Secondary Mitral Regurgitation in Heart Failure
Pathophysiology, Prognosis, and Therapeutic Considerations
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ABSTRACT

The development of secondary mitral regurgitation (MR) due to left ventricular dysfunction, also known as functional MR, is strongly associated with a poor prognosis in patients with heart failure. The mechanisms underlying secondary MR are multifactorial; accurate imaging assessment of secondary MR may be challenging and nuanced; and the appropriate roles of medical, surgical, and interventional therapies for management of secondary MR are controversial and evolving.

In this review, the pathophysiology, evaluation, and prognosis of secondary MR in patients with heart failure are discussed, and we evaluate in detail the evidence for the various therapeutic approaches for secondary MR, including guideline-directed medication for left ventricular dysfunction, cardiac resynchronization therapy and revascularization when appropriate, and mitral valve surgery and transcatheter interventions. The role of a multidisciplinary heart team in determining the optimal management strategy for secondary MR is also discussed. (J Am Coll Cardiol 2015;65:1231–48) © 2015 by the American College of Cardiology Foundation.

Mitral regurgitation (MR) is among the most common valvular heart disorders, with an estimated prevalence in the United States of ~1.7%, increasing with age to ~9.3% in those >75 years of age (1). MR is classified as primary (also known as organic) when principally due to a structural or degenerative abnormality of the mitral valve (MV), whether of the leaflets, chordae tendineae, papillary muscles, or mitral annulus. Secondary (also known as functional) MR occurs in the absence of organic MV disease, usually from left ventricular (LV) dysfunction. It is more common than primary MR (2), is associated with a worse prognosis (compounded by the underlying cardiomyopathy), and (in contrast to primary MR) the benefits of MV surgery are uncertain. The present report reviews the etiology, pathophysiology, prognostic implications, and diagnosis of secondary MR, as well as potential therapeutic approaches.

PATHOPHYSIOLOGY OF SECONDARY MR

The MV consists of 2 leaflets (anterior and posterior) sitting within the annulus (Figure 1). The posterior mitral leaflet originates from the left atrial (LA) endocardium. A subvalvular apparatus, comprising 2 papillary muscles (anterolateral and posteromedial) arising from the LV myocardium and the chordae tendineae, supports the leaflets. LV dilation due to ischemic or nonischemic cardiomyopathy secondarily impairs leaflet coaptation of a structurally normal MV, resulting in secondary MR. Specifically, LV...
dysfunction and remodeling lead to apical and lateral papillary muscle displacement, resulting in leaflet tethering (3), dilation and flattening of the mitral annulus, and reduced valve closing forces. Because these changes are dependent on loading conditions and the phase of the cardiac cycle, secondary MR is dynamic in nature.

Papillary muscle displacement occurs as a result of global LV enlargement or focal myocardial scarring, and can affect 1 or both papillary muscles, causing posteriorly directed or central MR (Figure 2) (4). With chronic MR, the mitral leaflet area may increase up to 35% over time, an adaptive response that minimizes the degree of regurgitation; insufficient leaflet remodeling may contribute to severe MR (5,6). However, even in patients with increased mitral leaflet area, papillary muscle displacement with subsequent decreased coaptation length may still result in significant MR (6).

The normal saddle-shape of the annulus is important for maintaining normal leaflet stress (7). Loss of this shape and annular flattening with LV remodeling result in increased leaflet stress with secondary MR. In addition, LV systolic dysfunction reduces the strength of MV closing, which opposes the leaflet tethering forces created by papillary muscle displacement. These pathological changes culminate in failure of leaflet coaptation and decreased valvular closing forces due to LV dysfunction, resulting in MR. The Carpentier classification, commonly used by surgeons to describe MV pathology, categorizes MR using a mechanistic and functional approach to the mitral leaflets (8). Secondary MR is most commonly Carpentier type IIIB, and occasionally type I.

**ISCHEMIC VERSUS NONISCHEMIC MR.** MR can be further classified as either ischemic or nonischemic. In ischemic MR (the more frequent etiology), LV remodeling after myocardial infarction (MI) results in papillary muscle displacement, causing systolic tenting of the MV. Global left ventricular ejection fraction (LVEF) does not have to be reduced; regional wall motion abnormalities with remodeling may result in sufficient MV tethering to cause severe MR, despite preserved LVEF (9). Symmetric or asymmetric leaflet tethering may occur. Symmetric tethering is associated with substantial systolic dysfunction, global remodeling, and increased LV sphericity with a central regurgitant jet. Asymmetric tethering most frequently results from localized remodeling affecting the posterior papillary muscle, with posterior tenting of both leaflets (most pronounced at the medial or P3 portion of the posterior leaflet) causing a posteriorly directed asymmetric regurgitant jet (Carpentier Type IIIb) (10). Mitral annular dilation typically occurs late in the pathophysiology of secondary MR, and is often asymmetric, with greater involvement of the posterior annulus (11). Papillary muscle infarction is rarely the cause of secondary MR (12).

Nonischemic MR, most commonly due to longstanding hypertension or idiopathic dilated cardiomyopathy, is characterized by global LV dilation with increased sphericity and (typically) a centrally located regurgitant jet. Symmetric mitral annular dilation is greatest in the septal-lateral direction, and correlates with the severity of LV dysfunction (13).

**MR DUE TO ATRIAL FIBRILLATION.** An additional, although relatively infrequent, cause of severe secondary MR is isolated LA enlargement, with or without atrial fibrillation, resulting in a dilated mitral annulus and reduced leaflet coaptation (without tenting or prolapse), with normal LV function and mitral leaflets (Carpentier Type I) (14). In patients with atrial fibrillation, improvement in MR severity may occur with restoration of sinus rhythm, suggesting a causal relationship (14).

**PROGNOSTIC IMPLICATIONS OF SECONDARY MR**

A strong association between secondary MR severity and both all-cause mortality and heart failure (HF) hospitalizations has been reported. Among 303 patients with a completed Q-wave MI, any ischemic MR was detected by echocardiography in 194 patients (64.0%) and was a powerful, independent correlate of long-term all-cause mortality (relative risk: 1.88 [95% confidence interval CI]: 1.23 to 2.86], p = 0.003) (15). In a study from the Duke Cardiovascular Databank, qualitatively assessed 3+ to 4+ MR on left ventriculography was present in 29.8% of 2,057 HF patients with an LVEF <40% and was an independent predictor of 5-year mortality (adjusted hazard ratio [HR]: 1.23 [95% CI: 1.13 to 1.34]) (16). Among 1,256 patients with dilated cardiomyopathy at the Mayo Clinic, quantitatively assessed severe secondary MR (defined as an effective regurgitant orifice area [EROA] >0.2 cm², a regurgitant volume >30 ml, or a vena contracta width >0.4 cm) was present in 24% of patients, and was an independent predictor of death or HF hospitalization at median 2.5-year follow-up (adjusted HR: 1.5 [95% CI: 1.2 to 1.9]), independent of LVEF (17). This relationship was present separately for death and HF hospitalizations, and in patients with ischemic and nonischemic MR (Figure 3). Secondary MR is a powerful predictor of death or transplant, even with less severe HF (18). However,
although secondary MR is widely accepted to predict a poor prognosis in patients with primary LV dysfunction and HF, whether this relationship is causal and whether reducing MR improves patient prognosis remain unknown.

