min despite treatment with a beta-blocker

SGLT2 inhibitor Dapagliflozin	10 mg once daily	10 mg once daily	Monitor for renal dysfunction, and hypovolemia; monitor for hypoglycemia in patients whok receive additional agents for diabetes mellitus
Guanylate cyclase stimulator:	2.5 mg once daily	10 mg once daily	Monitor blood pressure and hemoglobin levels; under FDA

sodium–glucose cotransporter 2 inhibitors.[18-21] Stepped therapy with these agents and others is implemented over a period of weeks to months. Both carvedilol[22] and sacubitril–valsartan[23] have been shown to reduce the degree of secondary mitral regurgitation.

Cardiac resynchronization therapy can improve left ventricular function, decrease left ventricle size, and reduce the magnitude of mitral regurgitation in selected patients who have heart failure with a reduced ejection fraction and left bundle-branch block, particularly when the QRS duration exceeds 150 msec.[24,25] In patients with atrial functional mitral regurgitation due to atrial fibrillation, restoration and maintenance of sinus rhythm can reduce the left atrium size, the mitral annular dimensions, and the degree of mitral regurgitation.[26] Attention to the principles of secondary prevention of coronary artery disease events (including lipid management) and reduction in the risk of sudden death (with an ICD) and stroke (with anticoagulation for atrial fibrillation) is important.

SURGERY

In contrast to primary mitral regurgitation, for which valve repair is indicated when symptoms develop or when certain thresholds for left ventricle size, function, or both are met,[14-16] surgical or transcatheter intervention for secondary mitral regurgitation should be pursued only in patients with persistent symptoms and residual moderately severe or severe mitral regurgitation despite an adequate 3-month trial of guideline-directed medical therapy.[9] Surgery for secondary mitral

In a randomized trial comparing mitral-valve repair with chordal-sparing mitral-valve replacement in 251 patients with severe ischemic mitral regurgitation (mean effective regurgitant orifice area, 0.4 cm^2), those assigned to mitral-valve replacement had a lower incidence of moderate-to-severe mitral regurgitation after surgery, fewer serious adverse events related to heart failure, and fewer readmissions for cardiovascular causes at 2 years, although there was no significant difference in survival at 2 years.[29] Thus, in contrast to severe primary mitral

difference in survival at 2 years.[29] Thus, in contrast to severe primary mitral regurgitation (for which valve repair is preferred over replacement), valve replacement may be preferred for treatment of severe ischemic mitral regurgitation. In another randomized trial involving patients with moderate ischemic mitral regurgitation (mean effective regurgitant orifice area, 0.2 cm^2), there was no difference between mitral-valve repair plus CABG and CABG alone with respect to the magnitude of left ventricular reverse remodeling, and survival was not longer with mitral-valve repair plus CABG than with CABG alone.[30]

Table 1. 2017 Guidelines for Intervention in Patients with Chronic Severe Secondary Mitral Regurgitation.*

American College of Cardiology–American Heart Association

Class IIa recommendation

Mitral-valve surgery is reasonable for patients with chronic severe secondary mitral regurgitation who are undergoing CABG or aortic-valve replacement. (Level of evidence: C)

It is reasonable to choose chordal-sparing mitral-valve replacement over repair with a downsized annuloplasty ring if the operation is considered for severely symptomatic patients with chronic severe ischemic mitral regurgitation and persistent symptoms despite the use of maximal doses of guideline-directed medical therapy without adverse effects. (Level of evidence: B)

Class IIb recommendation

Mitral-valve repair or replacement may be considered for severely symptomatic patients with chronic severe secondary mitral regurgitation who have persistent symptoms despite the use of maximal doses of guideline-directed medical therapy without adverse effects. (Level of evidence: B)

European Society of Cardiology and the European Association for Cardio-Thoracic Surgery

Class I recommendation

Surgery is indicated in patients with severe secondary mitral regurgitation who are undergoing CABG and who have an LVEF >30%. (Level of evidence: C)

Class IIa recommendation

Surgery should be considered in symptomatic patients with severe secondary mitral regurgitation and an LVEF <30% who have an indication for revascularization and evidence of myocardial viability. (Level of evidence: C)

Class IIb recommendation

When revascularization is not indicated, surgery may be considered in patients with severe secondary mitral regurgitation and an LVEF >30% who remain symptomatic despite the use of maximal doses of medical therapy without adverse effects (and cardiac resynchronization therapy if indicated) and have a low risk of surgery-related complications or death. (Level of evidence: C)

