Updates in Mitral Valve Repair and Replacement

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Mitral regurgitation (MR) is a condition that is associated with decreased survival rates among patients with heart failure [Cleland J et al. *J Am Coll Cardiol*. 2008]. In determining whether treatment of MR is necessary and which treatment option to pursue, it is important to consider the severity and underlying causes of the condition. The new 2014 American Heart Association (AHA)/American College of Cardiology (ACC) guideline for the management of patients with valvular heart disease distinguishes between primary and secondary MR [Nishimura RA et al. *J Thorac Cardiovasc Surg*. 2014]. Primary MR is caused by degenerative conditions such as myxomatous, endocarditis, mitral annular calcification, rheumatic heart disease, and radiation therapy, whereas secondary MR is caused by functional conditions such as ischemia, dilated cardiomyopathy, hypertrophic cardiomyopathy, and atrial fibrillation. Samir R. Kapadia, MD, Cleveland Clinic, Cleveland, Ohio, USA, provided an overview of the current AHA/ACC guideline recommendations for the treatment of MR.

An important part of determining how to treat MR is first establishing the severity of the condition and whether the patient is experiencing symptoms. Determining the severity requires accurate interpretation of echocardiography and understanding of hemodynamics. The AHA/ACC 2014 guideline uses different features to distinguish the severity of primary and secondary MR (Tables 1 and 2) [Nishimura RA et al. *J Thorac Cardiovasc Surg*. 2014]. Particularly in patients with secondary MR, not all criteria may be present in a given patient, and the quality of data and the integration of parameters, along with other clinical evidence, play an important role in determining severity.

Dr Kapadia commented that secondary MR is more difficult to assess because the location of the regurgitation, the extent of the regurgitation, and the types of outpouching must be considered. In addition, secondary MR is highly dependent on functional load since the effective regurgitation orifice (ERO) varies depending on blood pressure, filling pressure, and flow. It can be difficult to measure the orifice with 2D and even 3D imaging because it is not necessarily round. Therefore, ancillary measures—such as left atrial and ventricular size, diastolic filling, pulmonary artery pressure, and pulmonary vein flow—should be considered and multimodality imaging used. Of note, 2D proximal isovelocity surface measurements can underestimate the ERO in secondary MR.

The 2014 AHA/ACC guideline suggests that an ERO > 0.2—a regurgitant orifice that many providers do not consider severe—is associated with increased mortality. However, end-diastolic flow and volume determine the ERO; therefore, an ERO of 0.2 in secondary MR can be seen in patients with severe MR [Grayburn PA et al. *J Am Coll Cardiol*. 2014]. Scenarios such as these demonstrate the limitation of 2D data.

Treatment options for primary MR include surgery and the MitraClip. For secondary MR, medical therapy, cardiac resynchronization therapy, surgery, and the MitraClip are all treatment options. However, Dr Kapadia stressed the importance of local expertise when determining the treatment options. Mitral valve (MV) repair is a class I recommendation for patients with chronic severe primary MR, with replacement considered in patients undergoing other cardiac surgery per the 2014 AHA/ACC guideline. In addition, MV surgery is recommended with class I evidence for symptomatic patients with a left ventricular (LV) ejection fraction > 30% or in asymptomatic patients with an LV ejection fraction of 30% to 60% and/or an LV end-systolic diameter ≥ 40 mm. MV repair is preferred over MV replacement in patients whose MR involves only the posterior leaflet. For secondary MR, there are no class I recommendations, but the class II recommendations include surgery for patients with chronic severe MR who are undergoing coronary artery bypass grafting or aortic valve replacement, for severely symptomatic patients, or for those undergoing other cardiac surgery.

