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THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

The Evolution of Percutaneous Mitral Valve Repair Therapy

Lessons Learned and Implications for Patient Selection

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ABSTRACT

Mitral regurgitation (MR) is the most common valve disease in the United States. However, a significant number of patients are denied surgery due to increased age, poor ventricular function, or associated comorbidities, putting them at high risk for adverse events. Moreover, the benefit of surgery for MR is unclear in patients with functional (secondary) MR. Recently, percutaneous repair of the mitral valve with a particular device (MitraClip, Abbott, Menlo Park, California) has emerged as a novel therapeutic option for patients with secondary MR or those deemed to be high risk for surgery. We review data from its initial concept through clinical trials and current data available from several registries. We focused on lessons learned regarding adequate patient selection, along with current and future perspectives on the use of device therapy for the treatment of MR. (J Am Coll Cardiol 2014;64:2688–700) © 2014 by the American College of Cardiology Foundation.

Mitral regurgitation (MR) is the most common valve disease in the United States (1,2). Worldwide, there are an estimated 50,000 operations for MR per year, of which about 55% are isolated mitral valve (MV) procedures (3). Patients with severe MR need to be monitored to prevent the consequences of chronic volume overload, such as: shortness of breath, heart failure, pulmonary hypertension, and reduced left ventricular (LV) function. Additionally, chronic severe MR leads to enlargement of the left atrium (LA).

MR pathogenesis can be divided into either a primary abnormality of the valve, degenerative mitral regurgitation (DMR) (**Figures 1A to 1C**), or an abnormality secondary to LV dysfunction, functional mitral regurgitation (FMR). Mixed situations, involving both a primary leaflet abnormality and a functional component, can also occur. MR may worsen or develop in the setting of atrial fibrillation. Patients with FMR usually have a worse prognosis than those with DMR. FMR is a consequence of ischemic or nonischemic LV dysfunction and remodeling, in which LV geometry becomes more spherical, leading to apical and posterior displacement of the papillary muscles and tenting of the (usually morphologically normal) MV leaflets along with dilation, and often with loss of annular contraction during systole (4,5) (**Figures 1D and 1E**). Current American Heart Association (AHA)/American College of Cardiology (ACC) guidelines recommend that surgery be performed (Class I) for symptomatic patients with chronic severe MR due to a primary valvular abnormality, and also state that surgery may be considered (Class IIb recommendation) as a therapeutic option for

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symptomatic patients with secondary (functional) severe MR (6). In these cases, there is no consistent data showing improved outcomes with surgery in terms of patient survival or quality of life (7,8). A recent analysis from Europe showed that about one-half of patients with severe symptomatic MR are denied surgery, mostly due to older age, impaired ventricular function, and associated comorbidities (9).

In the early 1990s, Alfieri developed the surgical edge-to-edge technique to treat MR (10,11). The edge-to-edge technique consists of suturing the free leaflet edges in the midportion of the anterior and posterior MV leaflets, creating a double orifice valve. Whether treating FMR or DMR, surgical edge-to-edge repair of the MV is generally associated with implantation of a flexible or semirigid prosthetic ring to increase the coaptation surface. Alfieri's group found this technique to be safe and durable. It is less optimal in patients with complex MR or with ischemic or functional etiology. Edge-to-edge repair with a flexible band had good short-term results in ischemic MR, but there was a high recurrence of ≥3+ MR in this patient group (12). Edge-to-edge repair's effectiveness has been debated because of variable results, a perceived nonphysiological approach, and the potential risk of causing secondary mitral stenosis.

The MitraClip System (Abbott, Menlo Park, California) was developed on the basis of Alfieri's edge-to-edge technique (**Figure 2**). The first porcine experience demonstrating feasibility was reported in 2003 (13), and the first human case was performed the same year (14). The percutaneously-delivered device (**Figure 3**) reduces MR by approximating the anterior and posterior MV leaflets. The procedure is done under fluoroscopic and echocardiographic guidance (15). **Figure 4** demonstrates the steps in device deployment. The system is introduced through the femoral vein and is advanced under fluoroscopic and echocardiographic guidance into the LA through a transseptal puncture. After being oriented perpendicular to the line of coaptation of the anterior and posterior MV leaflets in the LA, the system is advanced into the LV, where the anterior and posterior MV leaflets are grasped, creating a double MV orifice. If necessary, more than 1 clip can be deployed to achieve adequate MR reduction.

PATIENT ELIGIBILITY CRITERIA

Table 1 defines and **Figure 5** demonstrates the echocardiographic criteria for inclusion and exclusion of patients for the procedure on the basis of criteria used in U.S. clinical trials (16) and from additional experience in other locations (17). At present, this procedure is mostly used for central MR. However, investigators have started using the device for noncentral MR, where the medial or lateral scallops are involved, and in patients with moderate to severe MR after failed MV annuloplasty rings.

EVOLVING EXPERIENCE

INITIAL EXPERIENCE AND COMPARISON TO SURGERY. Major studies and their outcomes are summarized in **Table 2** and the **Central Illustration**. The first trial to evaluate MitraClip safety, EVEREST I (Endovascular Valve Edge-to-Edge REpair Study) (18), demonstrated its safety and feasibility for treatment of MR. Hemodynamic improvement of patients was noted post-procedure; however, 30% of patients had surgery due to MR ≥3+ within 3 years of the procedure (19). Subsequently, EVEREST II, a multicenter, randomized controlled trial, compared percutaneous repair versus surgery (either replacement or repair) (15) in patients with symptomatic severe MR (≥3+) who were also candidates for MV surgery.

Of note, as this study randomized surgery-eligible patients, those with severe LV dysfunction (ejection fraction [EF] ≤25%) or LV end-systolic dimensions >55 mm were excluded. The 279 patients were randomized in a 2:1 ratio in favor of percutaneous therapy. FMR was present in 27% of patients, and 52% of patients were New York Heart Association (NYHA) functional class (FC) III or IV (16). In the intention-to-treat analysis, both groups exhibited similar MR reductions at 1 year (MR reduction to ≤2+ was 80% for surgery and 79% for percutaneous repair, p = 1). However, patients assigned to a specific arm but who did not undergo the procedure (15 of 95 patients referred for surgery, 6 for percutaneous repair) were considered to have the same degree of MR at follow-up, accounting for most patients in the surgery group with residual MR. Among those assigned to and treated with surgery, only 4% had grade 3+ or 4+ mitral regurgitation at 1 year of follow-up, compared with 19% of those assigned to and treated with the device. In retrospect, the suboptimal reduction of MR using percutaneous therapy in this study may have been due to a number of factors: lack of operator experience (only 4 of 37 centers had performed more than 20 cases); suboptimal patient selection; and, in many cases, insufficient use of a second clip. It should be noted that this procedure has a significant learning curve. Schillinger et al. (20) found that procedural times progressively decrease after 25, 50, and 75 percutaneous valve repair cases. Similar findings support the importance of the learning curve for

