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Percutaneous treatment of mitral valve disease

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Mitral valve disease is one of the most common valvular heart conditions. A true incidence of mitral valve disease is unknown (1,2). The prevalence of rheumatic disease in developed countries is declining with an estimated incidence of 1 in 100 000. The prevalence is higher in developing nations than in the United States (3). In Africa, for example, the prevalence is 35 cases per 100 000. Today, the most common cause of mitral stenosis is rheumatic fever, but the stenosis usually appears clinically relevant only after several decades. Uncommon causes of mitral stenosis are calcification of the mitral valve leaflets and congenital heart disease. Other causes of mitral stenosis include infective endocarditis, mitral annular calcification, endomyocardial fibroelastosis, malignant carcinoid syndrome, systemic lupus erythematosus, Whipple disease, Fabry disease, and rheumatoid arthritis (3-6). MS is significantly more prevalent in women (1.6 % vs 0.4 %, $P < .001$).

Incidence of MR increases from 0.5 % (18-44 years of age) to 9.3 % (≥ 75 years of age). Prevalence of mitral valve disease is 2-fold higher than aortic valve disease in people ≥ 65-year-old. More than 1 in 8 patients > 75-year-old have moderate or severe mitral regurgitation. MR affects more than 2 million people in the US and is expected to almost double by 2030 in aging population and growth (1,2). Treatment options include medical therapy, surgical MV repair or replacement, and percutaneous mitral valve repair. A total of 210 529 MR surgeries/year were performed (from 2000 – 2009). Approximately 30 000 MV surgeries/year were performed in the USA (combined and isolated mitral procedures) and bio prosthetic valves were implanted in 60 % of the patients. Operative mortality was 7.1 % with higher mortality in female gender. There is a limited durability of surgical MV repair and mitral valve replacements at 2 years, with 44 % rate of primary valvular failure at 15 years. Patients can have residual symptomatic mitral regurgitation, stenosis, or stenosis causing symptomatic heart failure (related to valve dysfunction after surgery) (1,2).

Novel percutaneous and surgical techniques that involves percutaneous restoring and/or surgically reconstructing the mitral valve so that it functions normally are now considered for the treatment of symptomatic patients with significant mitral valve disease. As compared with surgical minimally invasive procedures, percutaneous techniques provide patients with a quicker recovery time, less blood loss and even a cosmetic benefit (7).

Mitral stenosis occurs when the mitral valve does not open completely during left ventricular filling. Symptoms of mitral stenosis usually

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manifest during the third or fourth decade of life and nearly half of the patients do not recall a history of acute rheumatic fever. Patients are generally asymptomatic at rest during the early stage of the disease. However, factors that increase heart rate such as fever, severe anemia, thyrotoxicosis, exercise, excitement, pregnancy, and atrial fibrillation may result in dyspnea. Hemoptysis may occur and is usually not fatal. Pregnant women with mild mitral stenosis may become symptomatic during their second trimester of pregnancy because the concomitant increase in blood volume and cardiac output with pregnancy.

In contrast, Mitral valve regurgitation occurs when the valve does not close completely during cardiac contraction, causing the blood to flow backward instead of forward. Traditionally a cardiac surgeon removes the diseased area of the valve, and then reconstructs it using area tissue. There are many advantages to a repaired mitral valve versus the alternative of an artificial mitral valve. Severe mitral regurgitation is a common and complex disease that is associated with an adverse prognosis. For decades, surgical treatment has been the standard of care. Recently, multiple technologies for transcatheter mitral therapy have emerged, with the potential for both repair and replacement in patients with native mitral regurgitation. Transcatheter mitral technologies have potential as solutions for unmet clinical needs. Further rigorous clinical studies are needed to determine their efficacy and safety, as well as the appropriate patient candidates. These evaluations will help to define the role of transcatheter mitral therapy as a potentially exciting new strategy to improve the lives of patients with mitral regurgitation.

The Mitral Valve

To appreciate the mechanistic role of current percutaneous therapies, it is important to understand the anatomic and functional properties of the mitral valve apparatus (Figure 1). The mitral valve is a complex anatomic structure. Its proper function strictly depends on the structural and functional integrity of its individual components, which include the mitral valve annulus, both mitral valve leaflets, chordae tendineae, and subvalvular apparatus, including the papillary muscles and left ventricular wall. Disarrangement of one or more of these components characteristically typically results in flow-limiting (ie, stenosis) or regurgitant valvular dysfunction. In either case, a thorough appreciation of the disease mechanisms is essential for the conceptualization and development of alternative, less-invasive, percutaneous mitral valve therapies.