Treatment of MR with percutaneous MV procedures, specifically with the MitraClip, was discussed in more detail by Ted Feldman, MD, Evanston Hospital, Evanston, Illinois, USA. One of the more well-studied approaches is with the MitraClip, with which there have been

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Table 1. Classification of the Severity of Primary MR

Grade	Definition	Valve anatomy	Valve hemodynamics*	Hemodynamic consequences	Symptoms
A	At risk of MR	• Mild mitral valve prolapse with normal coaptation • Mild valve thickening and leaflet restriction	• No MR jet or small central jet area <20% LA on Doppler • Small vena contracta <0.3 cm	• None	• None
B	Progressive MR	• Severe mitral valve prolapse with normal coaptation • Rheumatic valve changes with leaflet restriction and loss of central coaptation • Prior IE	• Central jet MR 20%–40% LA or late systolic eccentric jet MR • Vena contracta <0.7 cm • Regurgitant volume <60 mL • Regurgitant fraction <50% • ERO <0.40 cm^2 • Angiographic grade 1–2+	• Mild LA enlargement • No LV enlargement • Normal pulmonary pressure	• None
C	Asymptomatic severe MR	• Severe mitral valve prolapse with loss of coaptation or flail leaflet • Rheumatic valve changes with leaflet restriction and loss of central coaptation • Prior IE • Thickening of leaflets with radiation heart disease	• Central jet MR >40% LA or holosystolic eccentric jet MR • Vena contracta ≥0.7 cm • Regurgitant volume ≥60 mL • Regurgitant fraction ≥50% • ERO ≥0.40 cm^2 • Angiographic grade 3–4+	• Moderate or severe LA enlargement • LV enlargement • Pulmonary hypertension may be present at rest or with exercise • C1: LVEF >60% and LVESD <40 mm • C2: LVEF ≤60% and LVESD ≥40 mm	• None
D	Symptomatic severe MR	• Severe mitral valve prolapse with loss of coaptation or flail leaflet • Rheumatic valve changes with leaflet restriction and loss of central coaptation • Prior IE • Thickening of leaflets with radiation heart disease	• Central jet MR >40% LA or holosystolic eccentric jet MR • Vena contracta ≥0.7 cm • Regurgitant volume ≥60 mL • Regurgitant fraction ≥50% • ERO ≥0.40 cm^2 • Angiographic grade 3–4+	• Moderate or severe LA enlargement • LV enlargement • Pulmonary hypertension present	• Decreased exercise tolerance • Exertional dyspnea

ERO, effective regurgitation orifice; IE, infective endocarditis; LA, left atrium/atrial; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; MR, mitral regurgitation.

*Several valve hemodynamic criteria are provided for assessment of MR severity, but not all criteria for each category will be present in each patient. Categorization of MR severity as mild, moderate, or severe depends on data quality and integration of these parameters in conjunction with other clinical evidence.

>20 000 implants worldwide. The MitraClip was approved by the FDA in 2013 for the treatment of symptomatic primary grade ≥3 MR in patients who are not eligible for surgery.

In the pivotal EVEREST II trial, 279 patients with moderate or severe MR were randomly assigned 2:1 to undergo percutaneous repair with the MitraClip or conventional surgery for MV replacement or repair [Feldman T et al. *N Engl J Med*. 2011]. Although there were positive clinical outcomes in the MitraClip arm at 1 year, it was less effective than surgery for MR reduction but with superior safety. The as-yet unpublished 5-year data demonstrate that a greater proportion of patients who underwent the MitraClip procedure experienced residual grade 2 and 3 MR compared with surgery. Yet, the systolic and diastolic septal lateral annular dimensions were similar between both groups. When failed procedures were discounted, the proportion of patients who were free from reintervention was similar at 5 years, regardless of the presence of primary or secondary MR. According to Dr Feldman, failed procedures and single-leaflet clip detachments are no longer frequent occurrences, as they were in the first 6 months of the trial. An exploratory subgroup analysis from the trial found that the MitraClip procedure performed better in older patients, those with secondary MR, and patients with a low ejection fraction.

A further analysis from a registry of the high-risk patients in the EVEREST II trial was performed, in which 86% of patients had grade ≥3 MR and the mean Society of Thoracic Surgeons (STS) score was 18% [Glower DD et al. *J Am Coll Cardiol*. 2014]. In these patients, LV end