ABBREVIATIONS AND ACRONYMS

DMR = degenerative mitral regurgitation

EF = ejection fraction

FC = functional class

FMR = functional mitral regurgitation

HRR = high-risk registry

LA = left atrium

LV = left ventricular

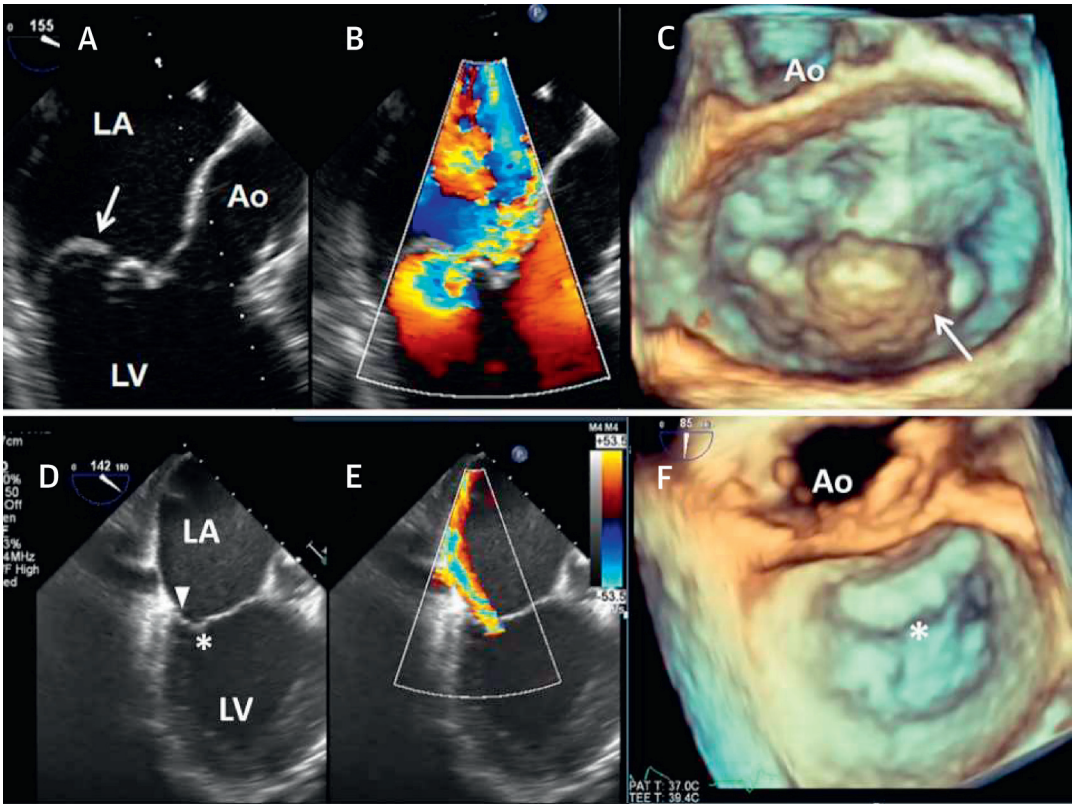
MR = mitral regurgitation

MV = mitral valve

NYHA = New York Heart Association

STS = Society of Thoracic Surgeons

FIGURE 1 Pathogenesis of MR



(Top) primary, degenerative mitral regurgitation (MR), and **(bottom)** secondary, functional MR. **(A)** 2-dimensional transesophageal echocardiogram (TEE) demonstrating prolapse of the posterior middle segment of the mitral valve (MV) **(arrow)**. **(B)** Color-flow Doppler shows an extensive, eccentric, anteriorly-directed regurgitation jet, signifying the presence of severe MR. **(C)** In this 3-dimensional TEE en face view, the middle part of the posterior mitral valve leaflet is clearly seen prolapsed, corresponding to the 2-dimensional findings **(arrow)**. **(D)** TEE demonstrating normal MV leaflet morphology; however, there is tenting of both MV leaflets, predominantly of the posterior leaflet **(arrowhead)**. **(E)** Color-flow Doppler shows an extensive, eccentric, posteriorly-directed regurgitation jet, signifying the presence of severe MR. **(F)** In this 3-dimensional TEE en face view, the valve leaflet failed to coapt adequately, corresponding to the 2-dimensional findings **(*)**. This provides the mechanism for the secondary MR. Ao = aorta, LA = left atrium, LV = left ventricle.

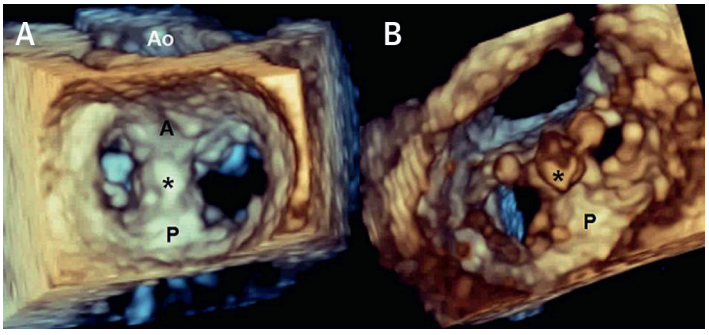
procedure time (18,21). Nevertheless, both surgical and percutaneous repair patients experienced significant improvement in LV dimensions and in end-systolic and -diastolic volumes at 1 year. Patients' quality of life improved from baseline to 1 year in both study groups, with NYHA FC ≥III reduced from 52% to 2% of patients in the percutaneous repair group and from 47% to 13% in the surgery group at 1 year ($p = 0.002$). The rate of major adverse events at 30 days (including death, myocardial infarction, reoperation due to a failed surgical repair or replacement, urgent or emergency cardiovascular surgery for adverse event, major stroke, renal failure, deep wound infection, mechanical ventilation for >48 h, gastrointestinal complications requiring surgery, new onset AF, septicemia, and transfusion of ≥2 U of blood) was 15% in the percutaneous repair group compared with 48% in the surgical group. However, this was driven mainly by the need for transfusion; with its exclusion from major outcomes, the rate of major adverse events at 30 days did not significantly differ between the groups (5% for the percutaneous repair group vs. 10% in the surgical group). At 4 years of follow-up of EVEREST II patients, there was no significant difference in mortality between the 2 groups (17% vs. 18%, $p = 0.9$). MR ≥3+ was present in 22% of the percutaneous repair group versus 25% of the surgical group ($p = 0.745$); however, surgery for significant MV regurgitation occurred in 25% of percutaneous repair-treated patients versus only 5.5% of surgically-treated patients ($p < 0.001$), with most surgeries performed within the first year in

both groups (20% vs. 2.2%). The improvement in NYHA FC at 1 year was sustained at 4 years, with 94% of the total study cohort with NYHA FC ≤II (22). The 5-year results were recently presented and demonstrated no mortality difference between the 2 groups, a low rate of MV surgery in the percutaneous repair group beyond the first 6 months of therapy, and a low rate of adverse events from 1 to 5 years in both groups (23).