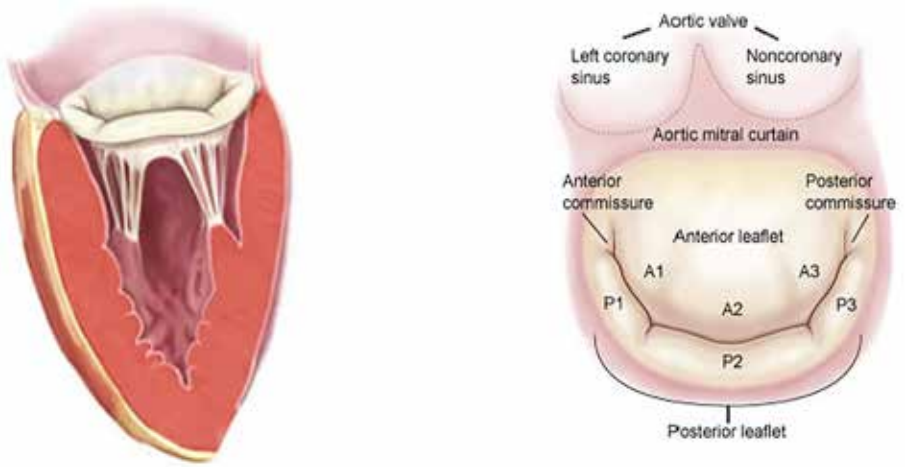
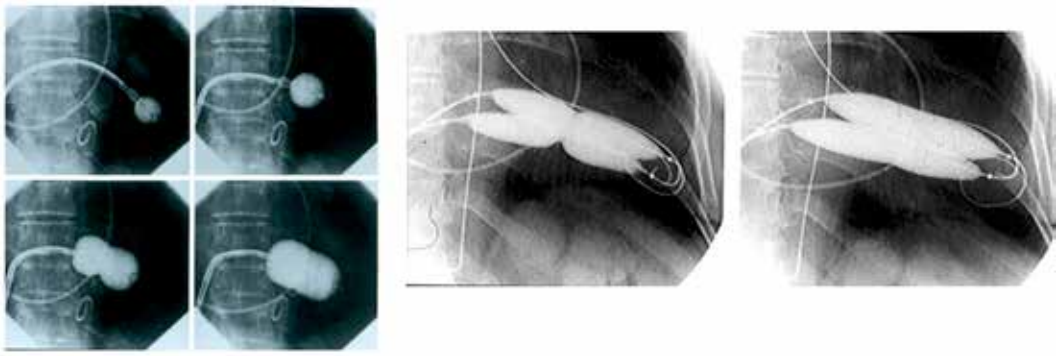


Figure 1. The Mitral Valve Apparatus. The mitral valve is complex anatomic structure. Its proper function strictly depends on the structural and functional integrity of its individual components, which include the mitral valve annulus, leaflets, chordae tendineae, and subvalvular apparatus, including the papillary muscles and left ventricular wall.