Table 2. Classification of the Severity of Secondary MR

Grade	Definition	Valve anatomy	Valve hemodynamics*	Associated cardiac findings	Symptoms
A	At risk of MR	• Normal valve leaflets, chords, and annulus in a patient with coronary disease or cardiomyopathy	• No MR jet or small central jet area <20% LA on Doppler • Small vena contracta <0.30 cm	• Normal or mildly dilated LV size with fixed (infarction) or inducible (ischemia)regional wall motion abnormalities • Primary myocardial disease with LV dilation and systolic dysfunction	• Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
B	Progressive MR	• Regional wall motion abnormalities with mild tethering of mitral leaflet • Annular dilation with mild loss of central coaptation of the mitral leaflets	• ERO <0.20 cm^2† • Regurgitant volume <30 mL • Regurgitant fraction <50%	• Regional wall motion abnormalities with reduced LV systolic function • LV dilation and systolic dysfunction due to primary myocardial disease	• Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
C	Asymptomatic severe MR	• Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet • Annular dilation with severe loss of central coaptation of the mitral leaflets	• ERO ≥0.20 cm^2† • Regurgitant volume ≥30 mL • Regurgitant fraction ≥50%	• Regional wall motion abnormalities with reduced LV systolic function • LV dilation and systolic dysfunction due to primary myocardial disease	• Symptoms due to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
D	Symptomatic severe MR	• Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet • Annular dilation with severe loss of central coaptation of the mitral leaflets	• ERO ≥0.20 cm^2† • Regurgitant volume ≥30 mL • Regurgitant fraction ≥50%	• Regional wall motion abnormalities with reduced LV systolic function • LV dilation and systolic dysfunction due to primary myocardial disease	• HF symptoms due to MR persist even after revascularization and optimization of medical therapy • Decreased exercise tolerance • Exertional dyspnea

2D, 2-dimensional; ERO, effective regurgitant orifice; HF, heart failure; LA, left atrium; LV, left ventricular; MR, mitral regurgitation; TTE, transthoracic echocardiogram.

*Several valve hemodynamic criteria are provided for assessment of MR severity, but not all criteria for each category will be present in each patient. Categorization of MR severity as mild, moderate, or severe depends on data quality and integration of these parameters in conjunction with other clinical evidence.

†The measurement of the proximal isovelocity surface area by 2D TTE in patients with secondary MR underestimates the true ERO due to the crescentic shape of the proximal convergence.

diastolic volume and systolic volume (LVEDV, LVESV) were decreased at 1 and 5 years. The safety profile of the MitraClip was better than that of surgery, with shorter time in the intensive care unit and hospital; lower rates of death, stroke, and bleeding; and shorter time of ventilation use [Philip F et al. *Catheter Cardiovasc Interv*. 2014]. In another study in patients who could not undergo surgery, the MitraClip resulted in functional improvement, decreased rehospitalization, and less ventricular remodeling, with good safety outcomes at 1 year [Lim DS et al. *J Am Coll Cardiol*. 2014]. The COAPT trial [NCT01626079], which will randomly assign high-risk patients 1:1 to receive the MitraClip or undergo the standard of care, is ongoing with about 430 patients currently enrolled in the United States.

MV annuloplasty is the surgical treatment most commonly utilized in patients with MR. Indirect annuloplasty—in particular, coronary sinoplasty and the Mitralign device—was discussed by Saibal Kar, MD, Cedars-Sinai Medical Center, Los Angeles, California, USA.

The coronary sinus is located posterolateral to the MV and is fairly easy to access. The Carillon Mitral Contour System is a device that applies tension and cinches the coronary sinus, which leads to the reduction in MR. The 30-day safety of the Carillon devices has been excellent, with no device-related deaths, myocardial infarction, perforation, embolization, or surgery in the AMADEUS, TITAN, and TITAN II trials [Haude M et al. *J Am Coll Cardiol.* 2014 (abstr TCT-815); Siminiak T et al. *Eur J Heart Fail*. 2012; Schofer J et al. *Circulation*. 2009]. In the TITAN trial, LV end-diastolic diameter, LV end-systolic diameter, LVEDV, and LVESV were significantly decreased in the Carillon arm over 12 months ($P = .004$, .005, .015, and .015, respectively) [Siminiak T et al. *Eur J Heart Fail*. 2012]. In addition, long-term data demonstrated that the 6-minute walk test and NYHA class

improved from baseline by 1 month and these changes were sustained to at least 48 months.

The Carillon system may be preferred in some patients who are not candidates for the MitraClip due to the poor possibility of leaflet grasp. In addition, the procedure may be considered when there is inadequate resolution of MR symptoms or an increasing MV gradient with the MitraClip. In addition, Dr Kar pointed out that clinicians may want to consider Carillon before the MitraClip because of the Carillon's excellent safety profile.