SELECTED PATIENT POPULATIONS

HIGH-RISK PATIENTS. The percutaneous repair procedure appears to be a good option for patients who are too frail to undergo surgery (9). The EVEREST II High Risk Registry (HRR) (24), a prospective, single-arm study, was conducted in North America to gather clinical data on the effectiveness and safety of percutaneous valve repair in 78 patients deemed to be at high risk for surgery (Society of Thoracic Surgeons [STS]) mortality risk ≥12%) with MR ≥3+. As in EVEREST II, patients were excluded due to severe LV dysfunction (those with EF ≤25% or LV end-systolic dimensions >55 mm). Procedural results were relatively comparable to the original EVEREST II trial, with 74% of patients with NYHA FC ≤II and 78% free from MR ≥3+ at 1 year. There were no procedural deaths or device embolizations (**Central Illustration**, **Table 3**). The REALISM (Real World Expanded Multicenter Study of the MitraClip System) continued-access registry, which enrolled both standard and high-risk patients, was designed to collect "real-world" data and provide additional effectiveness and safety data. Eligibility criteria are similar to those for the EVEREST II HRR. The REALISM cohort's high-risk group, which enrolled its last patient in November 2013, includes patients on average 10 years older than those randomized in the EVEREST II trial and with more severe comorbidities (STS score of 11.3 vs. 4.6), predominantly with FMR (70% vs. 27%), and with a lower EF (47 ± 14% vs. 60 ± 10%). Initial analysis from this cohort showed that MR reduction from 3+ or 4+ (moderate to severe or severe MR) to 2+ (moderate MR) is associated with a decrease in LA and LV size (reverse remodeling). Although there was a reduction in LA size and reduction of the LV end-diastolic volume in patients with DMR (suggesting correction of the primary volume overload), in patients with FMR, there was a reduction in LA size and both LV end-systolic and -diastolic volumes, suggesting reverse LV remodeling. The magnitude of reverse remodeling was similar whether MR was reduced to either 2+ or 1+. The sustained reduction in MR also translated into clinical benefits, such as improvement in functional class and reduction in hospitalization due to heart failure (25).

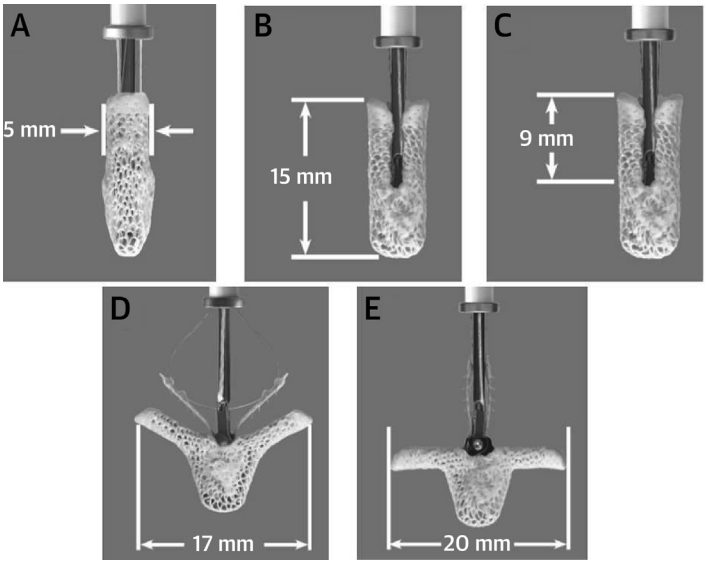
FIGURE 2 A Double-Orifice Valve Post-Procedure



Views of the mitral valve from **(A)** above (left atrium) and **(B)** below (left ventricle) showing the characteristic double orifice after device deployment, similar to results obtained from the surgical Alfieri stich. A = anterior mitral valve leaflet; Ao = aorta; P = posterior mitral valve leaflet. **Asterisk** marks the tissue bridge between the anterior and posterior mitral leaflet created by the MitraClip.

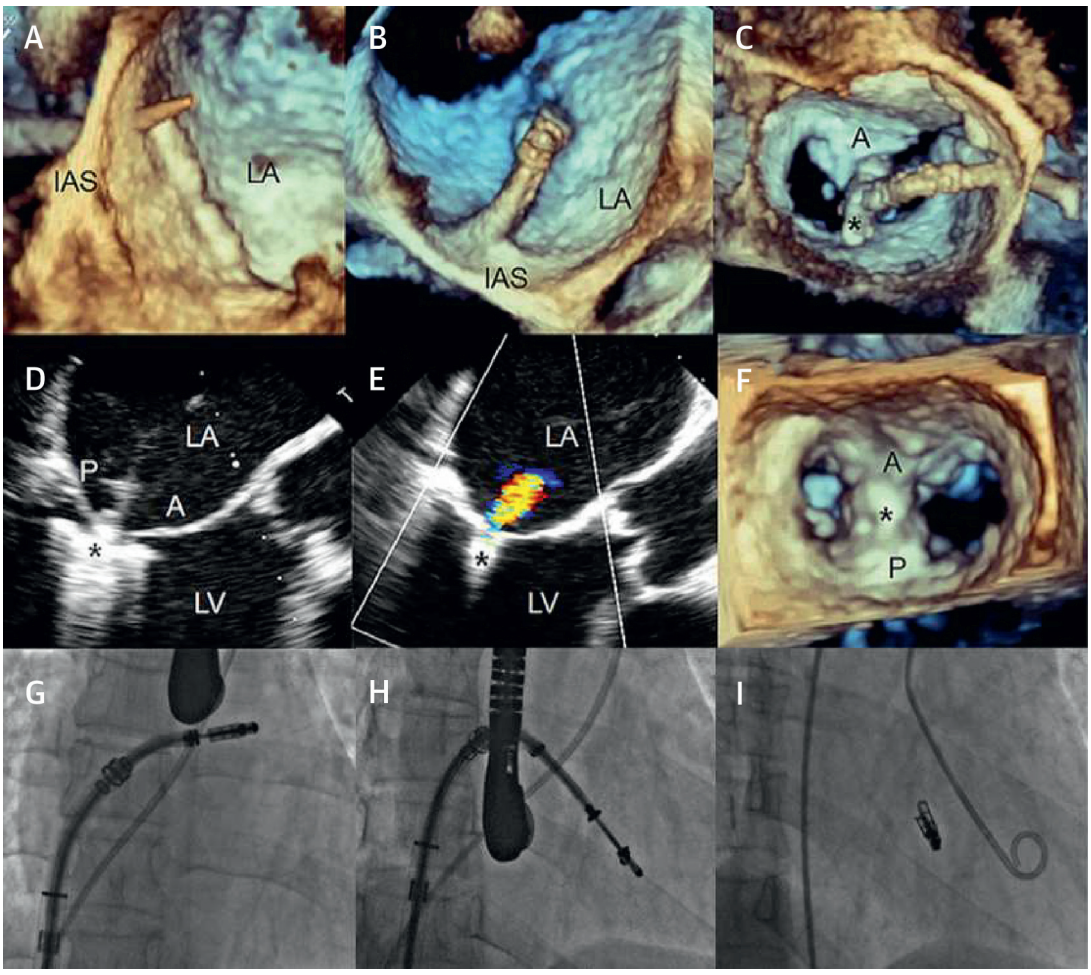
In 2008, the MitraClip system received approval for use in Europe. On the basis of wide experience and clinical evidence from trials and registries, the latest European Society of Cardiology guidelines on the management of patients with valvular heart disease