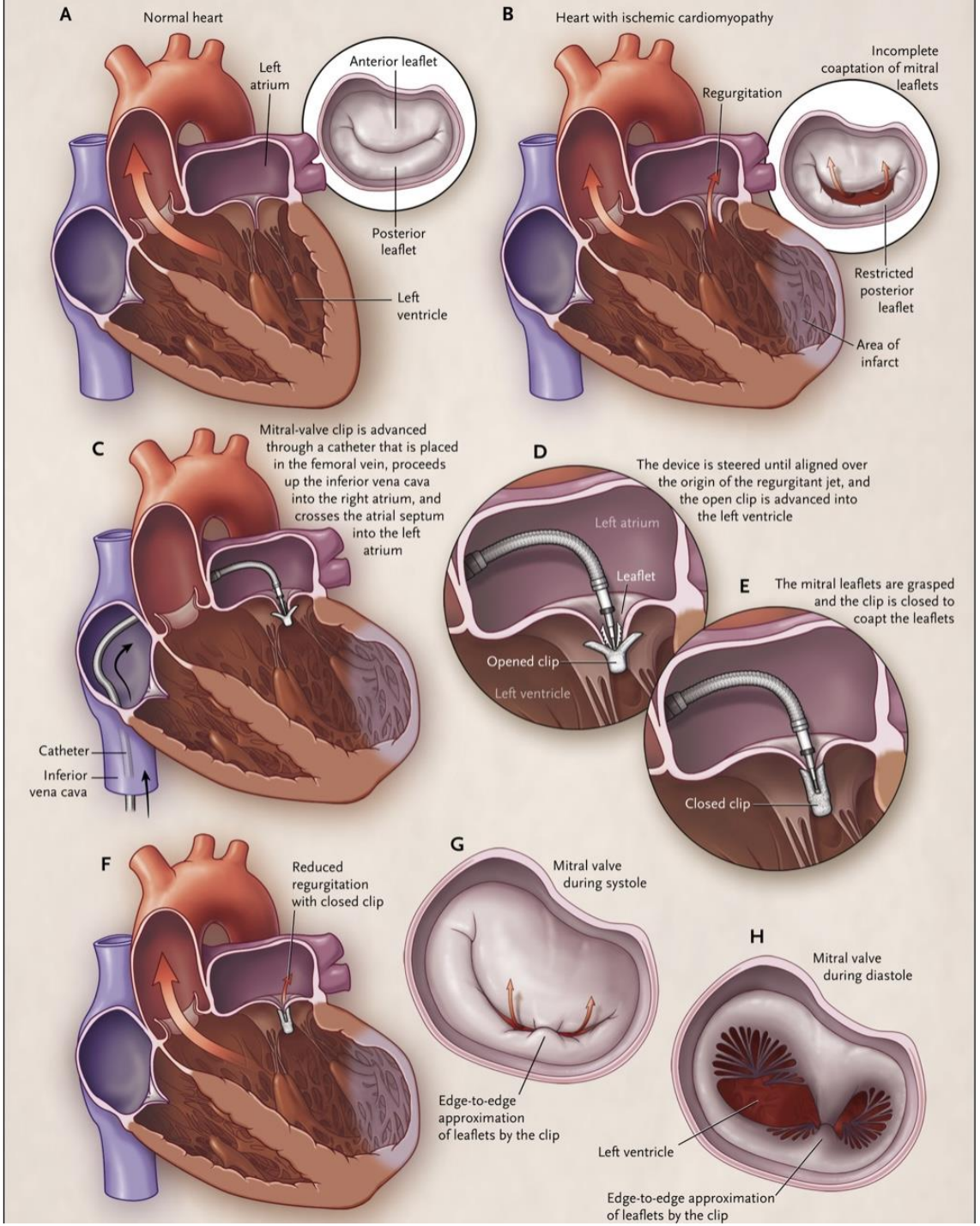
When revascularization is not indicated and the risk of surgery-related complications or death is not low, a percutaneous edge-to-edge procedure may be considered in patients with severe secondary mitral regurgitation and an LVEF >30% who remain symptomatic despite the use of maximal doses of medical therapy without adverse effects (and cardiac resynchronization therapy, if indicated) and who are found to have suitable valve morphologic characteristics on echocardiography, if the heart team thinks there is a reasonable chance for clinical improvement. (Level of evidence: C)

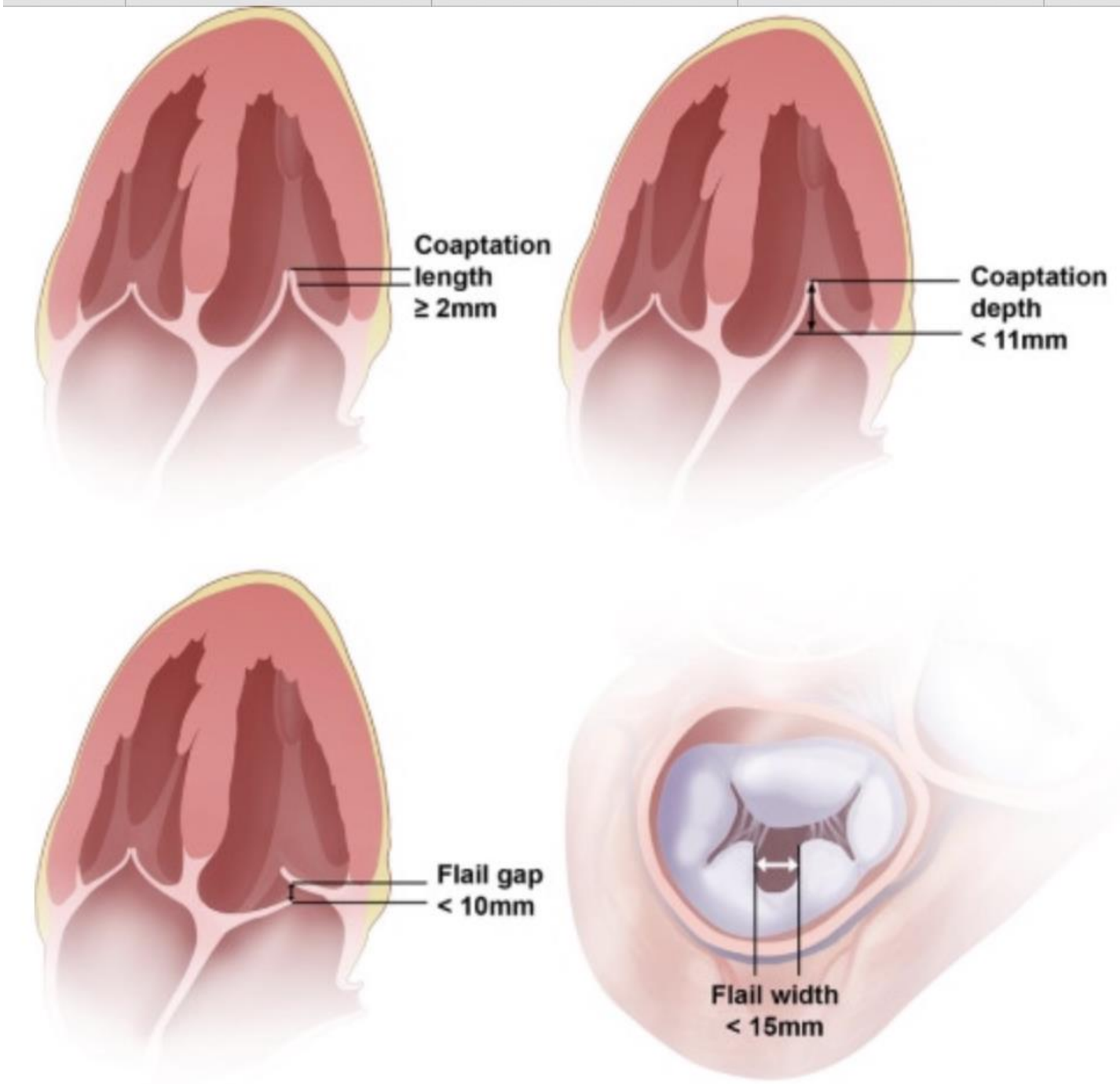
In patients with severe secondary mitral regurgitation and an LVEF <30% who remain symptomatic despite the use of maximal doses of medical therapy without adverse effects (and cardiac resynchronization therapy if indicated) and who have no option for revascularization, the heart team may consider a percutaneous edge-to-edge procedure or valve surgery after careful evaluation for a left ventricular assist device or heart transplantation according to individual patient characteristics. (Level of evidence: C)