EVALUATION OF SECONDARY MR

Comprehensive evaluation of the patient with HF and secondary MR requires a detailed medical history and physical examination, with laboratory, electrocardiographic, and echocardiographic assessment. Most important is an accurate appraisal of the functional limitations attributable to HF, the MV anatomy and severity of MR, and evaluation of the left and right heart circulation, including measurement of chamber size and cardiac pressures. By integrating these findings, secondary MR can be categorized into 4 stages that define prognosis and guide therapy: 1) at risk of secondary MR; 2) progressive secondary MR; 3) asymptomatic severe secondary MR; and 4) symptomatic severe secondary MR (Table 1) (19).

ECHOCARDIOGRAPHY. The cornerstone of diagnostic evaluation of MR is echocardiography, with transesophageal and transthoracic echocardiography playing complementary roles. Transesophageal echocardiography most often accurately identifies the underlying cause and mechanism of MR, whether primary or secondary. A mixed etiology is not uncommon (e.g., secondary MR with leaflet thickening or mitral annular calcification). Transesophageal echocardiographic measurements of leaflet length and angles (particularly the posterolateral angle, signifying posterior leaflet tethering), coaptation distance and length, and tenting area are useful in evaluating the suitability of secondary MR for various interventional options. Conversely, because LV unloading may lessen regurgitation, quantification of MR severity is most accurately assessed in the awake patient by transthoracic echocardiography, thereby avoiding the vasodilatory effects of sedation, hypovolemia, and/or anesthesia with transesophageal echocardiography. Echocardiography is also indispensable for determining LV volumes, function, and sphericity; for assessing pulmonary artery pressures and right ventricular function and quantifying tricuspid regurgitation; for assessing the anatomic likelihood for successful MV repair or transcatheter approaches; for guiding surgical and transcatheter repair procedures; and for appraising the durability and functional effect of MV therapies through serial assessments over time.

The echocardiographic degree of MR, evaluated by integrating qualitative and quantitative assessments, is classified as mild, moderate, or severe (20). Qualitative findings include MV morphology and color flow and continuous wave signals of the MR jet. Semi-quantitative insights into MR severity are provided by pulmonary vein flow and mitral inflow patterns. Quantitative measures include EROA, regurgitant volume, and regurgitant fraction. Enlarged LA and LV chamber size and increased pulmonary artery pressures provide supportive data for severe MR.

Conventional 2-dimensional (2D) assessment for MR quantification relies on measurement of the MR jet core at its vena contracta or proximal convergence zone using methods that assume circular orifice geometry. MR severity may, therefore, be significantly underestimated when the orifice is elliptical (as is typical in secondary MR) (4), a situation that is compounded if multiple jets are present. Three-dimensional (3D) echocardiography overcomes this limitation by permitting direct planimetry of the vena contracta, regardless of orifice shape or number of jets (21). Conversely, both 2D and 3D color flow Doppler tend to overestimate the orifice area because of their inability to resolve the high velocity jet core due to aliasing and blooming artifacts. Secondary MR severity also varies during the cardiac cycle, and can peak in early or late systole, further complicating evaluation, which is traditionally done in mid-systole. No single parameter is sufficient to quantify the degree of MR, and multimodality assessment using both 2D and 3D echocardiography is optimal (22). Although somewhat controversial, outcomes studies suggest that lesser absolute quantitative degrees of regurgitation in secondary MR may have the same or greater effect on mortality than in
primary MR (15,20). Whereas severe primary MR is usually defined as an EROA of $\geq 40$ mm$^2$ and a regurgitant volume of $\geq 60$ ml, Sarano et al. (15) proposed and the most recent U.S. and European valve guidelines have accepted EROA $\geq 20$ mm$^2$ and regurgitant volume $\geq 30$ ml as consistent with severe secondary MR (19,23) (Table 2). However, the amount of MR (assessed by either EROA or regurgitant volume) resulting in loss of $>50\%$ of total stroke volume (i.e., the regurgitant volume) depends on the LV end-diastolic volume and LVEF (24). This likely explains why some studies show an adverse prognostic effect of lesser EROA values, whereas others do not.

Exercise echocardiography may be useful when symptoms appear disproportionate to resting MR severity (25). Exercise results in greater pre-load and afterload, a more spherical ventricle, increased coaptation distance, and systolic expansion of the mitral annulus. Such changes can occur in the absence of ischemia (26) and may result in acute pulmonary edema (27). Exercise-induced severe MR may identify patients at heightened risk for death or HF hospitalization (28). Quantitatively, an exercise-induced EROA increase of $\geq 13$ mm$^2$ has been associated with increased morbidity and mortality, although measuring EROA during or immediately after exercise is technically challenging due to tachycardia and tachypnea (29). Exercise echocardiography may also demonstrate increasing pulmonary artery pressures and lack of LV contractile reserve, findings associated with LV dysfunction and poor prognosis after MV surgery (30,31). Exercise may also induce greater LV dyssynchrony with increased MR, which might improve with cardiac resynchronization therapy (CRT) (see later discussion). However, the predictive value of exercise echocardiography is
imperfect, given the technical issues of measuring key parameters at or just after peak exercise; confounding interpretations due to concomitant ischemia and/or patient deconditioning (with limited exercise capacity); and the potential for LV remodeling with changing loading conditions after MV repair in some patients. Larger studies are required to determine the role of exercise echocardiography in evaluation of the patient with secondary MR.

Echocardiography is also useful in determining the likelihood of successful MV repair by either surgery or transcatheter procedures (e.g., the MitraClip, Abbott Vascular, Menlo Park, California) in patients with secondary MR. In patients with secondary MR undergoing surgery, successful repair is less likely in the presence of: 1) MV deformation (coaptation distance ≥1 cm, tenting area >2.5 to 3 cm², and/or complex jets originating centrally and posteromedially, posterolateral angle >45° [high posterior leaflet tethering]); 2) global LV remodeling (LV end-diastolic dimension >65 mm, end-systolic dimension >51 mm, or systolic sphericity index >0.7); and 3) local LV remodeling (interpapillary muscle distance >20 mm, posterior papillary-fibrosa distance >40 mm, or lateral wall motion abnormality) (32). In a series of 300 patients with severe MR undergoing MitraClip (68% of whom had secondary MR), failure to achieve ≤2+ MR occurred in 31 patients (10.3%). By multivariable analysis, predictors of failed MitraClip included greater EROA (odds ratio [OR]: 1.21 per 10 mm² increase, p = 0.005) and baseline transmitral pressure gradient ≥4 mmHg (OR: 1.26, p = 0.03). Success rates were similar with primary and secondary MR (33). Of note, due to the double MV orifice and artifacts from the clip(s), quantifying MR severity after the MitraClip with echocardiography can be challenging.