FIGURE 3 The System and Dimensions



The MitraClip is shown along with the clip "grippers." The system dimensions corresponding to requirements for inclusion of patients for the procedure are indicated. **(A)** Arm width; **(B)** closed clip length; **(C)** arm length (coaptation length); **(D)** grasping width with the grippers open to 120°; and **(E)** clip width with the grippers open to 180°. Images provided courtesy of Abbott Vascular © 2014. All rights reserved.

FIGURE 4 Steps of Deployment



These 2- and 3-dimensional TEE images show the steps of MitraClip deployment. **(A)** Trans-septal puncture. **(B)** Introduction of the catheter system to the LA through the intra-atrial septum (IAS). **(C)** Advancement of the delivery system and positioning of the MitraClip in between the MV leaflets. **(D)** 2-dimensional TEE demonstrating positioning of the MitraClip between the anterior and posterior MV leaflets. **(E)** 2-dimensional TEE with color Doppler showing mild MR after deployment of the percutaneous valve repair system. **(F)** 3-dimensional TEE showing the result post-deployment along with the typical double-orifice appearance. Fluoroscopic images showing the device within the LA **(G)**, advanced towards the LV **(H)**, and post-deployment **(I)**. **Asterisk** points to the location of the MitraClip. Abbreviations as in Figures 1 and 2.

recommended percutaneous valve repair as a treatment option for patients with symptomatic severe MR who were inoperable or at high surgical risk with a life expectancy of >1 year (Class IIb, Level of Evidence: C) (26). Since its approval in Europe, more than 16,000 percutaneous repair procedures have been performed worldwide. The ACCESS-EU (Two-Phase Observational Study of the MitraClip System in Europe) observational study (27) consisted of 567 elderly (mean age 74 years), high-risk (logistic EuroSCORE of 23 ± 18.3) patients, with predominantly FMR (69%), low EF (53% with EF ≤40%), low functional status (85% in NYHA FC ≥III), and multiple comorbidities, who underwent the device therapy at 14 European centers. There was a high procedural success rate of 99.6%. The procedure was found to be safe, with a 30-day mortality rate of 3.4% (19 patients). At 1 year, 82% of the patients were alive. Procedural adverse events were low and included 36 patients (6.3%) who subsequently underwent MV surgery within 12 months of device therapy. At 1 year, significant improvement in MR grade was observed, with 79% of patients having ≤2+ MR and 71% of patients at NYHA FC ≤II. Positive outcomes with

MitraClip were also observed in the German TRAMI (Transcatheter Mitral Valve Interventions) registry, which to date includes 1,064 patients who are older and with more comorbidities than those initially enrolled in the EVEREST II trial (28,29). Analysis from the TRAMI registry, specifically looking at patients older than age 76 years (29), showed that, similar to younger patients, elderly patients may benefit from device therapy, with a procedural success rate of 95% along with a reduction in MR ≤2+ in 96% of patients. During follow-up of about 2.5 months, there was also comparable improvement in NYHA FC, with 76% of the entire cohort in NYHA FC ≤II; however, death was higher in the elderly patient group (9% vs. 15%, $p < 0.05$). Results from a systematic review of 16 studies (12 from Europe and 4 from the United States; 13 prospective and 3 retrospective), including data on 2,980 patients, 2,689 of who were considered to be at high risk for surgery, showed that during a mean follow-up of 310 days (range 80 days to 4 years), the number of patients with ≥3+ MR was significantly reduced from 96.3% to 14.7% and the number of patients reporting NYHA FC ≥III symptoms decreased from 83% to 23.4% at the end of follow-up (30). A recent meta-analysis of cohorts, including high-risk patients, who underwent percutaneous valve repair therapy, found that procedural success (MR ≤2+) between 73% and 100% was achieved. The 30-day mortality ranged from 0% to 7.8%. At 6 to 12 months, 61% to 99% of patients reported ≤2+ MR. At 1 year, patient survival in this meta-analysis was 75% to 90% (31).

PRIMARY VERSUS SECONDARY MR. For the young patient with DMR and without comorbidities, surgical MV repair can be performed with minimal risk and good results. However, the durability of MV surgical repair is an issue. There are variable results regarding freedom from recurrence of moderate or severe MR (≥3+). Flameng et al. (32) found a recurrence rate of ≥3+ MR of 35% at 10 years, for which Barlow's disease was a risk factor. David et al. (33,34) reported a recurrence rate of 35% at 12 years when the anterior mitral leaflet was involved. Conversely, more contemporary studies from multiple centers reported that surgical repair is durable and survival is improved, with a low reoperation rate (35-38). A recently published analysis from the EVEREST cohort of 127 patients with DMR, mean age 82 years, 87% NYHA FC ≥III, and prohibitive surgical risk (regarded as STS risk ≥8%, porcelain aorta or extensively calcified ascending aorta, frailty, severe liver disease, severe pulmonary hypertension, or other unusual extenuating circumstances) found percutaneous repair therapy successful in 95%. Death was 6.3% at 30 days and 23.6% at 1 year. At 1 year, 83% of patients had MR grade ≤2+ and 87% were in NYHA FC ≤II, compared with all having MR ≥3+ and 87% at NYHA FC ≥III at baseline. At 12 months, MR reduction to ≤2+ was associated with improvement in NYHA FC, improved quality of life, reduced hospitalization for heart failure, and reverse LV remodeling. Moreover, patients with MR grade ≤2+ at discharge demonstrated better survival at 12 months than those discharged with MR ≥3+ (39). A subanalysis of 117 high-risk patients, all with DMR, from the ACCESS-EU registry showed that percutaneous repair therapy reduced MR significantly, with 75% of patients with an MR grade of ≤2+ at 1 year and 81% with NYHA FC ≤II (40).