MITRAL STENOSIS – Percutaneous Therapies

Since its introduction in 1984 by Inoue and colleagues (7) percutaneous mitral balloon valvuloplasty (PMV) has been used successfully as an alternative to open or closed surgical mitral commissurotomy in patients with symptomatic rheumatic mitral stenosis. PMV is safe and effective and results in excellent immediate hemodynamic outcome, low complication rates, and improved clinical benefit. Sustained clinical and hemodynamic improvements have been previously reported and are similar to those of surgical mitral commissurotomy (23-31). Nevertheless, because of the less invasive nature of PMV, currently this technique is considered the preferred therapy for relief of mitral obstruction in symptomatic patients with rheumatic mitral valve stenosis. Different techniques of PMV result in satisfactory immediate and long-term results. Today the Inoue and the double balloon techniques are the more widely used techniques of PMV (Figure 2). However, there is controversy as to which technique provides superior immediate and long-term results. When compared Inoue with the Double balloon technique of PMV we demonstrated no significant difference in hemodynamic results between these two techniques of PMV (28). The Inoue technique is faster and less cumbersome. The Inoue technique associated with less fluoroscopy time, and the Inoue balloon is easier to position and hold position across the mitral valve. The Inoue technique allows simple upsizing without withdrawing balloon from the left atrium. However, the Inoue technique may be responsible for slightly more MR. Compared with the Inoue technique, the double balloon technique results in larger post-PMV mitral valve area. This superior immediate outcome of the double balloon technique was observed only in the group of patients with echocardiographic score < 8. Both techniques result in similar degree of post-PMV severe mitral regurgitation. However, despite the difference in immediate outcome between both techniques, there were no significant differences in event-free survival at long term follow-up (28). Proper patient selection is a fundamental step when predicting the immediate results of PMV. Candidates for PMV require precise assessment of clinical features and mitral valve morphology. The echocardiographic score (Echo-Sc) is currently the most widely used method for predicting PMV outcome. Leaflet mobility, leaflet thickening, valvular calcification, and subvalvular disease are each scored from 1 to 4, yielding a maximum total Echo-Sc of 16. An inverse relationship exists between the Echo-Sc and PMV success. Both Immediate, and intermediate follow-up studies have shown that



A The Inoue technique B The double balloon technique

Figure 2. Relationship between the Echo-Sc and changes in mitral valve area after PMV (bar graph) and relationship between the Echo-Sc and PMV success (line with filled triangles). Numbers at the top of rectangular bars represent mean mitral valve areas before (black bars) and after (shaded bars) PMV for each Echo-Sc. Percentages in parentheses represent PMV success rate at each Echo-Sc. (From Palacios IF, Sanchez PL, Harrell LC, et al. Which patients benefit from percutaneous mitral balloon valvuloplasty? Prevalvuloplasty and postvalvuloplasty variables that predict long-term outcome. Circulation 2002;105(12):1465–71; with permission.).

patients with Echo-Sc ≤ 8 have superior results and significantly greater survival and combined event free survival than patients with Echo-Sc greater than 8 (14,21) (Figure 3). Long-term follow-up results, however, are scarce, and although earlier studies have reported that PMV results in good immediate hemodynamic and clinical improvement in most patients with mitral rheumatic stenosis, superior long-term follow-up results are seen in a selected group of patients with Echo-Sc less than or equal to 8. The authors have recently reported a multifactorial score derived from clinical, anatomic, echocardiographic, and hemodynamic variables that would predict procedural success and clinical outcome from PMV. Six independent predictors of PMV success were identified: age less than 55 years, New York Heart Association classes I and II, pre-PMV mitral area of ≥ 1 cm^2, pre-PMV mitral regurgitation grade < 2, echocardiographic score of 8 or greater, and male sex were used to construct a score from the arithmetic sum of variables present per patient (24). Comparison between the new score and the Wilkins echocardiographic score confirmed that the new index was more sensitive and specific (P < .001). This new score also predicts long-term outcomes (P < .001). Thus, this score derived from clinical, anatomic, and hemodynamic variables predicting PMV success and clinical outcome may be formulated in a scoring system that would help to identify the best candidates for PMV (24).

In summary, PMV results in excellent immediate and long-term results similar to those of surgical commissurotomy. Randomized trials have demonstrated no significant difference between strategies (29-31). As previously discussed, patient selection is essential in predicting PMV results and requires proper preprocedural evaluation of mitral valve morphology. The determinants of PMV success are multifactorial and include demographic, clinical, and hemodynamic variables in addition to the more important echocardiographic Wilkins score. The recently reported multifactorial score may be used to further identify the subset patients who derive the greatest clinical benefit from PMV. We reported the immediate and long-term clinical follow-up (mean, 4.2±3.7 years; range, 0.5 to 15) of 879 consecutive patients who underwent 939 PMV procedures. Patients were divided into 2 groups, Echo-Sc < or =8 (n=601) and Echo-Sc >8 (n=278). PMV resulted in an increase in mitral valve area from 1.0±0.3 to 2.0±0.6 cm^2 in patients with Echo-Sc ≤ 8 and from 0.8±0.3 to 1.6±0.6 cm^2 in patients with Echo-Sc >8 (P<0.0001). Although adverse events (death, mitral valve surgery, and redo PMV) were low within the first 5 years of follow-up, a progressive number of events occurred beyond this period. Nevertheless, survival (82 % versus 57 %) and event-free survival (38 % versus 22 %) at 12-year follow-up was greater in patients with Echo-Sc < or =8 (P<0.0001). Cox regression analysis identified post-PMV mitral regurgitation > or =3+, Echo-Sc >8, age, prior surgical commissurotomy, NYHA functional class IV, pre-PMV mitral regurgitation > or =2+, and higher post-PMV pulmonary artery pressure as independent predictors of combined events at long-term follow-up. In conclusion, the immediate and long-term outcome of patients undergoing PMV is multifactorial (23). The use of the Wilkins Echo-Score in conjunction with other clinical and morphological predictors of PMV outcome allows identification of patients who will obtain the best outcome from PMV (23,24,29-30) (Figure 3).