* The class of recommendation indicates the strength of the recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. In general, a class I recommendation indicates that the intervention is indicated or useful and should be performed. A class IIa recommendation implies that the intervention is reasonable and can be effective, whereas a class IIb recommendation implies that the usefulness or effectiveness of the intervention is less certain. The guidelines differ with respect to methods and language, although the recommendations are directionally concordant. The level of evidence rates the quality of scientific evidence that supports the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources. Level B evidence may derive from randomized trials, observational studies, and registries, and it is considered to be of moderate quality. Level C evidence relies on limited data, expert opinion, or both. These guideline recommendations reflect the strength of the evidence base in existence in 2017. CABG denotes coronary-artery bypass grafting, and LVEF left ventricular ejection fraction.

TRANSCATHETER REPAIR OR REPLACEMENT

In transcatheter intervention for mitral regurgitation, the use of a clip (MitraClip, Abbot Vascular) to create an edge-to-edge approximation of the midportion of the mitral-valve leaflets results in a double-orifice


A
Normal heart
Left atrium
Anterior leaflet
Posterior leaflet
Left ventricle
B
Heart with ischemic cardiomyopathy
Incomplete coaptation of mitral leaflets
Regurgitation
Restricted posterior leaflet
Area of infarct
C
Mitral-valve clip is advanced through a catheter that is placed in the femoral vein, proceeds up the inferior vena cava into the right atrium, and crosses the atrial septum into the left atrium
Catheter
Inferior vena cava
D
The device is steered until aligned over the origin of the regurgitant jet, and the open clip is advanced into the left ventricle
Left atrium
Leaflet
Opened clip
Left ventricle
E
The mitral leaflets are grasped and the clip is closed to coapt the leaflets
Closed clip
F
Reduced regurgitation with closed clip
G
Mitral valve during systole
Edge-to-edge approximation of leaflets by the clip
H
Mitral valve during diastole
Left ventricle
Edge-to-edge approximation of leaflets by the clip


Coaptation
length
≥ 2mm
Coaptation
depth
< 11mm
Flail gap
< 10mm
Flail width
< 15mm

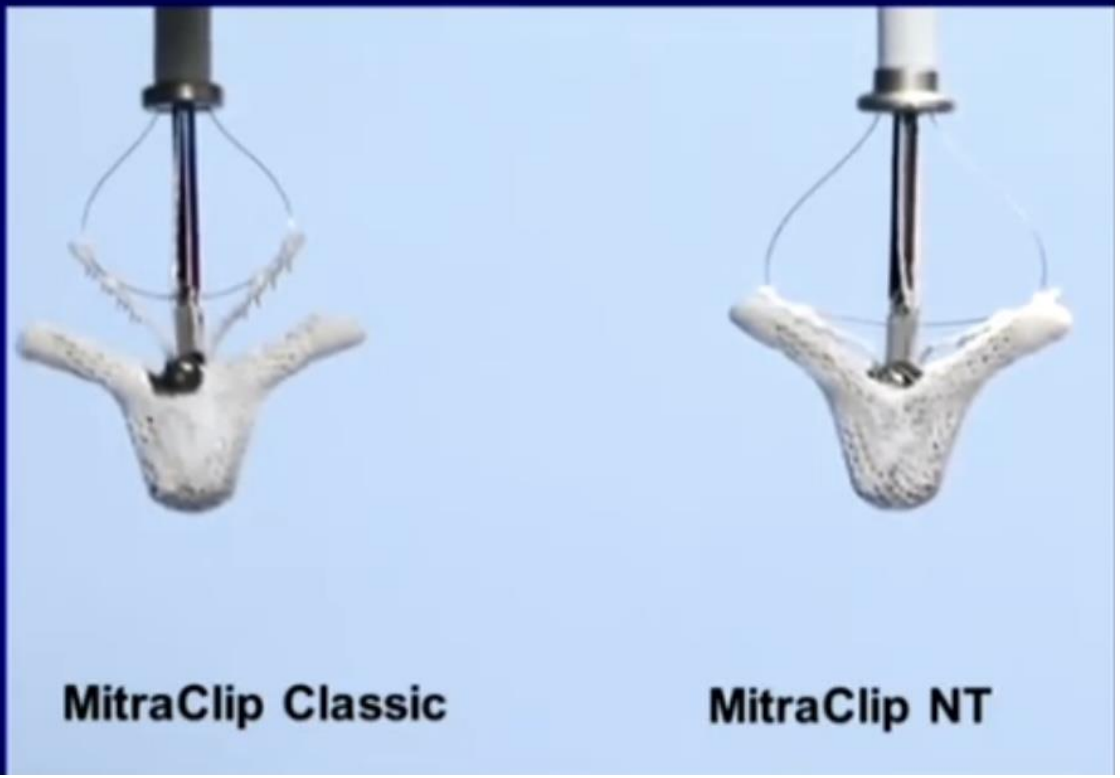
MitraClip
Patient Selection Echo Considerations