A survival benefit with surgery has not been demonstrated in patients with secondary FMR (41). Moderate or severe regurgitation has been reported in up to 30% of FMR patients at 1 to 5 years post-repair, prompting some surgeons to consider either MV replacement or not addressing the problem of FMR surgically (42,43). In the EVEREST II 4-year outcome subgroup analysis, DMR patients had greater benefit from surgery compared with percutaneous valve repair. However, in FMR patients at high risk for recurrent MR after surgery (44), the efficacy endpoint

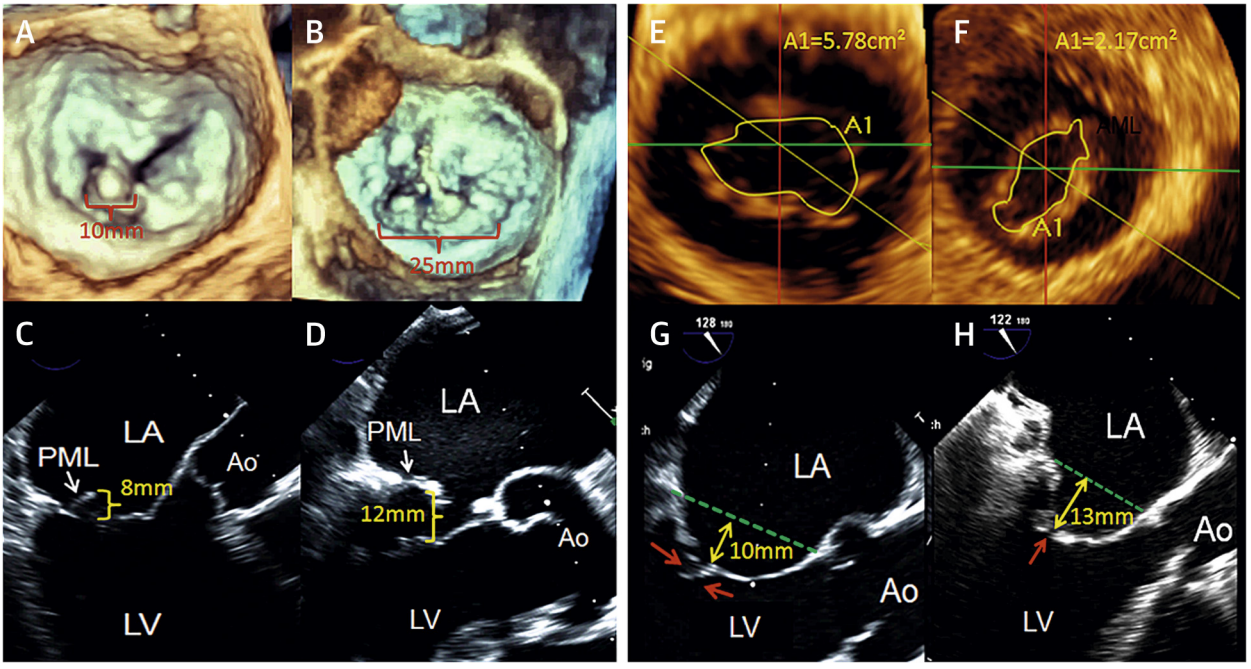
TABLE 1 Echocardiographic Morphological Characteristics for Determining Patient Eligibility for Percutaneous Valve Repair Therapy

Criteria Suggesting Patient Suitability	Criteria Suggesting Patient Might Not Be Suitable
Nonrheumatic etiology	Rheumatic etiology, endocarditis-related valve disease, or prior MV surgery
Central mitral regurgitation jet	Cleft or perforated mitral leaflets
MV orifice area ≥40 mm^2	Lack of secondary chordal support
If a flail leaflet is present	Posterior leaflet length <7 mm
Flail gap* <10 mm	
Flail width* <15 mm	
Posterior leaflet length ≥10 mm	Leaflet gap >2 mm
If leaflet tethering present	Presence of severe calcifications in the grasping area
Coaptation depth <11 mm	
Coaptation length† <10 mm	
Absence of calcifications in the grasping area	Transmitral pressure gradient ≥4 mm Hg‡ Effective regurgitant orifice area >70.8 mm^2‡ MV orifice area <30 mm^2‡
	Evidence of intracardiac mass, thrombus, or vegetation, or evidence of an inferior vena cava or femoral venous thrombus

Patient eligibility characteristics were on the basis of criteria used in the EVEREST trial (16). See Figure 5 for corresponding images. *These criteria are derived from the device design (see also Figure 3). The MitraClip arm width is 5 mm, thus a flail width of more than 15 mm would necessitate implantation of many clips and adversely cause valve obstruction. The arm length, when fully open at 180°, is 20 mm. As both clip arms close simultaneously, if the distance between the leaflets is too great, it would be more than difficult to grasp both simultaneously (Figure 5). †If the gap between the leaflets is too big, the clip will not be able to build a sufficient tissue bridge (Figure 5). ‡On the basis of findings from Lubos et al. (17): patients with these findings carry an increased risk of procedural failure.

MV = mitral valve.

FIGURE 5 Echocardiographic Measurements for Determining Patient Suitability for MitraClip Implantation