Mitral regurgitation is the most common type of valvular insufficiency. The etiologies of MR can be related to primary degeneration of the mitral valve (DMR), functional mitral regurgitation (FMR) secondary to ischemic or non-ischemic cardiomyopathy, or a combination of both. It is estimated that approximately 5 million people in the United States and more than 20 million worldwide suffer MR, ischemic cardiomyopathy is the most common cause of heart failure in the United States dilated left ventricles and coexisting mitral regurgitation. Ischemic cardiomyopathy is the most common cause of heart failure in the United States. This disease is marked by diffuse myocardial damage, left ventricular remodeling, and often functional ischemic MR. It is frequently associated with high operative risk, disease recurrence and increased mortality. Currently, potential percutaneous options for the treatment of mitral regurgitation include leaflet coupling with edge-to-edge repair (E -valve MitraClip, Edwards Stitch); Coronary sinus reshaping (MONARCC device, Cardiac Dimensions Carillon device, Mitralife ev3, Viacor); annular plication with posterior annulus

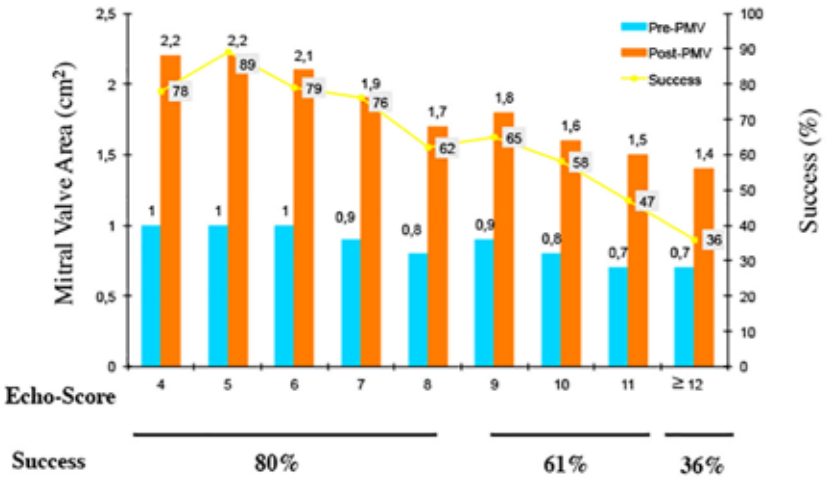


Figure 3. Inoue-balloon (A) and Double-balloon technique (B) of PMV. From Palacios IF. Balloon dilation of the cardiac valves. In: Willerson JT, Kohn JN, editors. Cardiovascular Medicine, Second Edition. New York: Churchill Livingstone, 1995; with permission.

reshaping (Mitralign, Guided Delivery Systems); left ventricular remodeling (Myocor, Ample PS3 percutaneous septal sinus shortening or ARTO device (1-2,6,29-35).

Percutaneous Leaflet Repair – The Alfieri Technique

In 2000, Alfieri and colleagues introduced a simplistic and revolutionary surgical technique to treat degenerative and functional MR (36-38). Although initially poorly accepted, the Alfieri stitch, or edge- to-edge, technique gained increasing popularity among many surgeons. By suturing the free edges of the middle anterior (A2) and posterior (P2) mitral leaflets and creating a double-orifice inlet valve, the edge-to-edge technique improves leaflet coaptation and thus decreases MR. Acceptable results have been reported for degenerative and more recently for functional MR, with 5-year freedom from recurrent MR greater than 21 and reoperation rates of up to 90 (± 5 %).The results have triggered the development of less-invasive trans- catheter edge-to-edge techniques. To date, two major mitral valve programs have been developed to mimic the double-orifice strategy using a catheter-based approach: the MitraClip (Evalve, Menlo Park, California) and the MOBIUS (Edwards Life-sciences, Irvine, California) system (39-40,44).

