Chapter 24: Diagnostic workup and evaluation: eligibility, risk assessment, FDA guidelines

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Mitral regurgitation, regurgitant flow between the left ventricle and left atrium during ventricular systole, can be classified as either primary or secondary based on the etiology of the failure of the mitral valve apparatus to prevent regurgitant flow. Primary mitral regurgitation refers to regurgitation as a consequence of principal pathology of the mitral valve apparatus, , such as myxomatous/degenerative or rheumatic disease. Secondary mitral regurgitation, or functional mitral regurgitation, is due to abnormalities of the left ventricle and resultant distortion of the mitral valve apparatus causing poor coaptation of the mitral valve leaflets. The principle pathology in secondary mitral regurgitation is left ventricular remodeling and dilation in the setting of cardiomyopathy or left ventricular wall motion abnormalities due to ischemia

The approaches to therapy for primary and secondary mitral regurgitation are different. For patients with primary mitral regurgitation who have symptoms or evidence of left ventricular dysfunction or dilation, mitral valve repair surgery is the treatment of choice for operable patients [1,2]. Mitral valve replacement surgery is an alternative treatment for operable patients with primary mitral regurgitation in whom repair cannot be performed successfully or is not feasible. Surgery is rarely considered for secondary mitral regurgitation, where the primary pathology is due to left ventricular distortion. Instead, therapies in secondary mitral regurgitation focus on medical therapy to reverse left ventricular remodeling, and intervention is considered only after goal directed medical therapy [1,2].

In a subset of patients with primary mitral regurgitation, comorbidities may make the risk of open surgery prohibitive or high risk. In these patients, percutaneous mitral valve repair can be attempted to ameliorate the symptoms and minimize regurgitant flow.

MitraClip

The MitraClip (Abbott Laboratories, Abbott Park, IL) procedure is a percutaneous modification of the Alfieri stitch or edge-to-edge technique that was described in the 1990's [3]. This strategy for mitral valve repair attempts to anchor the free edge of a prolapsing leaflet to the corresponding free edge of the facing leaflet. Instead of suture, the MitraClip anchors the two mitral leaflets with a clip that cinches the mitral valve leaflets together from the ventricular side. The MitraClip device is now FDA-approved for treatment of severe primary degenerative mitral regurgitation in patients who are high-risk candidate for surgical repair.

<u>Eligibility</u>

The MitraClip is indicated in patients with severe, symptomatic primary mitral regurgitation (NYHA class III or IV) who are deemed to have a 'prohibitive risk' for mitral valve surgery by a heart team (Table 1). 'Prohibitive risk' is defined as a Society of Thoracic Surgeons Score predicted risk of mortality of over 8% for mitral valve replacement or 6% for mitral valve repair. Other factors that may make surgery unfavorable include a porcelain aorta or an

extensively calcified ascending aorta, frailty, a hostile chest, severe liver disease with cirrhosis, and severe pulmonary hypertension [4].

Conversely, the MitraClip is contraindicated in patients who cannot tolerate procedural anticoagulation or the necessary post-procedural anti-platelet regimen (Table 1). Further contraindications include active endocarditis of the mitral valve, rheumatic mitral valve disease, and evidence of intracardiac, inferior vena cava or femoral venous thrombus that would preclude device delivery [4].

Anatomic Criteria for MitraClip Use

As in surgical mitral valve replacement, pre-procedural transesophageal echocardiographic assessment of the mitral valve apparatus is imperative in identifying those patients who would benefit most from this procedure [5] (Table 2). The highest success with MitraClip comes from those patients with primary mitral regurgitation that originates from the mid portion of the valve, involving the A2 and P2 segments of the mitral valve. In order for the MitraClip to be able to adhere reliably to the leaflets, a lack of calcification in the grasping area is imperative. Furthermore, to avoid the risk of iatrogenic mitral stenosis as a result of MitraClip placement, choosing patients with a starting mitral valve area of greater than $4cm^2$ is recommended [5]. Important leaflet considerations include a length of the posterior leaflet of greater than 10mm, a flail width less than 15mm, and flail-gap less than 10mm, in order to have sufficient leaflet tissue for grasping and to maximize the likelihood of successful reduction in mitral regurgitation.

Unsuitable valve morphology for the MitraClip procedure includes patients who have perforated mitral leaflets and lack of primary or secondary chordal support (Table 2). Further, severe calcification in the grasping area makes leaflet apposition difficult and puts the patient at risk for thromboembolic events through disruption of a calcific shelf. Patients who have underlying mitral stenosis are not candidates for MitraClip, as placement of a clip may worsen existing mitral stenosis. Leaflet characteristics that preclude the use of the MitraClip include a length of the posterior leaflet of under 7mm, rheumatic valve disease with restriction in systole and diastole, and a gap between the leaflets of greater than 2 mm.