**NONECHOCARDIOGRAPHIC IMAGING TECHNIQUES.** Cardiac magnetic resonance (CMR) imaging and

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**FIGURE 3** Prognosis of Quantitatively Determined Secondary Mitral Regurgitation in Patients With Ischemic and Nonischemic Cardiomyopathy

*(Top) Freedom from death or heart failure (HF) hospitalization in 1,256 patients according to the degree of functional mitral regurgitation (FMR). *(Bottom) Freedom from death according to the degree of FMR in patients with ischemic (lower left) and nonischemic (lower right) cardiomyopathy. Adapted with permission from Rossi et al. (17). HR = hazard ratio.
multidetector row computed tomography (MDCT) can provide complementary information to echocardiography in patients with MR. CMR, in particular, is highly accurate for quantifying the degree of MR (34). Given its high spatial resolution, MDCT can accurately depict MV structure and morphology (35), and is useful in demonstrating the relationship of the MV complex to other cardiac structures (e.g., the relationship of the coronary sinus to the mitral annulus and circumflex coronary artery) (36). Both techniques provide true volumetric measures of chamber dimensions and function and also assess myocardial fibrosis (scar). In the future, CMR and MDCT will likely be increasingly used in the evaluation of patients with HF and MR.

**Therapeutic Considerations for Secondary MR**

The goals of therapy in patients with secondary MR are to improve symptoms and quality of life, reduce HF hospitalizations, and potentially improve survival. To date, the most effective therapies for secondary MR are aimed at the underlying LV dysfunction, including guideline-directed medical therapy (GDMT) for HF and biventricular pacing (CRT) when appropriate. Coronary revascularization may also be considered in patients with extensive ischemia and preserved myocardial viability, although it rarely markedly reduces or eliminates secondary MR. The role of surgical and transcatheter MV repair or replacement to interrupt the progressive cycle of LV volume overload → LV dilation → secondary MR → increasing LV volume overload and dilation → increasing MR is less well established, although some patients may symptomatically benefit. Finally, in patients with severe HF and secondary MR refractory to standard therapies, consideration should be given to mechanical LV assist devices and heart transplantation.

**Medical Therapy for Secondary MR**

GDMT for HF is first-line treatment for patients with secondary MR (19), although the morbidity and mortality of patients with LV dysfunction and secondary MR remain high. Among 404 secondary MR patients treated with GDMT, 4-year cardiac mortality occurred in 43% and 45% with moderate and severe MR, respectively, compared with only 6% with mild MR ($p = 0.003$) (37). Moderate or severe MR was also an independent predictor of new onset HF in patients...
with ischemic LV dysfunction (relative risk: 3.2 [95% CI: 1.9 to 5.2], p = 0.0001).

Beta-blockers and angiotensin-converting enzyme inhibitors (ACEIs) are recommended for all patients with LV dysfunction and secondary MR. By reversing LV remodeling, maximal GDMT may secondarily reduce severe MR. Surprisingly, however, few studies have examined the effect of medical therapies on secondary MR. In several small, nonrandomized studies, carvedilol in patients with HF and secondary MR was associated with improved LV systolic function with reduced MR severity lasting 6 to 12 months (38,39). In a randomized trial of 59 patients with HF and severe dilated cardiomyopathy, treatment with carvedilol versus placebo resulted in reduced LV mass and sphericity, with improved systolic function. The severity of MR, assessed by the ratio of MR jet area/LA area, increased during follow-up in the placebo group, but decreased in the carvedilol group (p = 0.04) (40). In the largest randomized trial, among 138 patients with dilated cardiomyopathy on stable doses of digoxin, diuretic agents, and ACEI assigned to metoprolol (titrated to 50 mg, 3 times a day) or placebo, the metoprolol group had greater 6-month reductions in LV end-diastolic and end-systolic volumes, which correlated with improved secondary MR (41). However, MR improved in only ~42% of metoprolol-treated patients (vs. 20% of control-group patients), and there were no significant differences in symptoms or rates of cardiac readmission or death during follow-up.

Less has been reported on the ability of ACEI and other agents to reduce secondary MR. In a small study of 19 patients with severe dilated cardiomyopathy (mean LVEF ~20%) and 3+/4+ MR on stable doses of digoxin, diuretic agents, and isosorbide dinitrate, lisinopril, and isosorbide mononitrate, lisinopril was up-titrated from a mean 16 to 55 mg/day, and isosorbide from 30 to 286 mg/day. At 12-month follow-up, MR had decreased to grade 0/1+ in 8 patients (42%; the MR responders), and remained 3+/4+ in the remainder. LVEF improved in both groups, but to a greater degree in the MR responders, and the LV end-diastolic dimension decreased in the responders, but increased in the nonresponders (42).

**CRT FOR SECONDARY MR**

CRT is a well-established treatment for HF in selected patients with LV dyssynchrony. CRT is a Class I recommendation for patients in sinus rhythm with New York Heart Association (NYHA) functional class II to IV symptoms on GDMT with LVEF ≤35%, left bundle branch block (LBBB), and QRS duration ≥150 ms. CRT may also be useful in patients with LVEF ≤35%, with sinus rhythm and non-LBBB pattern with QRS duration ≥150 ms, and in those with LBBB and QRS duration 120 to 149 ms (Class IIa indications) (43). Randomized trials demonstrated improvements in both survival and HF rehospitalization rates in patients treated with CRT with or without a defibrillator (44), along with reductions in LV end-diastolic and end-systolic dimensions and improved LVEF.

The effect of CRT on secondary MR is inconsistent, although most studies show a reduction in overall MR severity with restoration of synchronous ventricular contraction and LV remodeling. In the sham-controlled MIRACLE (Multicenter InSync Randomized Clinical Evaluation) trial of 450 NYHA functional class III/IV HF patients with LVEF ≤35% and QRS duration ≥130 ms, CRT resulted in marked reductions in LV end-diastolic and end-systolic volumes, improved LVEF, and sustained reductions in MR (assessed by the relative size of the mitral jet area in the LA) (45). Similarly, in a sham-controlled trial of 610 NYHA functional class I/II HF patients with LVEF ≤40% and QRS duration ≥120 ms, CRT resulted in sustained reductions in MR severity at 3 and 6 months, with parallel improvements in LV dimensions (46). In addition to reducing LV dimensions and restoring papillary muscle geometry, CRT can acutely reduce secondary MR by increasing the rise in the transmural pressure gradient and altering the balance between the closing and tethering forces on the MV (47). In a study of 63 patients with HF and moderate/severe MR, 43% experienced immediate improvement in MR by ≥1 grade, as assessed by vena contracta width after CRT, and an additional 20% demonstrated late improvement at 6 months (48).