(A and B) 3-dimensional TEE en face views demonstrating measurements of a flail width **(red brackets)** in patients with degenerative mitral valve disease. These measurements can be obtained alternatively from short-axis views where the flail width is largest (transthoracic echocardiogram/TEE; transgastric not shown). **(A)** An example of a suitable case for the percutaneous valve repair system, with a small flail width (ideally <15 mm). The pathology is located centrally. **(B)** An example of a case that is not suitable for percutaneous valve repair therapy due to multiple, extensive prolapses in the posterior mitral leaflet (PML). **(C and D)** 2-dimensional TEE images showing the flail gap. **Yellow brackets** indicate the distance between the tip of the anterior mitral leaflet (AML) and PML. This measurement should be taken in long-axis views, where the flail gap is largest (TEE 4-chamber, 5-chamber, long-axis view ~120° to 150°). **(C)** An example of a case with a suitable flail gap (<10 mm). **(D)** The flail gap is too large, in addition to the posterior leaflet being considerably calcified, making this case unsuitable for percutaneous valve repair therapy. **(E and F)** Measurements of the mitral valve area (MVA) from the LV side (post-processing analysis using QLAB software, Philips, Eindhoven, the Netherlands) are shown. **(E)** A case with a MVA (A1) of 5.78 cm^2, which is suitable for device implantation (>4 cm^2). **(F)** The MVA (A1) is 2.17 cm^2, a contraindication to percutaneous device implantation. **(G and H)** Examples of patients with functional mitral regurgitation. The tenting height (which equals the coaptation depth, demonstrated by the **yellow double arrow**) is measured from the base of the mitral annulus **(green dashed line)** to the tip of the leaflets in diastole. This measurement should be taken in either the 4- or 5-chamber view, where the tenting height is largest. The tenting height should ideally be <11 mm. **(G)** A suitable case; **(H)** severe retraction of both leaflets is seen, and the case is unsuitable for percutaneous valve repair therapy. To be a suitable candidate for percutaneous therapy, the coaptation length (overlap of the tip of the AML and the PML at the edges) should optimally be ≥2 mm. The measurement should be taken in long-axis views, where the coaptation length is shortest. **(G)** There is some overlap of the AML and the PML **(red arrows)**. **(H)** The tips of the leaflets just touch, without demonstrating real overlap; thus, this case is not ideal for device implantation **(red arrow)**. Abbreviations as in Figure 1.

was 34% in the percutaneous repair group versus 23% in the surgical group (p = 0.344). Of subjects with ≥3+ MR at 4 years, FMR was more prevalent in the surgical arm (22). Worsening LV dysfunction is also not an uncommon post-operative occurrence in patients with MR (45,46). In the past, this was attributed to the increase in afterload associated with surgical correction of MR. However, studies of the hemodynamic effects of the device therapy demonstrated that, in patients with LV dysfunction, the cardiac output increases, and LV and LA filling pressures, as well as pulmonary artery systolic pressures, are reduced (19,47,48). There have been no reported instances of low cardiac output syndrome as a consequence of percutaneous device therapy. Thus, reducing MR does not appear to promote post-procedural LV dysfunction. It is likely that the post-operative LV dysfunction seen in post-surgery patients might be attributed to several factors, including the systemic inflammatory response, myocardial oxidative stress, and free radical injury associated with the use of cardiopulmonary bypass (49), cardioplegia (50), and complete cardiac arrest; the development of reversed septal motion post-operatively; and the restraint of mitral annular motion (LV function) that may be caused by MV

TABLE 2 Characteristics of Patient Populations in MitraClip Trials/Registries

Study (Ref. #)	N	Study Objective	Age, Yrs	FMR	DMR	LVEF	Surgical Risk	NYHA FC ≥III
EVEREST I (18)	107	Percutaneous valve repair therapy initial safety, efficacy, and feasibility	Median: 71, 62% age >65 yrs	21	79	62		46
EVEREST II (15) randomized controlled trial	279 (MitraClip 184; surgery 95)	Percutaneous therapy vs. surgery	Median 67, 29% age >75 yrs	27	73	60		50
EVEREST II HRR (24)	78	High-risk registry for patients with STS risk ≥12%	Mean 77 ± 9.8, 62% age >75 yrs	59	41	54.4 ± 13.7	Mean STS score 14.2 ± 8.2	90
REALISM continued-access registry (25)	545 (273 high-risk, 272 non-high-risk)	High-risk study: 351 patients (273 + 78 from EVEREST II HRR)	Mean 76 ± 11	70	30	47 ± 14	Mean STS score 11.3	85
ACCESS-EU (27) observational study	567	Post-approval European registry ± 18%	Mean 74 ± 9.6	69	31	53% with LVEF ≤40%	Mean logistic EuroSCORE 23	85
TRAMI registry (28,29) observational study	1,064	German registry designed to assess device in daily practice	Median 75, interquartile range: 70–81	71	29	30% with LVEF ≤40%	EuroSCORE: 18/25* STS score: 7/11.5*	87
Vakil et al. (30) systematic review of	2,980, of which 2,689 were considered high risk	Pooled analysis (12 European, 4 United States; 13 prospective and 3 retrospective)	Mean 74 ± 0.6	65	35	46 ± 3.2	Mean logistic EuroSCORE 23.4 ± 1.5 STS score 12 ± 0.7	83

Values are % unless otherwise indicated. *Patients <76/≥76 years, respectively.

ACCESS-EU = Two-Phase Observational Study of the MitraClip System in Europe; DMR = degenerative mitral regurgitation; EVEREST = Endovascular Valve Edge-to-Edge REpair Study; FC = functional class; FMR = functional mitral regurgitation; HRR = high-risk registry; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; MV = mitral valve; NYHA = New York Heart Association; REALISM = Real World Expanded Multicenter Study of the MitraClip System; STS = Society of Thoracic Surgeons; TRAMI = Transcatheter Mitral Valve Interventions.

annuloplasty rings or prosthetic valves. Data from trials and registries, such as the EVEREST II HRR (24) (of which 69% of patients had FMR) and those detailed in **Table 4** (21,51–54), support MitraClip therapy as a valuable treatment option, especially in those with severely reduced LV function (EF <30%), where current therapeutic options are limited. In nonresponders to cardiac resynchronization therapy, percutaneous valve repair therapy improved NYHA FC, increased EF, and reduced LV volumes in about 70% of patients (52); a similar improvement in NYHA FC after cardiac resynchronization therapy failure was also found by Pleger et al. (55). As demonstrated in **Table 4**, data on the device in patients with FMR shows a reduction in MR, symptomatic improvement in NYHA FC III to IV patients, and reverse LV remodeling; there is no data demonstrating improvement in survival. As shown in the **Central Illustration**, data from the REALISM cohort looking at outcomes by MR etiology show some different outcomes with regard to LV remodeling when comparing patients with FMR to those with DMR. Although LV end-diastolic volume improved proportionally to the degree of MR reduction at 1 year in both groups, patients with FMR also exhibited a proportional decrease in LV end-systolic volume, which was not statistically evident in the DMR group (25). Additional analyses from small trials, evaluating percutaneous therapy in those with FMR, also suggest that the procedure is safe and effective in this patient population (21,51–54).