Clinical Trial Data

The EVEREST II clinical trial was a Phase III randomized clinical trial that compared MitraClip versus surgical repair or replacement for patients with moderate or severe primary mitral regurgitation [6]. Inclusion criteria included echocardiographic criteria for moderate or severe mitral regurgitation and a left ventricular ejection fraction of greater than 25% and left ventricular end systolic diameter of less than 55 mm in the presence of symptoms, or asymptomatic patients with a left ventricular ejection fraction between 25-60%, left ventricular end systolic diameter greater than 40 mm, new onset atrial fibrillation, or pulmonary artery systolic pressure of greater than 50 mm at rest or 60 mm with exercise. The primary safety endpoint was a 30-day composite of death, myocardial infarction, reoperation or failed mitral valve surgery, non-elective cardiovascular surgery for adverse events, stroke, renal failure, deep wound infection, mechanical ventilation for greater than 48 hours, gastrointestinal complications requiring surgery, new onset permanent atrial fibrillation, septicemia or transfusion of greater

than two units of blood. The primary efficacy endpoint was a 12-month composite of freedom from death, surgery for mitral valve-dysfunction and grade 3+ or 4+ mitral regurgitation. The primary safety endpoint occurred in 48% of patients undergoing surgery and 15% of patients who received the MitraClip ($p<0.001$), though this was driven primarily by a difference in transfusion rates in the two groups. If transfusions were removed as an endpoint, major adverse events occurred in 10% of patients undergoing surgery and 5% of patients undergoing MitraClip placement ($p=0.23$). In the patients randomized to surgery, the majority had a successful mitral valve repair, with only 14% requiring valve replacement. The primary efficacy endpoint occurred in 73% of patients undergoing surgery and 55% of patients undergoing MitraClip placement at 12 months ($p=0.007$); there were no significant differences in the incidence death or that of moderate or severe MR between the two groups, and the difference in endpoint was driven by the higher incidence of need for mitral valve surgery in the percutaneous therapy arm (20% vs. 2% in patients randomized to initial surgery). There was also a greater reduction of mitral regurgitation severity at 1 year with mitral valve surgery as compared to MitraClip placement ($p<0.001$). Based on the results of the EVEREST II trial, the FDA determined that the data did not demonstrate an appropriate risk-benefit profile when compared to standard mitral valve surgery for patients with moderate to severe primary mitral regurgitation, and were inadequate to support approval for the device in patients who are surgical candidates, particularly if they are likely to only need a mitral valve repair.

The EVEREST II High-Risk registry and REALISM Continued Access Study High-Risk Arm were prospective registries of high-risk patients who received the MitraClip device, with high-risk defined as having predicted surgical mortality risk of greater than 12%[7]. In that heterogeneous group of patients that included primary and secondary mitral regurgitation, the MitraClip device reduced the mitral regurgitation severity to less than 2+ in 84% of patients at 12 months, with significant reductions in left ventricular end systolic and diastolic volumes and NYHA functional classification. Based on the results of this registry, the FDA Advisory Panel determined that the MitraClip was safe for use in patients considered high risk for surgery, and that benefits of treatment outweighed risks in these high risk surgical patients. Upon further investigation, the majority of the benefits occurred in patients with primary mitral regurgitation, and thus, the device is approved for use in patients with primary mitral regurgitation who are ineligible for valve surgery due to prohibitive risk.

Recently, the 5-year follow up of the EVEREST II trial has been published. Patients randomized to the MitraClip device had a higher degree of mitral regurgitation at 5 years than those randomized to surgery first, with 12.3% of patients treated with MitraClip with 3+ or 4+ mitral regurgitation, as compared to 1.8% of patients treated surgically. While there were higher rates of subsequent mitral surgery in the group randomized to MitraClip for residual MR, 78% of these surgeries were performed within the first 6 months, with comparable rates of surgery and moderate-to-severe mitral regurgitation in both groups beyond 6 months, suggesting durability of the MitraClip if initially successful [8].

Carillon

The Carillon Mitral Contour System (Cardiac Dimensions, Kirkland, WA) is a percutaneous approach to mitral valve annuloplasty by taking advantage of the proximity of the

coronary sinus to the mitral annulus. The annulus is cinched using a shaping ribbon that is placed in the coronary sinus. This technique was initially described in an experimental dog model in 2004 [9], and since then, two small scale Phase I clinical trials have demonstrated efficacy of the Carillon system in patients with secondary mitral regurgitation. In AMADEUS [10] and TITAN [11], patients with moderate to severe secondary mitral regurgitation were enrolled, with roughly 60-70% of patients having the device successfully placed. In those patients with successful device placement, there was a decrease in the severity of secondary mitral regurgitation and improvement in 6-minute walk distances. Based on this data, the Carillon system received a European CE Mark and an investigational device exemption from the FDA in December of 2016. Further studies will demonstrate the potential benefits of this new technology.