Unfortunately, severe secondary MR improves in no more than one-half of patients after CRT, although such improvement identifies a cohort with an improved prognosis. In a study of 85 HF patients with

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**TABLE 2 Quantitative Echocardiographic Criteria for Severe MR in Primary and Secondary Disease of the Mitral Valve**

<table>
<thead>
<tr>
<th>Primary (Organic) MR</th>
<th>Secondary (Functional) MR</th>
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<tbody>
<tr>
<td>EROA ≥0.4 cm²</td>
<td>EROA ≥0.2 cm²</td>
</tr>
<tr>
<td>Regurgitant volume ≥60 ml</td>
<td>Regurgitant volume ≥30 ml</td>
</tr>
<tr>
<td>Regurgitant fraction ≥50%</td>
<td>Regurgitant fraction ≥50%</td>
</tr>
<tr>
<td>Vena contracta ≥0.7 cm</td>
<td>Vena contracta –</td>
</tr>
<tr>
<td>Jet area</td>
<td>Central jet &gt;40% LA</td>
</tr>
<tr>
<td></td>
<td>or holosystolic eccentric jet</td>
</tr>
</tbody>
</table>

*Measurement of the proximal isovelocity surface area by 2-dimensional transthoracic echocardiography in secondary MR underestimates the true EROA due to the crescent shape of the proximal convergence. Adapted with permission from Nishimura et al. (19). Abbreviations as in Table 1.*
3+/4+ secondary MR, MR grade at 6 months was reduced after CRT in 42 (49%). Two-year survival was 92% in MR responders versus 67% in nonresponders ($p < 0.001$) (49). In a recent study of 240 HF patients (114 with ≥2+ secondary MR), MR severity at 6 months decreased in 48 (42%), remained stable in 42 (37%), and worsened in 24 (21%). The 4-year adverse event rates were strongly predicted by the presence of at least moderate MR after (but not before) CRT (50). It is not clear whether CRT improves the prognosis of secondary MR independent of its effects on LV dysfunction or whether MR responders after CRT represent a cohort with a more favorable prognosis. In this regard, CRT-treated HF patients with versus without secondary MR have a worse prognosis; EROA $\geq 0.20$ cm$^2$ predicts poor response to CRT, increased mortality, and HF rehospitalizations (51). Nonetheless, if otherwise indicated, CRT is a reasonable front-line therapy for secondary MR in HF patients (along with GDMT), and should be performed prior to MV surgery or transcatheter intervention.

**SURGERY FOR SECONDARY MR**

Surgical options for secondary MR include surgical MV repair and replacement, mechanical LV assist devices, and orthotopic heart transplantation. Although secondary MR can be acutely corrected by MV surgery, the surgery has never clearly been demonstrated to alter the natural history of the primary disease (dilated cardiomyopathy) or improve survival (52–55). Moreover, whether the response to surgery is different in secondary MR due to ischemic versus nonischemic cardiomyopathy has not been established.

**MV ANNULOPLASTY.** MV reconstruction with preservation of annular-chordal-papillary muscle continuity results in maintenance of LV systolic function with reduced LV volumes and end-systolic wall stress. The most commonly performed surgical technique is MV annuloplasty, which addresses only 1 component of secondary MR: mitral annular dilation. “Undersizing” the annuloplasty ring by matching the ring size to the anterior leaflet overcorrects the annular dilation, minimizing the effects of leaflet tethering (56). Annular dilation is most pronounced in the septal lateral dimension, and various ring designs have been used to overcorrect in this dimension, thus restoring leaflet coaptation.

The risk-benefit ratio for MV annuloplasty in patients with secondary MR not requiring coronary artery bypass grafting (CABG) compared with medical therapy alone is uncertain. Although initial results of undersized annuloplasty were encouraging, long-term follow-up failed to demonstrate a survival benefit. Isolated MV annuloplasty was performed in 126 of 419 patients with severe secondary MR and LVEF $\leq 30\%$ at the University of Michigan (52). At a mean 5.5-year follow-up, the propensity-adjusted freedom from death, LV assist device, or United Network for Organ Sharing-1 transplant listing occurred in 41% of patients treated with medical therapy alone versus 49% with annuloplasty. Mortality occurred in 38% versus 48% of patients in the medical versus surgical groups, respectively. Unfortunately, quality of life and functional outcome measures were not assessed.

Recurrent MR is frequent after MV annuloplasty for secondary MR. Despite its initial abolition in nearly all patients, moderate or greater MR recurs in 15% to 25% of patients at 6 to 12 months, increasing to ~70% at 5 years (55). Risk factors for MR recurrence include more severe pre-operative MR, centrally directed or multiple jets, greater degree of LV dilation, symmetric anterior leaflet tethering, presence of a basal aneurysm/dyskinesis, ≥11 mm coaptation height, and a posterior leaflet angle of $>45^\circ$ (56). Recurrent MR is also more frequent with use of partial bands or flexible complete rings (57–59), although recurrence rates remain high even with complete rigid rings (60). The current standard repair uses a complete rigid ring, most commonly 28 mm in men and 26 mm in women. Various ring designs have been developed, including 1 specifically for ischemic MR, which overcorrects for the increased tethering of the P3 segment (61). In patients with severe tethering, chordal-sparing replacement may be preferable to annuloplasty due to less frequent MR recurrence, as discussed in the following text.

**STUDIES IN NONISCHEMIC MR.** In 54 patients with dilated cardiomyopathy at a single center, secondary MR was treated primarily with undersized annuloplasty rings with or without concomitant edge-to-edge repair (57). At 5-year follow-up, 30% of patients had died, and moderate/severe MR had recurred in 19%. In the ACORN trial, 193 patients with predominately nonischemic MR underwent MV surgery (84% with an annuloplasty ring) with or without placement of the CorCap LV restraint device (Acorn Cardiovascular, St. Paul, Minnesota). ACORN patients were younger and more often female than in most surgical series of secondary MR, and 30-day mortality was only 1.6% (62). However, during 5-year follow-up, 30% of patients died, 15% had recurrent MR, and 5% underwent repeat MV surgery (63). Additional studies are required before surgery can routinely be recommended for secondary MR in nonischemic cardiomyopathy.
MV ANNULOPLASTY VERSUS REPLACEMENT. MV replacement was used initially for secondary MR, but was quickly abandoned due to frequent ventricular decompensation. LV dysfunction in this setting was due to early techniques including excision of the mitral leaflets and subvalvular apparatus, resulting in annular-ventricular discontinuity. Current valve-sparing MV replacement techniques, which leave the leaflets and subvalvular apparatus intact, preserve LV function. In general, valve-sparing MV replacement is preferred in patients with the most severe degrees of tethering, as determined by a tenting height >11 mm, a posterior leaflet angle >45°, or a basal aneurysm or dyskinesia (64-69). Other situations in which replacement is preferred include: ruptured papillary muscle (acute ischemic MR); patients in cardiogenic shock; complex MR leaks with multiple jets; failure of an initial repair; and for surgeons who do not do many repairs. Clinical studies suggested that repair is associated with lower perioperative mortality, whereas replacement provides better long-term correction with a lower risk of recurrence (an important consideration, because MR recurrence predisposes to HF, atrial fibrillation, and readmission). This perceived tradeoff between reduced operative morbidity and mortality with repair versus better long-term correction of ischemic MR with replacement has generated substantial variation in surgical practice for this high-prevalence condition.