Everest criteria[1]

- Moderate to severe/Severe MR (Grade 3 – 4)
- Pathology in A2-P2 area
- Coaptation length > 2 mm (depending on leaflet mobility)
- Coaptation depth < 11 mm
- Flail gap < 10 mm
- Flail width < 15 mm
- Mitral valve orifice area >4cm^2 (depending on leaflet mobility)
- Mobile leaflet length > 1cm

MitraClip NT

- Improved leaflet engagement
- Enhanced steering control
- Designed for challenging cases



MitraClip in Specific Patient Populations

Patient groups in which significant clinical benefits have been reported:

- Degenerative MR, declined for surgery[1]
- Severe LV dysfunction refractory to medical therapy[2]
- Severe Heart Failure, despite optimal medical therapy[3]
- CRT non-responders[4]
- Bivalvular Disease: Severe Aortic Stenosis and Mitral Regurgitation[5]

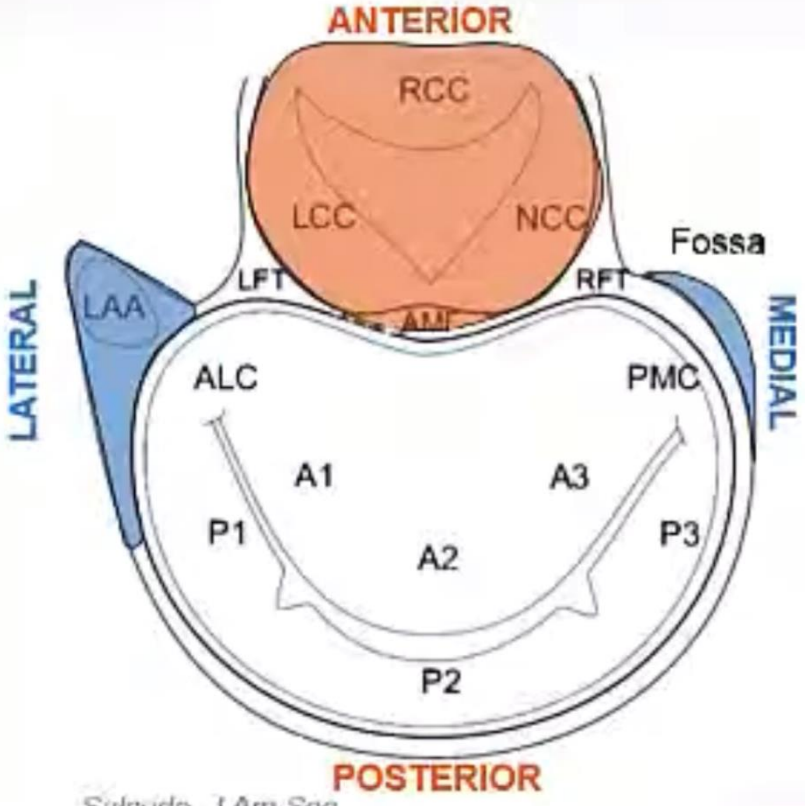
The following parameters should be taken into consideration by the Heart Team[6]:

- Moderate to severe or severe MR (Functional or Degenerative)
- Echocardiographic criteria for eligibility
- Level of surgical risk
- Greater than one year life expectancy

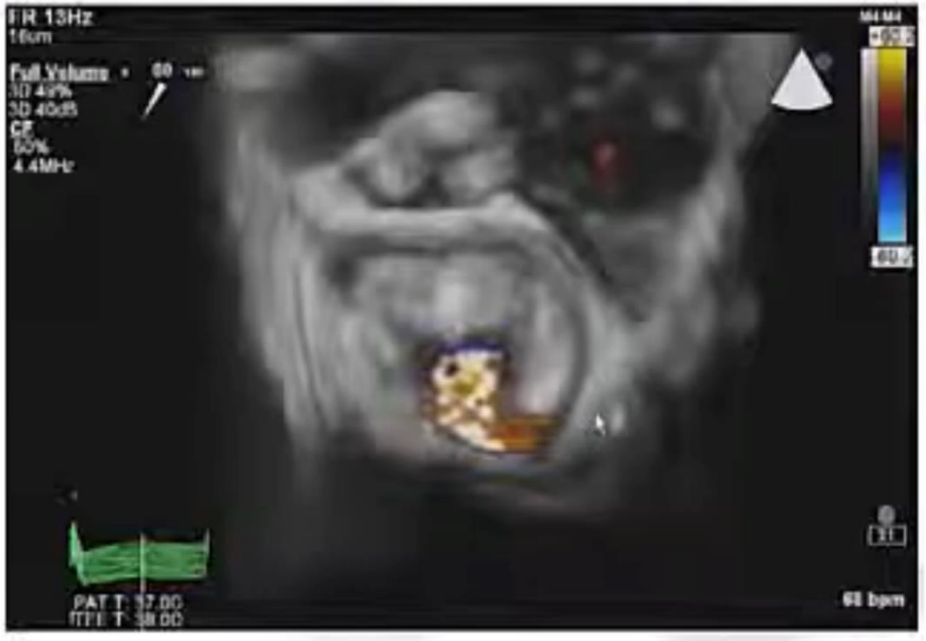
1. Reichenspurner, H. et al. Clinical Outcomes through 12 months in patients with Degenerative Mitral Regurgitation treated with the MitraClip device in the ACCESS-Europe Phase I trial Eur J Cardiothoracic Surgery. 2013: 44 e 280-288. 2. Franzen O, Baldus S, Rudolph V, et al. Acute outcomes of MitraClip therapy for mitral regurgitation in high-surgical-risk patients: Emphasis on adverse valve morphology and severe left ventricular dysfunction. Eur Heart J. 2010, 31 1373-1381. 3. Franzen et al. MitraClip Therapy in Patients With End-Stage Systolic Heart Failure. Eur J Heart Failure. 2011; 13: 569-576. 4. Auricchio et al. Correction of Mitral Regurgitation in Nonresponders To Cardiac Resynchronization Therapy By MitraClip Improves Symptoms And Promotes Reverse Remodeling. JACC 2011; 58: 2183-2189. 5. Rudolph V, Schirmer J, Franzen O, Schüler M, Seiffert M, Treede H, Reichenspurner H, Blankenberg S, Baldus S. Bivalvular transcatheter treatment of high-surgical-risk patients with coexisting severe aortic stenosis and significant mitral regurgitation. Int J Cardiol. 2013; 167(3):718-20. 6. ESC/EACTS 2012 Guidelines on the management of valvular heart disease. Eur Heart J (2012) 33, 2451–2496.