The MitraClip

The MitraClip is a unique device that is delivered using a triaxial catheter system to create a double-orifice mitral valve Figures 4-5). After the initial encouraging results in animal models, the revolutionary transcatheter technique was first implanted in humans in June 2003. At 2-year follow-up, the 56-year-old woman with heart failure and severe 4+ MR remained symptom-free with less than 2+ MR. Safety and feasibility results of the MitraClip system have now been tested in the Endovascular Valve Edge-to-Edge Repair Study (EVEREST) phase I and phase II study (39-40, 43, 44). Preliminary results of the initial 107 patients (EVEREST I, and EVEREST II) with degenerative (79 %) or functional MR (21 %) are encouraging. Implant success occurred in 90 % of patients, of which acute success (MR grade 2+%) was reported in 84 % of the cases (43-44). Among these patients, improvement in NYHA functional class was reported in 73 % at 1-year follow-up. In the EVERETT II trial 279 patients with moderately severe or severe (grade 3+ or 4+) mitral regurgitation were randomized in

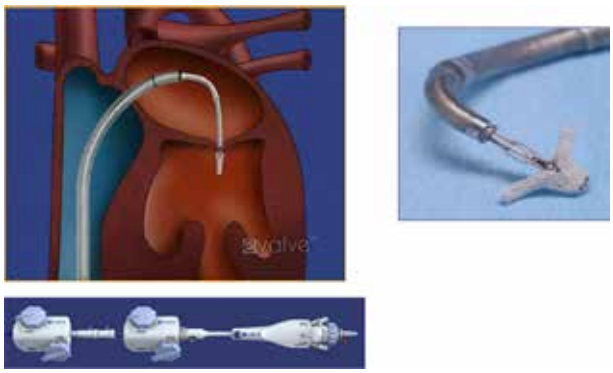


Figure 4. The Mitra Clip technique.

Figure 5. The Mitra Clip technique.

a 2:1 ratio to undergo either percutaneous repair or conventional surgery for repair or replacement of the mitral valve. The primary composite end-point for efficacy (freedom from death, from surgery for mitral-valve dysfunction, and from grade 3+ or 4+ mitral regurgitation) at 12 months are shown in Figure 6. The primary safety end-point was a composite of major adverse events within 30 days. At 12 months, the rates of the primary end-point for efficacy were 55 % in the percutaneous-repair group and 73 % in the surgery group (P=0.007). The respective rates of the components of the primary end-point were as follows: death, 6 % in each group; surgery for mitral-valve dysfunction, 20 % versus 2 %; and grade 3+ or 4+ mitral regurgitation, 21 % versus 20 %. Major adverse events occurred in

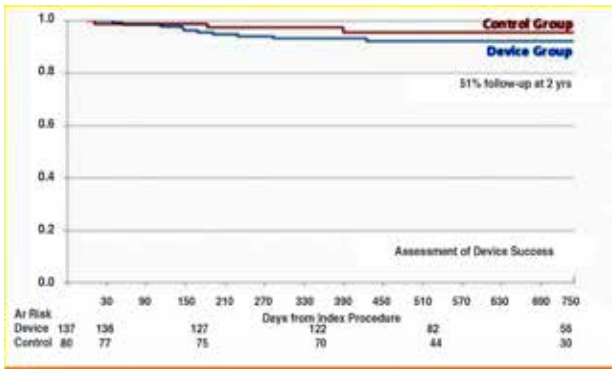


Figure 6. Event Free survival (end point of the EVEREST II trial). The favorable acute procedural success rates were maintained over the long term; 71 % of patients were event-free (death/mitral valve surgery/MR > 2) at 36 months.

15 % of patients in the percutaneous-repair group and 48 % of patients in the surgery group at 30 days (P<0.001). At 12 months, both groups had improved left ventricular size, New York Heart Association functional class, and quality-of-life measures, as compared with baseline. The authors concluded that although percutaneous repair was less effective at reducing mitral regurgitation than conventional surgery, the procedure was associated with superior safety and similar improvements in clinical outcomes (43-44).