A meta-analysis of 9 retrospective, nonrandomized studies from 2004 to 2009, comprising 1,730 total patients, compared MV repair with replacement for ischemic MR, with the majority of patients also undergoing CABG (69). The OR for short-term mortality with MV replacement versus repair was 2.67 (95% CI: 1.86 to 3.82), with a long-term mortality HR of 1.35 (95% CI: 1.13 to 1.62). A more recent single-center fi-
rmed this observation: recurrent moderate/severe MR 32.6% 2.3% (p < 0.001). The strongest predictor of MR recurrence after repair was a basal aneurysm/dyskinesia at baseline (present in 62.1% of patients with vs. 20.5% without recurrence, p < 0.001) (71). Hence, MV replacement should be strongly considered when an inferobasal aneurysm is present.

OTHER SURGICAL PROCEDURES FOR SECONDARY MR. Although MV annuloplasty and replacement are the most common surgical procedures, a number of other techniques have been employed with varying degrees of success. In at least 2 series, cutting of the 2 critical secondary chords to the anterior leaflet corrected secondary MR without significant ventricular decompensation (72,73). This technique is most commonly employed in patients with severe replacement (with either mechanical or bioprosthetic valves) at 13 Italian centers between 1996 and 2011, although the 8-year mortality rate was similar between the 2 groups, recurrent MR and MV reoperation was 2.8-fold more common with repair (70).

The issue of repair versus replacement was addressed in a recently reported National Institutes of Health-sponsored trial from the Cardiothoracic Surgical Trials Network (CTSN), in which 251 patients with severe ischemic MR were randomized to undergo either MV repair with an undersized rigid or semirigid complete annuloplasty ring or chordal-sparing MV replacement (60). As seen in Table 3, there were no significant differences in the 1-year primary endpoint of LV end-systolic volume index or mortality. However, recurrence of at least moderate MR at 1 year was substantially greater with MV repair compared with replacement (32.6% vs. 2.3%, p < 0.001). The strongest predictor of MR recurrence after repair was a basal aneurysm/dyskinesia at baseline (present in 62.1% of patients with vs. 20.5% without recurrence, p < 0.001) (71). Hence, MV replacement should be strongly considered when an inferobasal aneurysm is present.

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**Table 3 Selected 1-Year Outcomes of MV Repair Versus Replacement for Severe Ischemic MR (From the Cardiothoracic Surgical Trials Network)**

<table>
<thead>
<tr>
<th></th>
<th>MV Repair (n = 126)</th>
<th>MV Replacement (n = 125)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVESVI (ml/m²; primary endpoint)</td>
<td>54.6 ± 25.0</td>
<td>60.7 ± 31.5</td>
<td>0.18*</td>
</tr>
<tr>
<td>Recurrent moderate/severe MR</td>
<td>32.6%</td>
<td>2.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderate</td>
<td>28.4%</td>
<td>2.3%</td>
<td>—</td>
</tr>
<tr>
<td>Severe</td>
<td>4.2%</td>
<td>0%</td>
<td>—</td>
</tr>
<tr>
<td>Death</td>
<td>14.3%</td>
<td>17.6%</td>
<td>0.45</td>
</tr>
<tr>
<td>MV reoperation</td>
<td>2.4%</td>
<td>0%</td>
<td>0.25</td>
</tr>
<tr>
<td>Major adverse cardiac events†</td>
<td>32.5%</td>
<td>33.6%</td>
<td>0.86</td>
</tr>
<tr>
<td>New York Heart Association functional class III/IV</td>
<td>9.0%</td>
<td>14.0%</td>
<td>0.28</td>
</tr>
<tr>
<td>Minnesota Living With Heart Failure score</td>
<td>24.3 ± 23.1</td>
<td>19.6 ± 19.4</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Values are mean ± SD or %. *Adjusted for death. †Death, stroke, New York Heart Association functional class increase by ≥1 grade, heart failure rehospitalization, or mitral valve reoperation.

Adapted with permission from Acker et al. (60).

LVESVI = left ventricular end-systolic volume index; MV = mitral valve.
tethering of the anterior leaflet by the secondary chords (seagull deformity). The restriction of the anterior leaflet can be relieved and coaptation restored with the free margin of the leaflet left intact. Kron et al. (74) described subvalvular repositioning of the displaced posterior papillary muscle toward the right, fibrous trigone as an adjunct to annuloplasty when severe degrees of tethering are present. Another technique employed restoration of both papillary muscles from their apical and lateral distracted position into a more physiological parallel alignment, resulting in less leaflet tethering.

In patients with severe mitral annular calcification in which the annulus has been rendered immobile, annuloplasty will not be effective, and replacement is often not feasible. In these patients, a free edge-to-edge approximation with suture (Alfieri technique) can improve the degree of MR (75). Likewise, in patients undergoing surgical aortic valve replacement with concomitant moderate secondary MR, an Alfieri suture can be placed through the LV outflow track after the aortic valve has been excised.

**VENTRICULAR APPROACHES TO SECONDARY MR.**

Two investigational extracardiac devices, the CorCap (Acorn Cardiovascular) and Coapsys (Myocor, Maple Grove, Minnesota), have been used to reshape the LV, which may secondarily reduce the degree of secondary MR (Figure 4). The CorCap is a passive external LV mesh restraint intended to reduce wall stress (62). In the 300-patient randomized ACORN trial, the CorCap reduced LV dimensions, but not MR severity or mortality compared with control patients (63). The Coapsys cardiac support device also reshapes the ventricle by placing a tether between anteriorly and posteriorly placed extracardiac pads, with some correction of the mitral annulus in the septal lateral dimension, thereby reducing secondary MR (76). The randomized RESTOR-MV (Randomized Evaluation of a Surgical Treatment for Off-Pump Repair of the Mitral Valve) trial in patients undergoing CABG with at least moderate secondary MR was terminated prematurely. Analysis of available data in 165 patients at mean 28-month follow-up showed a survival advantage for those treated with CABG plus Coapsys without MV repair compared with CABG plus selective MV repair (HR: 0.42 [95% CI: 0.20 to 0.87], p = 0.04). Although LV dimensions were reduced to a greater degree with Coapsys, MR reduction was greater with conventional MV repair (p < 0.0001).