Another emerging approach is the Mitralign system, in which the annulus is plicated on 2 sides, thus reducing the posterior annulus and increasing the coaptation. These changes can result in a decrease of the MR. The procedure consists of wire placement and pledget delivery to either side of the MV; then, the pledgets are pulled together and held by a plication and lock. This system is under evaluation in Europe and is not available in the United States.

In an ongoing CE Mark study, Mitralign was evaluated in 64 patients with a functional MR of ≥ 2 and NYHA class II to IV. At 30 days, the major adverse event rate was 15.9%, with 3 of 44 patients experiencing death and 2 experiencing cardiac tamponade. MV surgery, minor or major stroke, and myocardial infarction were not reported. Compared with baseline, there was substantial improvement in NYHA classification and MR grade.

Direct annuloplasty with the ENCOR$_{SQ}$, Cardioband, and Mitralign devices was discussed by Michael W. Cleman, MD, Yale University School of Medicine, New Haven, Connecticut, USA. The ENCOR$_{SQ}$ is a nitinol annuloplasty ring that is surgically implanted using standard annuloplasty techniques. An advantage of the ENCOR$_{SQ}$ is that application of radiofrequencies can change the shape of the band after implantation. In a multicenter European study, the 1- and 3-year survival rates in patients who received the ENCOR$_{SQ}$ were 93% [Andreas M et al. *Eur J Cardiothorac Surg*. 2015]. Adjustment of the ENCOR$_{SQ}$ was attempted in 12 patients, which led to decreased MR in 3 patients and no change in 6 patients.

The Cardioband is implanted through a transeptal procedure, in which multiple anchors attach the device to the annulus with echocardiography and fluoroscopic guidance. In high-risk patients with grade ≥ 2 secondary MR and a mean STS score of 7%, the overall rate of death was 6.8% at 30 days; however, no major adverse events were considered to be related to the device [Maisano F et al. *J Am Coll Cardiol*. 2015 (abstract A1969)]. At discharge, there was a substantial improvement in MR grade compared with baseline that was sustained up to 6 months.

The Accucinch LV Remodeling System involves cinching an implant that is anchored around the subvalvular space. As a result, the circumference and tenting of the annulus are reduced, and there is a decrease in LV base circumference, thus leading to reduced MR.

Although these direct methods of annular management appear to be safe and effective, Dr Cleman stated that more long-term studies are needed, as there is a limited amount of long-term data and it is difficult to determine the clinical and physiologic benefits of these approaches.

In addition to valve repair, replacement of the MV is a treatment option for MR. Maurice Buchbinder, MD, Stanford University, Stanford, California, USA, discussed MV replacement using percutaneous transcatheter techniques. He highlighted that surgical MV replacement is associated with a > 10% mortality rate in medium- to high-risk patients [Mehta RH et al. *Ann Thorac Surg*. 2002]; therefore, a transcatheter approach may be ideal in patients with primary or secondary MR with significant comorbidities.

Several case studies have demonstrated that the transcatheter MV-in-valve approach resulted in improved NYHA class and good prosthetic performance, with a median survival of 90.4% at over 2 years [Cheung A et al. *J Am Coll Cardiol*. 2013]. There are multiple prosthetic valves being evaluated, including EndoValve, Tendyne/Lutter Transaptical Mitral Valve, and the CardiAQ.

The CardiAQ device is self-positioning with a native valve annulus that is anchored to the annulus without radial force. After many successful implantations in acute and subchronic MR porcine models, the first human implant was performed in 2012. The second-generation CardiAQ uses a similar anchoring technology but is updated with changes that improve its performance, durability, and load distribution and that include minimization of paravalvular leak, improved left atrial flow, and LV contractility.

Another device is the Neovasc Tiara, which is self-expanding and repositionable. Preclinical trials have been completed, and the first-in-human implant was performed in 2014. Another self-expanding prosthetic MV is Fortis, which was first implanted in a human in 2014 and has since been implanted in an additional 7 patients. Additional prosthetic valves in early development include the MValve, Medtronic, Valtech, MitrAssist, among others.

In conclusion, there are several options for the treatment of MR and many others in development. The severity and underlying cause of the MR are important to consider when determining if MV repair or replacement is needed.