Echo related valve anatomy

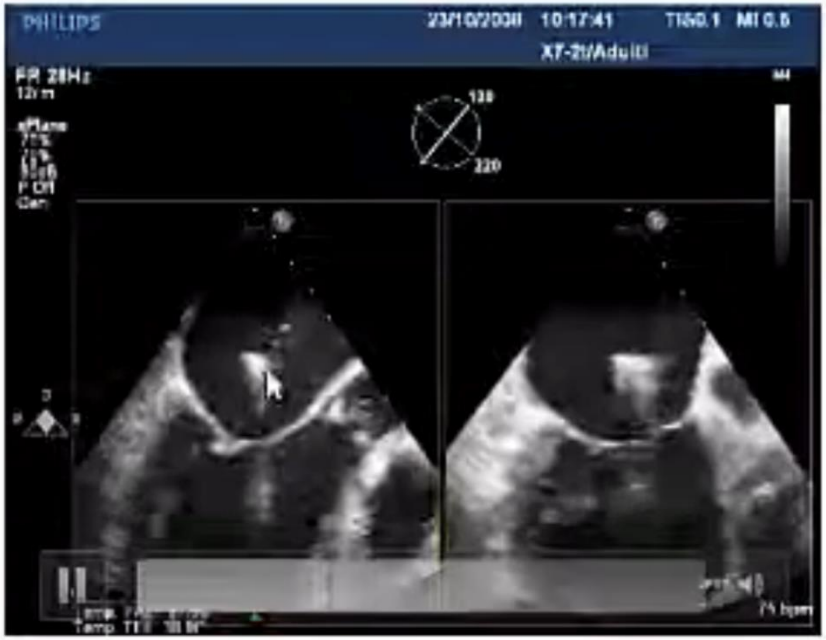
Use of common anatomically based vocabulary reinforces clear communication