**MANAGEMENT OF SECONDARY MR DURING CABG.**

Optimal management of concomitant secondary MR in patients undergoing CABG is still uncertain. There is general agreement that severe MR should be addressed at the time of CABG, because coronary revascularization alone will only occasionally ameliorate MR (77,78). In the RIME (Randomised Ischaemic Mitral Evaluation) trial, 73 patients with moderate secondary MR were randomized to CABG plus MV annuloplasty versus CABG alone (79). MV repair prolonged the duration of aortic cross-clamping, cardiopulmonary bypass, intubation, and hospitalization, and led to more blood transfusions, although operative mortality was 3% in both groups. At 1 year, MV annuloplasty resulted in improved peak oxygen consumption during exercise (the primary endpoint), LV remodeling, and reduced MR severity (80).

Several retrospective nonrandomized studies have failed to demonstrate a survival benefit of MV repair in patients undergoing CABG for ischemic heart disease with coexisting secondary MR (81,82). Conversely, in the prospective STICH (Surgical Treatment of Ischemic Heart Failure) trial, 220 patients had site-reported moderate/severe MR. Of 104 such patients assigned to CABG, MV repair was performed at operator discretion in 49, whereas 116 were assigned to medical therapy only (83). The 5-year adjusted HR for mortality in patients with MR treated with CABG plus MV repair versus medical therapy alone (without CABG) was 0.41 (95% CI: 0.22 to 0.77, p = 0.006), whereas no survival advantage was evident with CABG alone versus medical therapy. Thus, although surgical correction of severe MR in patients undergoing CABG is generally recommended to improve quality of life, in the absence of a large-scale randomized trial, it is uncertain whether survival is improved by mitral repair or replacement in this setting. The recent American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of valvular heart disease give MV surgery for secondary MR in the setting of CABG a Class IIa indication (Level of Evidence [LOE]: C), noting that addressing the MV at the time of surgery is reasonable to avoid leaving the patient with severe MR, despite the absence of conclusive evidence that this approach prolongs life or ameliorates symptoms (19).

The management of moderate MR in patients undergoing cardiac surgery has been controversial. In a recently reported National Institutes of Health-sponsored randomized trial from the CTSN, 301 patients with moderate ischemic MR undergoing CABG were randomized to coronary revascularization alone versus coronary revascularization plus MV annuloplasty with an undersized rigid annuloplasty ring (84). The addition of annuloplasty resulted in a longer duration of aortic cross clamping and
cardiopulmonary bypass, and a longer hospital stay. Annuloplasty did result in a reduction in the prevalence of moderate or severe MR at 1 year (11.2% vs. 31.0%, p < 0.001), but no significant improvement in LV systolic volume index, the primary endpoint of the trial (p = 0.61). There were also no significant between-group differences in deaths, readmissions, functional status, or quality of life at 1 year, although the annuloplasty group had a higher 1-year rate of neurological events (9.6% vs. 3.1%, p = 0.03). Thus, although longer-term follow-up is required to determine whether there is late benefit from the observed difference in MR at 1 year, ring annuloplasty of moderate ischemic MR cannot be routinely recommended in patients undergoing CABG at this time.

CURRENT GUIDELINES FOR MV SURGERY IN SECONDARY MR. The 2014 ACC/AHA valvular heart disease guidelines contain 3 recommendations for surgery in secondary MR (19). The first states that MV surgery is reasonable for patients with chronic, severe secondary MR (stages C and D) undergoing CABG or aortic valve replacement (Class IIa, LOE: C). The second states that MV repair may be considered for patients with chronic moderate secondary MR (stage B) undergoing other cardiac surgery (Class IIb, LOE: C). This latter recommendation was reached prior to the negative results of the randomized moderate ischemic MR trial being known (84). The third recommendation states that isolated MV surgery may be considered for severely symptomatic patients (NYHA functional class III to IV) with chronic severe secondary MR (stage D) who have persistent symptoms despite optimal GDMT for HF (Class IIb, LOE: B). Similarly, the most recent European guidelines (2012) give a Class IIb (LOE: C) recommendation for MV repair for isolated severe secondary MR, but only for patients at low surgical risk with LVEF >30% (23).

TRANSCATHETER DEVICES FOR SECONDARY MR

Despite the poor prognosis with GDMT, most HF patients with secondary MR do not undergo MV surgery. Between 2000 and 2008 at the Cleveland Clinic, only 36% of 814 patients with 3+/4+ secondary MR underwent MV surgery, and secondary MR comprised 90% of all nonoperated patients with severe MR (85). Given the uncertain risk-benefit ratio, MV surgery is uncommon in patients not requiring CABG. As a result, lesser-invasive transcatheter technologies have been developed to treat secondary MR. These devices are designed to imitate surgical approaches that have proven to be successful in acutely reducing MR, and may be classified according to whether they perform direct or indirect annuloplasty, edge-to-edge repair, chordal plication or replacement, complete MV replacement, or other approaches (86). The present review is restricted to the MitraClip, the only device in widespread use (>15,000 implants to date) and with sufficient outcomes data to provide comment.

THE MITRACLIP DEVICE. The MitraClip is a polyester-covered cobalt-chromium clip inserted via the femoral vein and advanced under transesophageal echocardiographic guidance into the LA following trans-septal puncture (Figure 5). The clip is opened, positioned above the regurgitant jet, and advanced into the LV. It is then retracted to grasp the free edges of the mitral leaflets, the grippers are dropped, and the clip is closed and released, emulating a surgical edge-to-edge repair (Figure 6) (87). Multiple clips may be safely placed, if necessary. The MitraClip has CE mark approval for general use, and Food and Drug Administration approval in the United States for treatment of symptomatic patients with severe primary MR at prohibitive risk for MV surgery, although not for secondary MR.

In the EVEREST II (Endovascular Valve Edge-to-Edge REpair Study), 278 relatively low-risk patients with 3+/4+ MR were randomized to the MitraClip or surgical MV repair. Compared with MV surgery, the MitraClip was substantially safer, but not as effective in reducing MR and LV remodeling (88).
with this device, acute procedural success (MR \(\leq 2^+\) at discharge) was achieved in only 77% of patients, and 21% required MV surgery. Nonetheless, with follow-up to 4 years, NYHA functional class and overall survival were similar in the 2 groups (89). Of note, 73% of the patients had primary MR, and only 27% had secondary MR. A significant interaction was present between the randomized therapy and the primary composite endpoint of death, MV surgery, or \(3^+/4^+\) MR at both 1 and 4 years according to MR etiology; patients with primary MR had significantly improved results with surgical MV repair, whereas outcomes were at least as good with the MitraClip in patients with secondary MR (Central Illustration) (88,89).