On the basis of pooled results of the percutaneous valve repair device in high-risk patients with DMR, in 2013 the U.S. Food and Drug Administration approved device therapy for patients considered to be at prohibitive risk for surgery who have MR ≥3+ due to DMR (39). In addition, the 2014 AHA/ACC guidelines for management of patients with valvular heart disease included transcatheter MV repair as an option for patients with primary MR who are symptomatic despite optimal heart failure therapy and who are at prohibitive risk for surgery (Class IIb, Level of Evidence: C) (6). Future patient selection for percutaneous valve repair could potentially include other groups of patients where surgical risks are high, as in FMR (and a reduced LVEF), or where surgical results are less optimal and durable, such as patients with anterior leaflet prolapse/flail. The ongoing COAPT (Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy for High Surgical Risk Patients) (56) and RESHAPE-HF (Randomized Study of the MitraClip Device in Heart Failure Patients with Clinically Significant Functional Mitral Regurgitation) (57) trials are evaluating the role of MitraClip in patients with FMR who are not candidates for cardiac surgery.

CENTRAL ILLUSTRATION **Outcomes of MitraClip Trials/Registries**

TRIAL/REVIEW	MR REDUCTION	NYHA FC IMPROVEMENT	ADVERSE EVENTS	PATIENT MORTALITY
EVEREST I 107 patients	74% ≤2+	NA	9.1%	1%
EVEREST II 279 patients (MitraClip 184 Surgery 95)	**1 year** Intention-to-treat analysis: Surgery 80% MR ≤2+ MitraClip 79% MR ≤2+ (p = 1) Per-protocol analysis: Surgery 4% MR ≤2+ MitraClip 83% MR ≤2+ (p = 0.01) **4 years** Surgery 75% MR ≤2+ MitraClip 78% MR ≤2+ (p = 1)	**1 year** Surgery 87% FC<III MitraClip 98% FC<III (p = 0.002) LV volumes reduced significantly from baseline in both groups. Reduction in end-diastolic volume was greater with surgery	**30 Days** Intention-to-treat analysis: Surgery 48%, MitraClip 15% (p <0.001)* Per-protocol analysis: Surgery 57%, MitraClip 9.6% (p <0.001)† **1 year** Intention to treat analysis: Surgery 37%, MitraClip 32.6% (p = 0.42) Per protocol analysis: Surgery 2.2% MitraClip 17.6% (p <0.02)	**1 year** Intention-to-treat analysis: Surgery 5.6%, MitraClip 6.3% (p = 1) Per-protocol analysis: Surgery 6.8% MitraClip 4.5% (p = 0.7) **4 years** Surgery 18% MitraClip 17% (p = 0.9)
EVEREST II HRR 78 patients	**30 days** 73% MR ≤2+ **1 year** 78% MR ≤2+	**30 days** 73% FC <III **1 year** 74% FC <III	1 case of tamponade during transseptal puncture	**30 days** 7.7% **1 year** 24.4%
REALISM 545 patients (273 high risk + 272 non-high risk)	**Discharge** 82% MR ≤2+ **1 year** FMR 84% MR ≤2+| DMR 82% MR ≤2+	NA	NA	NA
ACCESS-EU 567 patients	**1 year** 79% MR ≤2+	**1 year** 71% FC <III	**1 year** 6.3% surgery due to MV dysfunction	**30 days** 3.4% (42% due to cardiac causes) **1 year** 18%
TRAMI 1,064 patients	96% MR ≤2+ post-procedure	**Median follow-up of 85 days** 76% FC <III	**Median follow-up of 85 days** MV Surgery 2.6%	**Peri-procedural** 2.8% **Median follow-up of 85 days** 12%
Vakil et al. Systematic review of 2,980 patients	**During a mean follow-up of 310 days** 85.3% MR ≤2+	**Median follow-up of 85 days** 76% FC <III	**Median follow-up of 85 days** MV Surgery 2.6%	**Peri-procedural** 2.8% **Median follow-up of 85 days** 12%

Beigel, R. et al. J Am Coll Cardiol. 2014; 64(24):2688–700.

*When excluding red blood cell transfusion, there was no significant difference in MACE: surgery 10%, MitraClip 5% (p = 0.23). †When excluding red blood cell transfusion, there was still a significant difference in MACE: surgery 11.4%, MitraClip 0.7% (p = 0.001). ACCESS-EU = Two-Phase Observational Study of the MitraClip System in Europe; DMR = degenerative mitral regurgitation; EVEREST = Endovascular Valve Edge-to-Edge REpair Study; FC = functional class; FMR = functional mitral regurgitation; HRR = high-risk registry; LV = left ventricular; MACE = major adverse cardiovascular event(s); MR = mitral regurgitation; MV = mitral valve; NA = not available; NYHA = New York Heart Association; REALISM = Real World Expanded Multicenter Study of the MitraClip System; TRAMI = Transcatheter Mitral Valve Interventions.

SAFETY

Potential complications associated with MitraClip implantation are detailed in Table 5. Initial studies of the percutaneous procedure in EVEREST I, and later in EVEREST II, showed it to be safe, with low morbidity. Real-world results from the ACCESS-EU registry in a higher-risk, older population than those evaluated in the EVEREST trials show low procedural and hospital mortality (<2%), with >90%

TABLE 3 Results From Studies Evaluating Effects of Percutaneous Valve Repair on MR, Hemodynamics, and Remodeling

First Author/Study (Ref. #)	MR Grade	CO, l/min	PCWP, mm Hg	Other
Biner/Siegel et al. (19,47) (N = 107, patients from EVEREST I and roll-in EVEREST II cohorts)	MR grade reduced: 3.3 ± 0.7 to 1.7 ± 0.9	CO increased: 5 ± 2 to 5.6 ± 1.9 (p = 0.0033) CI increased: 2.7 ± 1 to 3 ± 1 (l/min/m^2)	No change in PCWP LVEDP fell from 11.4 ± 9 to 8.8 ± 5.8 (p = 0.016)	SVR reduced: 1,253 ± 259 to 1,058 ± 475 dyne/cm^5 Right atrial pressure increased by 1 mm Hg from: 8.1 ± 4.7 to 9.3 ± 5.6 mm Hg No significant change in PASP, except in those with a baseline elevated PASP in whom it fell from 49 ± 7 mm Hg to 40 ± 9 mm Hg (p = 0.004)
EVEREST II HRR (24)	75% achieved MR reduction to ≤2+ 40% achieved MR of 1+ At 1 year: 78% with MR ≤2+	Pre: 4.6 ± 2.1 10 min post: 5.6 ± 2.7 (p = 0.001)	V-wave decreased: 26 ± 15 to 21.3 ± 9.6 (p = 0.023)	Blood pressure pre: 109.3 ± 21.1 mm Hg 10 min post: 113.5 ± 19.3 mm Hg (p = 0.09)
REALISM (25)	82% MR ≤2+ at discharge FMR: At baseline: 86% MR ≥3+ At 1 year: 84% MR ≤2+ DMR: At baseline: 94% MR ≥3+ At 1 year: 82% MR ≤2+			Reduction in MR severity, even to 2+, was associated with reverse LA and LV remodeling. Patients with FMR showed significant reductions in both LVEDV and LVESV (in contrast to those with DMR, who did not show significant reduction in LVESV).
ACCESS-EU (27)	91% achieved MR reduction to ≤2+ 51% achieved MR ≤1+	CO increased: 3.7 ± 1.5 to 4.4 ± 1.9	V-wave decreased: 23 ± 11 to 19.5 ± 9	All other hemodynamic measurements remained stable
Gaemperli et al. (48) (N = 50)	92% achieved MR reduction to ≤2+	CI increased: 3.1 ± 1 to 3.9 ± 1.1 (l/min/m^2) (p < 0.05)	PCWP decreased: 29 ± 12 to 24 ± 6	All other hemodynamic measurements remained stable