Data presented at the 2018 TCT meetings in San Diego, California from the randomized COAPT trial (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure patients with Functional MR (COAPT), have the potential to significantly change current clinical practice. The study was also published simultaneously in the *New England Journal of Medicine* (45). This study found that patients with heart failure and secondary mitral regurgitation (MR) who remained symptomatic despite maximally tolerated medical therapy demonstrated reduced rates of hospitalizations and death, as well as improved quality-of-life and functional capacity after being treated with the transcatheter MitraClip device (Figure 7). The prognosis for heart failure patients who develop severe secondary mitral regurgitation is poor with limited treatment options and there is a great need to help improve outcomes for these very sick patients. COAPT was a randomized,

parallel-controlled, open-label multicenter trial evaluating transcatheter mitral valve repair with the MitraClip device in symptomatic heart failure patients with moderate-to-severe or severe secondary MR. A total of 614 subjects were randomized at 78 centers in the United States and Canada. A total of 302 patients were assigned to the device and guideline-directed medical therapy (GDMT) in the device group and 312 patients were assigned to GDMT alone in the control group. The primary effectiveness endpoint was the annualized rate of all heart failure hospitalizations through 24 months and the primary safety endpoint was freedom from device-related complications at 12 months (Figure 7). After two years, there were 160 total heart failure hospitalizations among those who received the mitral clip versus 283 for the control group. The annualized rates of heart failure hospitalization were 35.8 % per patient-year in the device group versus 67.9 % per patient-year in the control group (HR 0.53, 95 % CI [0.40 to 0.70]; p<0.001) (45). In addition, the 12-month freedom from device-related complications was 96.6 % [lower 95 % confidence limit, 94.8 %], which exceeded the performance goal of 88.0 % for the primary safety endpoint (P<0.001). All-cause mortality at 24 months with the device was 29.1 % compared to 46.1 % in the control group (HR 0.62, 95 % CI [0.46 to 0.82]; P<0.001). In addition to the reductions in hospitalizations and mortality, device treatment also resulted in improvements in quality-of-life measures and functional capacity. The study found a mean 12.5-point increase in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score from baseline to 12 months after transcatheter mitral repair compared to a mean 3.6-point reduction in the control group. Similarly, exercise capacity as measured by six-minute walk distance (6MWD) decreased during 12-month follow-up by nearly 60 meters with GDMT alone but remained unchanged after transcatheter mitral repair. Heart failure classification (NYHA functional class) was also improved to a greater degree with the transcatheter device compared with GDMT alone at all follow-up times. Patients treated with the MitraClip also had a lower incidence of heart transplant or a left ventricular assist device (LVAD) (4.4 % for the device group versus 9.5 % for the control group).

At two years, transcatheter mitral valve repair with the MitraClip device was found to be safe and effective. It substantially reduced the rate of hospitalizations and mortality, while improving quality-of-life and functional capacity. In pts with HF and moderate-to-severe or severe secondary MR who remained symptomatic despite maximally-tolerated GDMT, transcatheter mitral leaflet approximation with the MitraClip was safe, provided durable reduction in MR, reduced the rate of HF hospitalizations, and improved survival, quality-of-life and functional capacity during 24-month follow-up. As such, the MitraClip is the first therapy shown to improve the prognosis of patients with HF by reducing secondary MR due to LV dysfunction. This

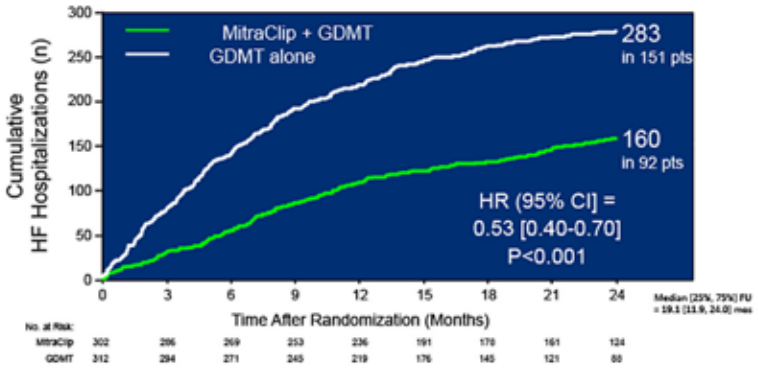


Figure 7. All Hospitalizations for HF within 24 months Primary Effectiveness Endpoint of the COAPT trial.

procedure gives cardiologists an important option for high-risk heart failure patients with secondary MR who remain symptomatic despite optimal medical therapy (45).