Since device approval in Europe, the MitraClip has been used extensively in patients at high risk or contraindicated for MV surgery, most commonly for secondary MR. Numerous registries have demonstrated high rates of procedural success and favorable short-term outcomes (Table 4) (90–103). The TRAMI (Transcatheter Mitral Valve Interventions) study is the largest published registry to date (90). Among 1,064 patients treated with the MitraClip at 20 German centers, the median age was 75 years; 87% had NYHA functional class III/IV HF symptoms; 69% had LVEF \(< 50\%\); secondary MR was present in 71% of patients; and the median Society of Thoracic Surgeons mortality score was 10. Procedural success was achieved in 95% of patients, with no procedural deaths. At ~3-month follow-up, 12% of patients had died and 12% had been hospitalized for HF, although 66% remained in NYHA functional class I/II. In the ACCESS-EU (MitraClip Therapy Economic and Clinical Outcomes Study Europe) registry, the MitraClip was implanted in 567 patients at 14 sites between April 2009 and April 2011 (91). The mean logistic EuroSCORE was 23, and 77% of patients had secondary MR. The clip implant rate was 99.6%, with multiple clips used in 40% of patients. MR was reduced to \(\leq 2^+\) in 91% of patients, and there were no procedural deaths. NYHA functional class and 6-min walk distance substantially improved at 1-year follow-up. Similarly, in the 25-center, 8-country, 2011 to 2012 European Sentinel Pilot Registry, 72% of 628 MitraClip-treated patients had secondary MR, 86% had NYHA functional class III/IV symptoms, and the mean EuroSCORE was 20.4 (92). Acute procedural success was high (95.4%), with multiple clips used in 39% of patients. In-hospital (2.9%) and 1-year (15.3%) mortality were similar in patients with secondary and primary MR, although rehospitalization for HF was more common in the secondary MR group (25.8% vs. 12.0%, \(p = 0.009\)). At 1 year, severe MR was present in only 6% of patients. Pooled data from the EVEREST II High-Risk Registry and U.S. REALISM (Real World Expanded Multi-center Study of the MitraClip System) registry were recently published in which the MitraClip was used in 351 patients with a Society of Thoracic Surgeons score or surgeon-predicted operative mortality of \(\geq 12\%\) (70% of whom had secondary MR) (93). By paired echocardiographic core laboratory analysis, MR was \(\geq 2^+\) in 89.7% of patients at discharge and in 83.4% of patients at 1 year. Mortality was 4.8% at 30 days and 22.8% at 1 year. LV end-diastolic and end-systolic dimensions decreased through 1-year follow-up, the physical and mental components of the Short Form-36 quality-of-life score improved, and the proportion of patients with NYHA functional class III/IV symptoms was reduced from 82.1% at baseline to 17.1% at 1 year.
The rate of hospitalizations for HF was significantly reduced in the year after MitraClip insertion, compared with the year before (median per patient 0.41 vs. 0.79, p < 0.0001). All outcomes were directionally consistent in patients with secondary and primary MR. The MitraClip has also been used successfully in HF patients who are nonresponders to CRT (an especially high-risk group), with resultant improvements in MR grade, functional capacity, and LV remodeling (104).

In a retrospective study, investigators in Italy compared the outcomes of 91 patients with 3+/4+ secondary MR undergoing surgical MV repair between 2001 and 2011 with those of 52 patients treated with MitraClip between 2008 and 2011.

The MitraClip cohort was significantly older, and had more diabetes and chronic kidney disease, higher logistic EuroSCOREs, lower LVEFs, and more comorbidities. Conversely, 35% of the surgical MV repair patients also underwent CABG (and other cardiac procedures). MitraClip-treated patients had significantly lower rates of hospital mortality and major infections, and a shorter length of stay compared with surgical patients, although MR was reduced to a lesser degree. Survival in the 2 groups was similar at 1 year (105). In contrast, comparable in-hospital and 6-month results were reported from a retrospective comparison of 171 patients with secondary MR treated with either the MitraClip (n = 95) or isolated MV repair (n = 76) from the
University of Hamburg (106). Differences in baseline characteristics and procedures between treated groups in these studies emphasize the challenges in interpreting the results of nonrandomized comparisons.

**CURRENT GUIDELINES FOR TRANSCATHETER DEVICE USE IN SECONDARY MR.** The 2012 European Society of Cardiology/European Association for Cardio-Thoracic Surgery valve and HF guidelines provide a Class IIB (LOE: C) recommendation to consider MitraClip use...

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### Table 4: Large-Scale Published Registries of the MitraClip: Baseline Characteristics and Acute Procedural Success

<table>
<thead>
<tr>
<th>Registry (Ref. #)</th>
<th>N</th>
<th>Mean Age (yrs)</th>
<th>Male</th>
<th>Mean or Median Risk</th>
<th>NYHA Functional Class III/IV</th>
<th>Mean LVEF</th>
<th>FMR Etiology</th>
<th>≥2- MR Post</th>
<th>Multiple Clips</th>
<th>Procedural Successa</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRAMI (90)</td>
<td>1,064</td>
<td>75</td>
<td>62%</td>
<td>10%†</td>
<td>87%</td>
<td>±</td>
<td>71%</td>
<td>96%</td>
<td>1.5 mean</td>
<td>95%</td>
</tr>
<tr>
<td>ACCESS-EU (91)</td>
<td>367</td>
<td>78</td>
<td>64%</td>
<td>23%§</td>
<td>85%</td>
<td></td>
<td></td>
<td>77%</td>
<td>91%</td>
<td>40%</td>
</tr>
<tr>
<td>European Sentinel (92)</td>
<td>628</td>
<td>74</td>
<td>63%</td>
<td>20%§</td>
<td>86%</td>
<td>43%</td>
<td>72%</td>
<td>98%</td>
<td>37%</td>
<td>95%</td>
</tr>
<tr>
<td>EVEREST II and REALISM (93)</td>
<td>351</td>
<td>76</td>
<td>61%</td>
<td>11%§</td>
<td>85%</td>
<td>48%</td>
<td>70%</td>
<td>86%</td>
<td>39%</td>
<td>-</td>
</tr>
<tr>
<td>GRASP (94)</td>
<td>171</td>
<td>71</td>
<td>62%</td>
<td>7%§</td>
<td>81%</td>
<td>37%</td>
<td>78%</td>
<td>93%</td>
<td>41%</td>
<td>99%</td>
</tr>
<tr>
<td>MARS (95)</td>
<td>142</td>
<td>71</td>
<td>64%</td>
<td>17%§</td>
<td>68%</td>
<td>47%</td>
<td>54%</td>
<td>77%</td>
<td>47%</td>
<td>94%</td>
</tr>
<tr>
<td>Taramasso et al. (96)</td>
<td>109</td>
<td>69</td>
<td>84%</td>
<td>22%§</td>
<td>82%</td>
<td>28%</td>
<td>100%</td>
<td>87%</td>
<td>65%</td>
<td>99%</td>
</tr>
<tr>
<td>MitraSwiss (97)</td>
<td>100</td>
<td>77</td>
<td>67%</td>
<td>17%§</td>
<td>82%</td>
<td>48%</td>
<td>62%</td>
<td>85%</td>
<td>40%</td>
<td>85%</td>
</tr>
<tr>
<td>French multicenter (98)</td>
<td>62</td>
<td>73</td>
<td>72%</td>
<td>19%§</td>
<td>81%</td>
<td>40%</td>
<td>74%</td>
<td>88%</td>
<td>17%</td>
<td>95%</td>
</tr>
<tr>
<td>Treede et al. (99)</td>
<td>202</td>
<td>75</td>
<td>63%</td>
<td>44%§</td>
<td>98%</td>
<td>44%</td>
<td>65%</td>
<td>92%</td>
<td>35%</td>
<td>92%</td>
</tr>
<tr>
<td>Bozdag-Turan et al. (100)</td>
<td>121</td>
<td>77</td>
<td>69%</td>
<td>11%§</td>
<td>96%</td>
<td>42%</td>
<td>59%</td>
<td>99%</td>
<td>28%</td>
<td>97%</td>
</tr>
<tr>
<td>Rudolph et al. (101)</td>
<td>104</td>
<td>74</td>
<td>62%</td>
<td>36%§</td>
<td>100%</td>
<td>43%</td>
<td>66%</td>
<td>92%</td>
<td>38%</td>
<td>92%</td>
</tr>
<tr>
<td>Braun et al. (102)</td>
<td>119</td>
<td>71</td>
<td>67%</td>
<td>28%§</td>
<td>86%</td>
<td>35%</td>
<td>35%†</td>
<td>-</td>
<td>-</td>
<td>86%</td>
</tr>
<tr>
<td>Neuss et al. (103)</td>
<td>157</td>
<td>74</td>
<td>67%</td>
<td>22%§</td>
<td>100%</td>
<td>41%</td>
<td>73%</td>
<td>100%</td>
<td>16%</td>
<td>98%</td>
</tr>
</tbody>
</table>