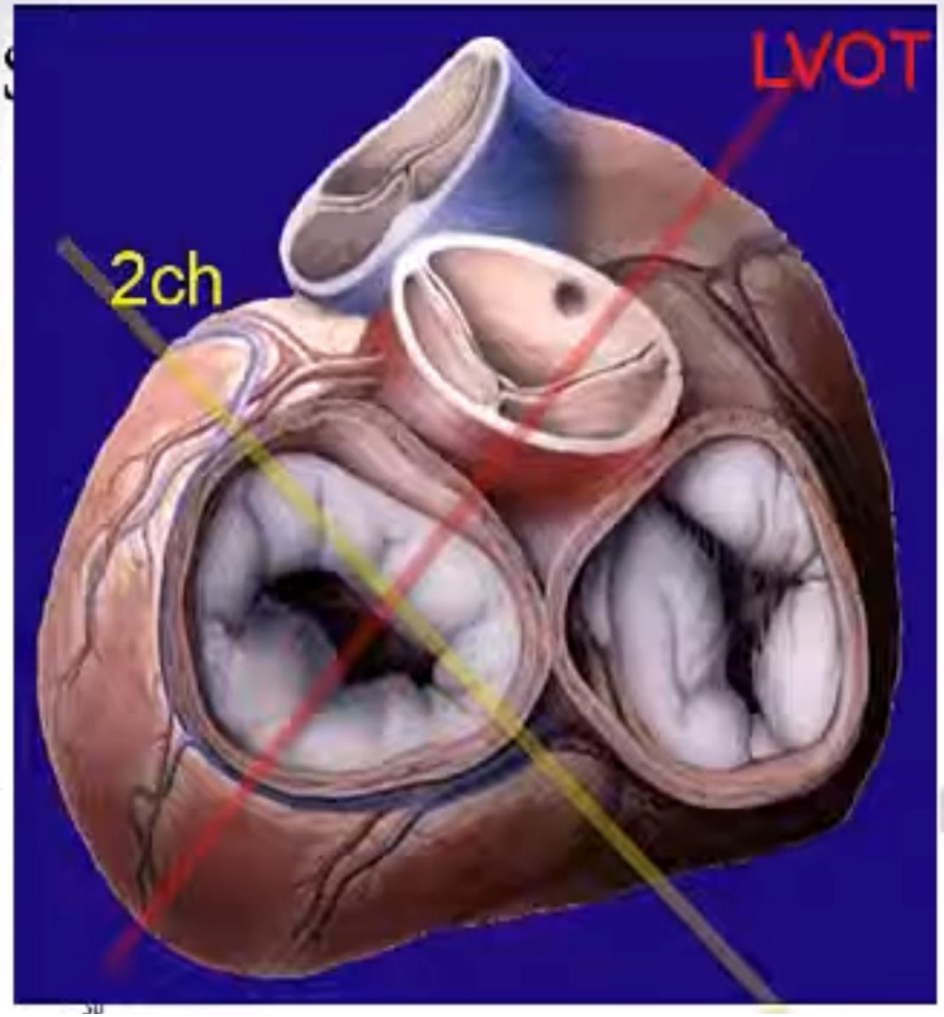
Salcedo, J Am Soc Echocardiogr, 2009



X Plane Allows Better Understanding of Where We Are

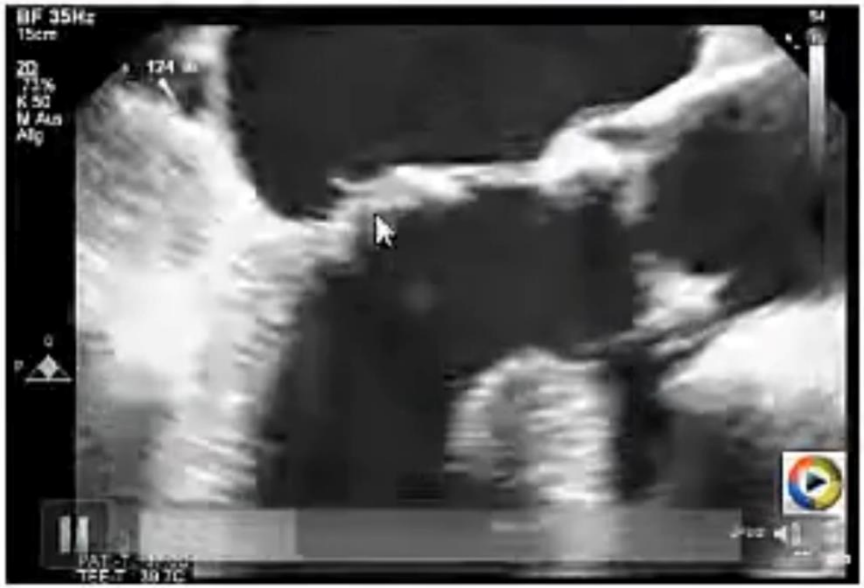


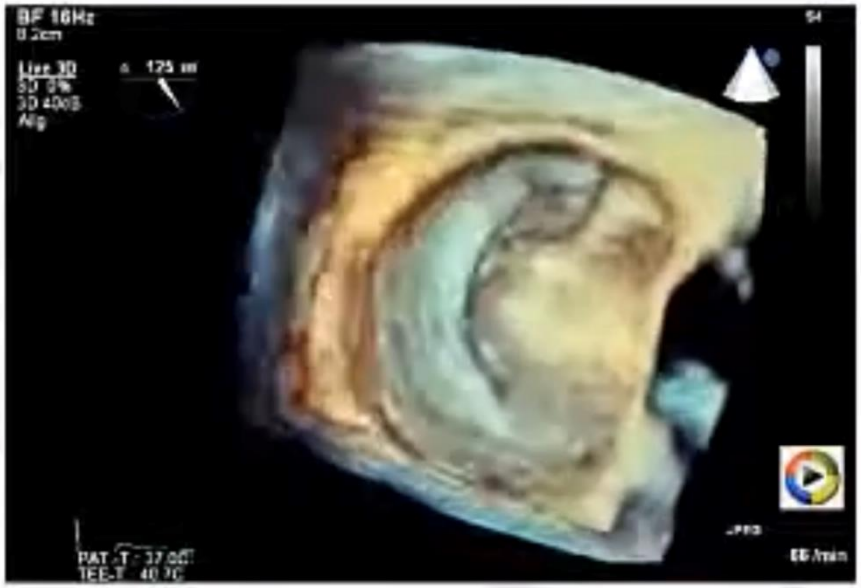
LVOT 2ch



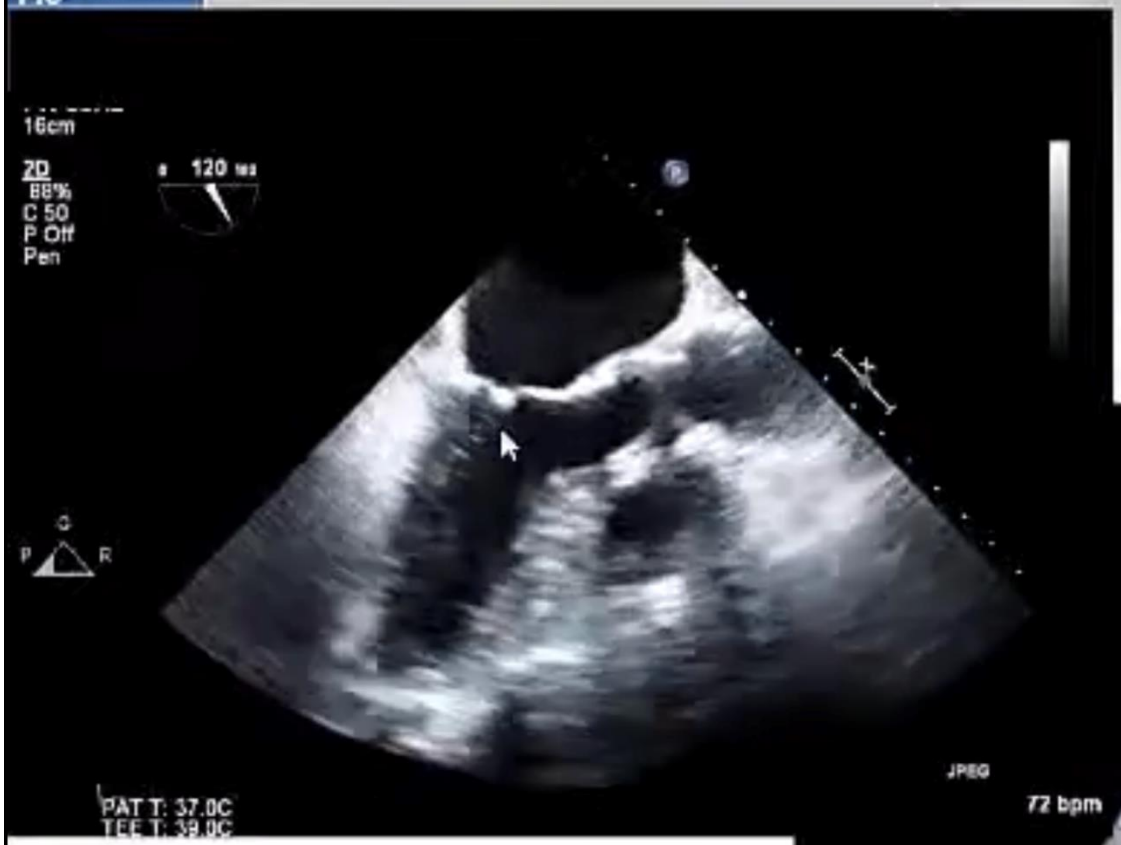
Rejected for MitraClip

Mitral valve stenosis (valve area < 4 cm^2)

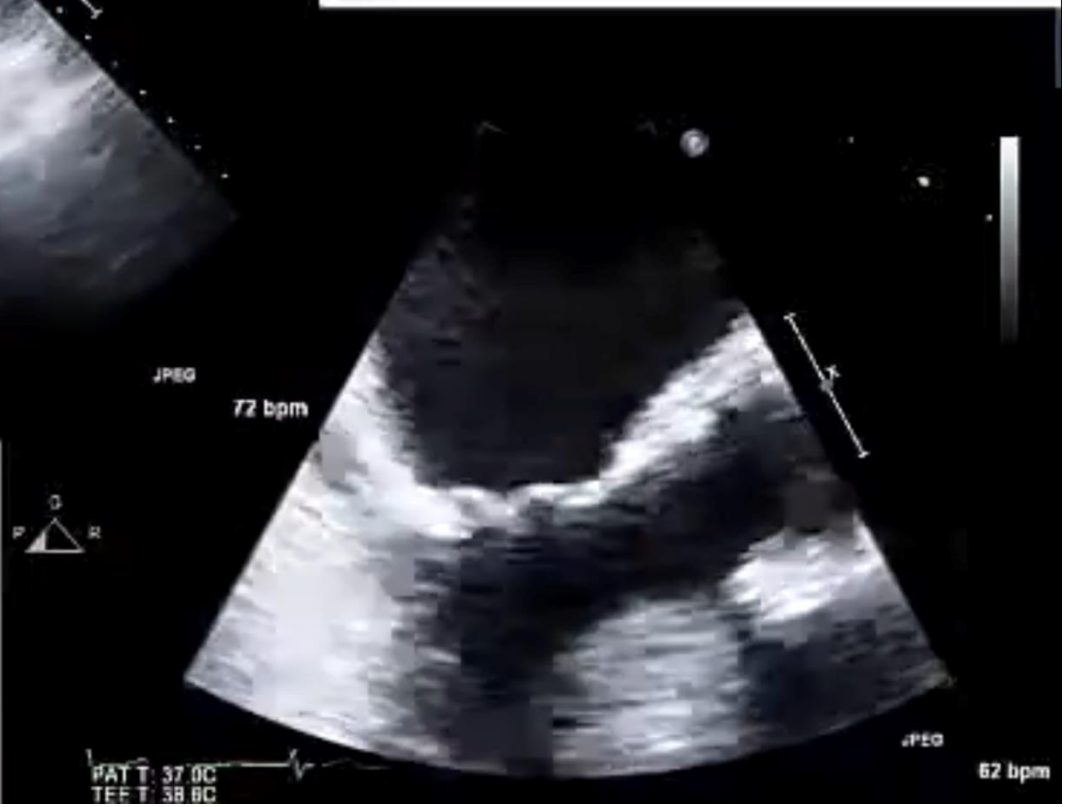




Rejected for MitraClip



Calcification in grasping area & short PML



Top 10 pearls for success of Clip

- Case selection
- Vascular access/closure
- Choose your imaging specialist
- Proper transseptal
- Real time Left atrial pressure monitoring
- Orientation of clip prior to grasping
- Holding the respirator during grasping and position of clip
- Confirming leaflet insertion
- Low threshold to use more then one clip
- Combined echo and invasive hemodynamic is helpful the final result

- Echo (TTE/TEE) is an essential diagnostic and a screening tool for mitral clip candidates
- TTE first, general assessment and look for exclusion criteria.
- Preprocedural TEE – good imaging, 2 D, 3D, X plane, understand the anatomy
- When needed - CT ?, MRI?
- Building a common language between all members of the Structural Heart Team will ensure successful results.

Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial randomly assigned 614 patients with secondary mitral regurgitation (approximately 60% of whom had ischemic cardiomyopathy) and symptomatic heart failure with a reduced LVEF to either transcatheter edge-to-edge repair (TEER) plus guideline-directed medical therapy or guideline-directed medical therapy alone.[32] The addition of TEER to medical therapy resulted in significantly fewer hospitalizations for heart failure and improved survival at 2 years, with a low incidence of device-related complications.

extent, and distribution of calcification.[9] The FDA approved the MitraClip device in March 2019 for use in patients with secondary mitral regurgitation who meet the inclusion criteria of the COAPT trial. These criteria are symptomatic heart failure with an ejection fraction of 20 to 50% and moderate-to-severe or severe mitral regurgitation despite guideline-directed medical therapy (plus cardiac resynchronization therapy, if indicated), a left ventricular end-systolic dimension of less than 7.0 cm, and a pulmonary-artery systolic pressure of less than 70 mm Hg.