To date, approximately more than 50 000 patients worldwide have been treated with the MitraClip system. The system is a well-established therapy with a growing body of clinical and real-world experience. Importantly, reports of clip failure are well tolerated and do not preclude patients from surgical mitral valve repair or replacement.

Technically, the MitraClip system consists of three major subsystems: a guide catheter, a clip delivery system, and the MitraClip implant with two arms used to grasp and fasten together the valve leaflets. The procedure consists of six steps: 1) transseptal approach and puncture; 2) introduction of the SGC into the left atrium; 3) navigation with the CDS into the left atrium to place the MitraClip® above the mitral valve; 4) crossing the valve and advancing the CDS into the left ventricle; 5) grasping the leaflets and assessment of the quality of the grasping; and 6) final mitral regurgitation assessment (39,40,43,44) (Figures 4-5). The guide catheter is 24F proximally and tapers to 22F distally. It is inserted from the femoral vein and advanced above the mitral valve following a transseptal puncture. The steering knob allows flexion and lateral movement of the distal tip so that the clip is positioned orthogonally. Real-time echocardiographic guidance is vital; and use of 3D transesophageal echocardiography to guide the procedure has improved reproducibility, reliability and safety.

The MOBIUS leaflet repair system

The MOBIUS Leaflet Repair system (Edwards Life- sciences), previously called the Milano Stitch, was introduced by Dr. Maurice Buchbinder as a similar catheter-based edge-to-edge technique (46,47). Contrary to the MitraClip, this strategy uses a small guiding catheter to stitch the free edges of the anterior and the posterior mitral leaflets, thus creating a double-orifice inlet valve. An innovative suction catheter is used to adhere the leaflets together and facilitate stitch placement under fluoroscopic and echocardiographic guidance. 39 After the successful animal model experience, the first human procedure was performed in Milan, Italy, in a 67-year-old woman with NYHC functional class III and severe MR secondary to a prolapsed posterior leaflet. 40 Subsequently, the percutaneous Alfieri-like stitch was tested in a feasibility trial of 15 patients with degenerative or functional MR. In this phase I study, acute procedure success occurred in 9 of 15 patients. Of these, three patients required a single stitch, five required two stitches, and one patient required three stitches. At 30-day follow-up, only 66 % of the patients (six of nine) had a successful stitch in place with at least one grade improvement in MR reduction. The acute failure patients (6 of 15) all underwent subsequent successful surgical repair. Unfortunately, the study's intermediate result has prompted the investigators to suspend further evaluation for this particular indication.

Percutaneous Annuloplasty

As previously discussed, mitral annular dilation is a common pathologic problem in patients with severe persistent MR. Accordingly, surgical annuloplasty results in septal-lateral annular shortening and decrease in MR severity. Long-term safety and efficacy results after surgical annuloplasty report freedom from recurrent MR and need for reoperation in 82 % and 95 % of patients during 7-year follow-up, respectively. Consequently, there has been a major drive to duplicate these results with catheter-based techniques.

Direct annuloplasty techniques

The Mitralign system

The Mitralign system (Mitralign) is one of the first insightful direct endovascular percutaneous annuloplasty systems. It consists of a deflectable catheter that is manipulated and advanced retrogradely across the aortic valve through a 14F femoral sheath into the subvalvular mitral valve space. Once properly aligned, anchor pledges are delivered from the left ventricle to the left atrium across the circumferential mitral valve annulus and pulled together with a guide wire

to decrease the annulus septal-lateral dimension. The approach uses standard fluoroscopic imaging. The feasibility and durability of this technique were confirmed in early animal studies wherein significant reductions in MR were demonstrated. Currently, the technique is being tested in a European-based safety and feasibility phase I clinical study; method of the technique and results of the first implant in man was reported (45,46).