Conclusion

Open heart surgical valve repair or replacement remains the treatment of choice for patients with severe primary mitral regurgitation. However, emerging technologies are providing options for those patients who have high surgical risk or are ineligible for surgical repair or replacement. Looking forward, as both minimally invasive surgical approaches and transcatheter technologies mature, it is likely that there will be more options for the treatment of mitral valve pathologies, particularly in higher risk cohorts.

Indications and Contraindications for MitraClip
Indications
Symptomatic MR (NYHA III or IV)
Severe MR (≥3+)
Primary MR
Prohibitive risk for mitral valve surgery assessed by heart team
30-day STS predicted operative mortality risk score of:
≥8% for mitral valve replacement
≥6% for mitral valve repair
Porcelain aorta or extensively calcified ascending aorta
Frailty
Hostile chest
Severe liver disease/cirrhosis (MELD > 12)
Severe pulmonary hypertension (systolic pulmonary artery pressure >2/3 systemic pressures)
Contraindications
Patients who cannot tolerate procedural anticoagulation or post procedural anti-platelet regimen
Active endocarditis of the mitral valve
Rheumatic mitral valve disease
Evidence for intracardiac, inferior vena cava or femoral venous thrombus

Table 1: Indications and contraindications for MitraClip procedure.

Valve Morphology for MitraClip	
Ideal	**Unsuitable**
MR originating from the mid portion of the valve	Perforated mitral leaflets or clefts, lack of primary and secondary chordal support
Lack of calcification in the grasping area	Severe calcification in the grasping area
Mitral valve area ≥ 4cm^2	Hemodynamically significant mitral stenosis
Length of posterior leaflet ≥ 10mm	Length of posterior leaflet < 7mm
Flail width < 15mm, flail-gap < 10mm	Rheumatic valve disease with restriction in systole and diastole
Sufficient leaflet tissue for mechanical coaptation:	Gap between leaflets > 2 mm
Coaptation depth < 11mm	
Coaptation length > 2mm	

Table 2: Echocardiographic assessment of characteristics that are favorable and unfavorable for MitraClip placement. Adapted from Wunderlich et al. [5]

References:

1. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology 2014;63:2438-88.
2. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Journal of the American College of Cardiology 2017: S0735-1097(17)36019-9.
3. Maisano F, Torracca L, Oppizzi M, et al. The edge-to-edge technique: a simplified method to correct mitral insufficiency. Eur J Cardiothorac Surg 1998;13:240-5.
4. MitraClip (R) NT Clip Delivery System. Abbott Laboratories, Abbott Park, IL, 2017. at http://www.abbottvascular.com/docs/ifu/structural_heart/eIFU_Mitraclip_NT.pdf.)
5. Wunderlich NC, Siegel RJ. Peri-interventional echo assessment for the MitraClip procedure. European Heart Journal - Cardiovascular Imaging 2013;14:935-49.
6. Feldman T, Foster E, Glower DD, et al. Percutaneous Repair or Surgery for Mitral Regurgitation. New England Journal of Medicine 2011;364:1395-406.
7. Glower DD, Kar S, Trento A, et al. Percutaneous Mitral Valve Repair for Mitral Regurgitation in High-Risk Patients: Results of the EVEREST II Study. Journal of the American College of Cardiology 2014;64:172-81.
8. Feldman T, Kar S, Elmariah S, et al. Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation: 5-Year Results of EVEREST II. Journal of the American College of Cardiology 2015;66:2844-54.
9. Maniu CV, Patel JB, Reuter DG, et al. Acute and chronic reduction of functional mitral regurgitation in experimental heart failure by percutaneous mitral annuloplasty. Journal of the American College of Cardiology 2004;44:1652-61.
10. Schofer J, Siminiak T, Haude M, et al. Percutaneous Mitral Annuloplasty for Functional Mitral Regurgitation. Circulation 2009;120:326.
11. Siminiak T, Wu JC, Haude M, et al. Treatment of functional mitral regurgitation by percutaneous annuloplasty: results of the TITAN Trial. European Journal of Heart Failure 2012;14:931-8.
12. Feldman T, Young A. Percutaneous Approaches to Valve Repair for Mitral Regurgitation. Journal of the American College of Cardiology 2014;63:2057-68.