Areas of Uncertainty

The disparate results of the COAPT and MITRA-FR trials have confused the clinical community. A third trial (A Clinical Evaluation of the Safety and Effectiveness of the MitraClip System in the Treatment of Clinically Significant Functional Mitral Regurgitation [RESHAPE-HF2]) (ClinicalTrials.gov number, NCT02444338) of the same device in similar patients is currently recruiting patients and is designed to provide additional data to guide the appropriate use of TEER in patients with secondary mitral regurgitation.

often not sufficient, and mortality among patients who have heart failure with a reduced ejection fraction and secondary mitral regurgitation remains high (e.g., 29% at 2 years in the device group of the COAPT trial); effective strategies are needed to improve guideline adherence.[43,44] Given the results of the COAPT trial, the role of surgery in the management of secondary mitral regurgitation has become less clear for patients in whom there is no other primary indication for operation, such as severe coronary artery disease, for which CABG would be preferred over percutaneous coronary intervention.

In the patient described in the vignette, the cause, mechanism, and severity of mitral regurgitation should be evaluated by means of transthoracic echocardiography, and an assessment of myocardial ischemia and viability should be performed. The first-line approach should be to initiate a regimen for heart failure that includes a low dose of an angiotensin-converting–enzyme inhibitor (or an angiotensin-receptor blocker), adjusted with attention to the patient's blood pressure, renal function, and potassium level, followed by an attempt to switch to an angiotensin receptor–neprilysin inhibitor. Efforts should be made to administer the doses of medications that have been shown to be useful in randomized heart failure trials. Cardiac resynchronization therapy should be considered if indicated.[45]

If severe heart failure symptoms persist after the use of maximal doses of guideline-directed medical therapy without adverse effects for 3 months, TEER can be considered if the patient meets the inclusion criteria of the COAPT trial noted above and transesophageal echocardiographic assessment of the leaflet structure and motion indicates that this is feasible. We would consult with a multidisciplinary team that includes a heart failure specialist, an echocardiographer, an interventionalist, and a surgeon to seek a consensus recommendation regarding the best treatment strategy, and we would pursue a shared decision-making process with the patient and his family.

COAPT TRIAL MITRA CLIP

CRITERI DI INCLUSIONE

Subjects must meet all of the following inclusion criteria to participate in the trial:

1. Symptomatic functional MR (≥3+) due to cardiomyopathy of either ischemic or non- ischemic etiology determined by assessment of a qualifying transthoracic echocardiogram (TTE) obtained within 90 days and transesophageal echocardiogram (TEE) obtained within 180 days prior to subject registration, with MR severity based principally on the TTE study, confirmed by the Echocardiography Core Lab (ECL). The ECL may request a transesophageal echocardiogram (TEE) to confirm MR etiology.

Note: Functional MR requires the presence of global or regional left ventricular wall motion abnormalities, which are believed to be the primary cause of the MR. If a flail leaflet or other evidence of degenerative MR is present, the subject is not eligible even if global or regional left ventricular systolic dysfunction is present.

Note: Qualifying TTE must be obtained after the subject has been stabilized on optimal therapy including GDMT and at least 30 days after:

a) a greater than 100% increase or greater than 50% decrease in dose of GDMT

b) revascularization and/or implant of Cardiac Resynchronization Therapy device (CRT or CRT-D) or reprogramming of an implanted CRT or CRT-D that results in increased biventricular pacing (from <92% to ≥92%)

2. In the judgment of the HF specialist investigator at the site, the subject has been adequately treated per applicable standards, including for coronary artery disease, left ventricular dysfunction, mitral regurgitation and heart failure (e.g., with cardiac resynchronization therapy, revascularization, and/or GDMT;

3. The subject has had at least one hospitalization for heart failure in the 12 months prior to subject registration and/or a corrected BNP ≥300 pg/ml or corrected NT-proBNP ≥1500 pg/ml measured within 90 days prior to subject registration ("corrected" refers to a 4% reduction in the BNP or NT-proBNP cutoff for every increase of 1 kg/m2 in BMI above a reference BMI of 20 kg/m2).

Note: BNP or NT-proBNP must be obtained after the subject has been stabilized on GDMT and at least 30 days after:

a) a greater than 100% increase or greater than 50% decrease in dose of GDMT

b) revascularization and/or implant of Cardiac Resynchronization Therapy device (CRT or CRT-D) or reprogramming of an implanted CRT or CRT-D that results in increased biventricular pacing (from <92% to ≥92%)

4. New York Heart Association (NYHA) Functional Class II, III or ambulatory IV.

5. The Local Site Heart Team (CT surgeon and HF specialist investigators) and the Central Eligibility Committee concur that surgery will not be offered as a treatment option and that medical therapy is the intended therapy for the subject, even if the subject is randomized to the Control group.

6. Left Ventricular Ejection Fraction (LVEF) is ≥20% and ≤50% within 90 days prior to subject registration, assessed by the site using any one of the following methods: echocardiography, contrast left ventriculography, gated blood pool scan or cardiac magnetic resonance imaging (MRI).

Note: The method must provide a quantitative readout (not a visual assessment).

7. Left Ventricular End Systolic Dimension (LVESD) is ≤70 mm assessed by site based on a transthoracic echocardiographic (TTE) obtained within 90 days prior to subject registration.

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8. The primary regurgitant jet is non-commissural, and in the opinion of the MitraClip implanting investigator can be successfully be treated by the MitraClip. If a secondary jet exists, it must be considered clinically insignificant.
9. Creatine Kinase-MB (CK-MB) obtained within prior 14 days < local laboratory ULN (Upper Limit of Normal)
10. Transseptal catheterization and femoral vein access is determined to be feasible by the MitraClip implanting investigator.
11. Age 18 years or older.
12. The subject or the subject's legal representative understands and agrees that should he/she be assigned to the Control group, he/she will be treated with medical therapy and conservative management without surgery and without the MitraClip, either domestically or abroad. If the subject would actively contemplate surgery and/or MitraClip if randomized to Control, he/she should not be registered in this trial.
13. The subject or the subject's legal representative has been informed of the nature of the trial and agrees to its provisions, including the possibility of randomization to the Control group and returning for all required post-procedure follow-up visits, and has provided written informed consent.