CI = cardiac index; CO = cardiac output, LA = left atrium; LV = left ventricle; LVEDP = left ventricular end-diastolic pressure; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; PASP = pulmonary artery systolic pressure; PCWP = pulmonary capillary wedge pressure, SVR = systemic vascular resistance; other abbreviations as in Table 2.

procedural success, along with hemodynamic and functional improvement (27) (**Central Illustration**, **Table 3**). From a pooled analysis of 16 studies totaling 2,980 patients, of whom 2,689 were considered high-risk for surgery, there was a very low incidence of procedural death (0.1%). Thirty-day mortality was 4.2%. During a mean follow-up of 310 days (range 80 days to 4 years), the incidence of death was 387 of 2,457 (15.8%) (30). The totality of these data clearly demonstrates this procedure's safety compared with other contemporary transcatheter valve therapies (58).

TABLE 4 Results of Percutaneous Valve Repair Therapy in FMR

First Author/Study (Ref. #)	N	Patient Characteristics	MR Reduction/NYHA FC	Mortality
Franzen et al. 2010 (21)	51	FMR 69% (35 of 51) LVEF 36 ± 17% NYHA FC ≥III 98% Logistic EuroSCORE 15 ± 11% STS score 16 ± 11	67% FC <III post-procedure NYHA FC improvement ≥1 FC 90% 96% with ≤2+ MR at 30 days	No mortality at 30 days
Franzen et al. 2011 (51)	50	All with FMR ≥3+ and LVEF ≤25% NYHA FC ≥III 100% Logistic EuroSCORE 34 ± 21%	92% with MR ≤2+ at 30 days 87% with MR ≤2+ at 6 months 72% FC <III at 6 months	6% at 30 days 19% at 6 months
Auricchio et al. 2011 (52)	51	All patients CRT nonresponders with FMR ≥3+ LVEF 27 ± 8.7% NYHA FC ≥III 98% Logistic EuroSCORE 29.7 ± 19.4% STS score 13.9 ± 14.6	NYHA FC at discharge, 73% (p < 0.001) More than 85% with MR ≤2+ at 1 yr Significant reduction of LVESV and LVEDV at 6 months Significant increase of LVEF at 6, 12 months	2.1% periprocedural 4.2% at 30 days 18% at a median follow-up of 14 months
Van den Branden et al. 2012 (53)	52	FMR, 90% (47 of 51) all ≥3+ NYHA FC ≥III, 98% Logistic EuroSCORE 27.1 ± 17% STS score 10.1 ± 7.6	84% NYHA FC <III at 6 months 79% with MR ≤2+ at 6 months LVESV, LVEDV: trend in reduction	3.6% (2 patients) periprocedural 11.5% at 6 months
Taramasso et al. 2013 (54)	109	FMR 100% Logistic EuroSCORE 22 ± 16.5% 82% NYHA FC ≥III Mean EF 27 ± 10%	86% NYHA FC <III at 1 yr 70% MR ≤2+ at 2.5 yrs Mean EF increased to 34.7 ± 10% at 1 yr (p = 0.002) Significant reduction in LVEDV at 1 yr	1.8% at 30 days 25% at 3 yrs

CRT = cardiac resynchronization therapy; EF = ejection fraction; other abbreviations as in Tables 2 and 3.

TABLE 5 Complications Associated With Percutaneous Valve Implantation

Partial clip detachment
Thrombus formation on the catheter
Chordae tendineae entrapment by the MitraClip
Pericardial effusion or tamponade
Persistent atrial septal defect
Cardiac arrhythmias
Air embolism

FUTURE PERSPECTIVES

Percutaneous valve repair therapy appears to have a favorable risk-benefit ratio in high-risk patient populations with both primary MR and FMR. The MitraClip is currently approved in the United States for prohibitive-risk primary MR patients. There is still no randomized data demonstrating that mechanical reduction of FMR in addition to medical therapy is superior to medical therapy only.

The 2014 AHA/ACC guidelines have less stringent criteria for severe FMR than the prior guidelines, which were used to define patients previously enrolled into percutaneous valve repair therapy clinical trials. Although the new criteria for severe FMR are controversial (59), they potentially allow more patients with FMR to be candidates for device therapy (if approved for this indication). The COAPT and RESHAPE-HF trials will prospectively evaluate percutaneous valve therapy's usefulness in patients with FMR, NYHA FC II to IV, and reduced LV function, by comparing percutaneous valve repair to nonsurgical standard of care.

Additional successfully-performed, but not yet extensively-studied, percutaneous valve applications include patients with severe MR due to medial and lateral jets and patients with failed MV surgical repairs. Future improvements in devices for edge-to-edge repair could include: a smaller, complete delivery system and device; a device that is catheter-based, rather than the MitraClip robotic arm delivery system; and new technologies that allow simpler, easier, and more rapid percutaneous MV repair. Other catheter-based technologies for treating MR are in development. Indirect and direct percutaneous annuloplasty approaches for MV repair have been done in humans (60). Percutaneous approaches to MV replacement have also been performed in animals and in human cadavers (61,62). Improvements in procedural guidance could shorten the procedure's duration and improve outcomes. Newer fusion imaging, combining computed tomography and the widespread use of 3-dimensional echocardiography, might further enhance imaging and device delivery, and may potentially shorten procedure time (63).

CONCLUSIONS

Percutaneous mitral valve repair therapy has emerged as a novel therapy that may be safe and effective in selected patients with MR. Although there is currently insufficient evidence to suggest that patients who are suitable for surgery should be candidates for the percutaneous therapy, recent data and results from current registries suggest that percutaneous therapy may be beneficial in high-risk patient populations. The percutaneous valve repair therapy system is most appropriate for patients with primary MR who are at high risk for surgery. Although nonrandomized data suggest its efficacy in patients with secondary/functional MR, ongoing randomized clinical trials are being conducted to confirm the superiority of the percutaneous approach to optimal medical management.

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