*aAccording to the registry protocol definition, which varied per study. 18y Society for Thoracic Surgery score. ILVEF ≤50% in 69% of patients. §By the logistic EuroSCORE. ACCESS-EU = MitraClip Therapy Economic and Clinical Outcomes Study Europe; EVEREST II = Endovascular Valve Edge-to-Edge Repair Study; FMR = functional mitral regurgitation; GRASP = Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation; LVEF = left ventricular ejection fraction; MARS = MitraClip Asia-Pacific Registry; MR = mitral regurgitation; NYHA = New York Heart Association; REALISM = Real World Expanded Multi-center Study of the MitraClip System; TRAMI = Transcatheter Mitral Valve Interventions.

### Table 5: Comparison of Ongoing Randomized Trials of the MitraClip in Patients With Heart Failure and Secondary Mitral Regurgitation

<table>
<thead>
<tr>
<th>COAPT</th>
<th>RESHAPE-HF</th>
<th>MITRA-FR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients and sites</td>
<td>430 patients at 75 U.S. and Canadian sites</td>
<td>800 patients at 50 U.E.I. sites</td>
</tr>
<tr>
<td>Secondary MR grade (core laboratory verified)</td>
<td>≥3+ (EROA ≥30 mm² and/or Rvol: 45 ml)</td>
<td>≥3+ (EROA ≥30 mm² and/or Rvol: 45 ml)</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>II, III, or ambulatory IV</td>
<td>III or ambulatory IV</td>
</tr>
<tr>
<td>LVEF</td>
<td>≥20% to ≤50%</td>
<td>≥15% to ≤40%</td>
</tr>
<tr>
<td>Surgical criteria</td>
<td>Not appropriate for mitral valve surgery (heart team)</td>
<td>None</td>
</tr>
<tr>
<td>Left ventricular volume entry criterion</td>
<td>LV end-systolic dimension ≤70 mm</td>
<td>LV end-diastolic dimension ≥55 mm</td>
</tr>
<tr>
<td>Control arm</td>
<td>Guideline-directed medical therapy (CRT, if indicated)</td>
<td>Guideline-directed medical therapy (CRT, if indicated)</td>
</tr>
<tr>
<td>Primary efficacy endpoint (superiority)</td>
<td>Heart failure rehospitalizations at 1 yr</td>
<td>Death or heart failure hospitalization at 1 yr</td>
</tr>
<tr>
<td>Primary safety endpoint (noninferiority)</td>
<td>The composite of: SLDA; device embolization; endocarditis requiring surgery; echocardiography core laboratory-confirmed mitral stenosis requiring surgery; LVAD implant; heart transplant; or any device-related complications requiring nonelective cardiovascular surgery at 12 months</td>
<td>None</td>
</tr>
<tr>
<td>Health economics</td>
<td>Assessed</td>
<td>Assessed</td>
</tr>
<tr>
<td>Follow-up, yrs</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

COAPT = Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation; EROA = effective regurgitant orifice area; LV = left ventricular; LVAD = left ventricular assist device; MITRA-FR = Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation; Rvol = regurgitant volume; RESHAPE-HF = Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation; SLDA = single leaflet device attachment; other abbreviations as in Table 4.
in symptomatic patients with severe secondary MR, despite GDMT and CRT, who are inoperable or at high risk (23). The 2013 ACCF/AHA HF guidelines provide a Class IIb (LOE: B) recommendation to consider MitraClip in symptomatic patients with severe secondary MR despite GDMT after “careful candidate selection” (43). Transcatheter MV repair for secondary MR did not receive an official recommendation in the 2014 ACCF/AHA valvular heart disease guidelines, although it is recommended with Class IIb (LOE: B) guidance for severe primary MR in symptomatic patients at prohibitive risk for MV surgery (19).

**ONGOING TRIALS.** Three large-scale trials are randomizing symptomatic HF patients with 3+/4+ secondary MR to the MitraClip plus GDMT versus GDMT alone (Table 5). The results of these trials will clarify the role of the MitraClip in secondary MR, as well as whether a therapy purely aimed at reducing secondary MR improves prognosis in patients with LV dysfunction as the primary pathophysiologic disturbance.

**CONCLUSIONS**

The development of secondary MR is strongly associated with a worsened prognosis in patients with HF, regardless of its etiology. Accurate assessment of MR severity in such patients can be challenging, but is essential to help define patient risk and guide treatment decisions. GDMT for HF is foundation therapy for moderate and severe secondary MR, along with CRT and coronary revascularization if indicated. When effectively applied, these measures will often reduce secondary MR and improve patient prognosis. The appropriate role of surgical and transcatheter interventions for persistent severe secondary MR is less clear and is evolving; both options may be considered in carefully selected patients after balancing the likely risks and benefits. Adequately designed randomized trials are essential to further guide optimal use of these invasive strategies, and several such trials with the MitraClip are ongoing. Collaboration among HF specialists, interventional cardiologists, cardiac surgeons, and imaging experts as a multidisciplinary heart team is imperative to reach consensus on appropriate care for patients with secondary MR.

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KEY WORDS cardiac resynchronization therapy, echocardiography, heart failure, mitral valve annuloplasty, prognosis, therapy