AccuCinch system

AccuCinch system (Guided Delivery Systems, California) is another promising strategy that recently commenced its first clinical investigation with humans in Europe. It too uses a specific endovascular retrograde catheter that crosses the aortic valve and accommodates within the sub annular mitral valve space (47). Once this first determinant step is accomplished, a series of interconnecting endomyocardial anchors are sequentially released across the subvalvular mitral annulus. An adjustable inter- communicating cinching wire permits effective percutaneous mitral valve septal-lateral annular reduction and MR improvement. To the authors' knowledge, the AccuCinch system has been successfully tested during open heart surgery in two patients with 2 + MR and coronary disease undergoing routine coronary artery bypass grafting. The surgically implanted device resulted in sustained and successful reductions in MR severity (from 2 + to 0 +) at 6- and 12- month follow-up (47).

The QuantumCor system

The QuantumCor system (QuantumCor) is a unique and different concept that has been tested in humans. It involves an end-loop catheter electrode system that delivers subablative radiofrequency energy to induce heating and shrinkage of the collagen tissue of the mitral annulus. The technique has been tested in acute and chronic sheep models where up to 20 % reductions in septal-lateral annular dimensions have been reported. 43 Histopathologic examination has shown no evidence of undesirable injury among the vicinity of related structures (47).

Indirect annuloplasty - Coronary sinus techniques

Considering the technical difficulties of percutaneous direct annuloplasty in the beating heart, other insightful, less-demanding technical approaches have been explored. Among them is the use of the coronary sinus, a distinct anatomic structure that lies in close relationship to the posterior-lateral circumference of the mitral valve annulus (49). Any conformation change of the coronary sinus may be used advantageously to reduce the septal-lateral annular dimensions and improve MR severity. Interest in this approach is reflected by the many programs that have been developed based on this premise.

The Monarc system

The Monarc system (Edwards Lifesciences) is a percutaneously implanted coronary sinus device that is designed to improve MR severity over an estimated 3- to 6-week period. The rationale is to remodel the mitral annulus by implanting a bio absorbable spring-like bridge that is connected between two self-expanding proximal and distal stents (Figure 8 B). The procedure is performed through a 12-F catheter under local anesthesia via the right internal jugular vein. The stent anchors, once delivered, provide the force necessary to draw the proximal coronary sinus and distal great cardiac vein together while the interconnecting bridge tenses and foreshortens over time. The conformational changes invoked over the posterior annular segment presumably shortens the septal-lateral dimension to reduce mitral regurgitation severity. The first human experience with the Monarc system was reported by Webb and colleagues in 2006 and included five patients with chronic ischemic severe MR. Implantation was successful in four of the five patients and resulted in mean decrease in MR grade from 13.0 (± 0.7) to 11.6 (± 1.1). Nonetheless, loss of efficacy was later seen in three of the patients due to asymptomatic separation and fracture of the bridging segment (51). After device modification and reinforcement of the bridging segment, the EVOLUTION phase I study was conducted. In this study, successful implantation was achieved in 59 of the 72 patients (82 %) with functional MR and heart failure. Freedom from death, MI, and cardiac tamponade at 30 days was 91 %. Coronary

artery compression was noted in 30 % of patients. Major adverse events at 18 months included one death, three myocardial infarctions, two coronary sinus perforations, one anchor displacement, and four anchor separations. The study proved that the Monarc system is feasible to implant and, although efficacy data is encouraging, coronary compression and anchor separations remain concerns and limitations (50,51). The EVOLUTION phase II clinical trial will hopefully serve to identify those that benefit most.

The Carillon Mitral Contour system

The Carillon Mitral Contour System (Cardiac Dimensions) is another unique coronary sinus annuloplasty device. It consists of two helical anchors and an intercommunicating nitinol bridge. It is delivered percutaneously under fluoroscopic guidance from the right internal jugular vein (Figure 8 A). Once access to the coronary sinus has been obtained and angiography performed, the distal smallest anchor is deployed, and gradual tension applied so that the posterior annulus moves anteriorly, and the septal-lateral dimensions shorten (Figure 8 A). The results are best appreciated by the immediate reduction in MR severity seen during transesophageal echocardiography. The Carillon system is simple and unique, as it is adjustable and recapturable in cases of malposition or inefficacy. Its delivery system measures 60 mm in length whereas the distal and proximal anchors vary in size from 7 to 14 mm and 12 to 20 mm, respectively. Initial experiments in dogs were encouraging and demonstrated acute and chronic reductions in mitral annular dimensions (from 2.7 [± 0.2] cm to 2.3 [± 0.1] cm, P<.05) and in the ratio of MR to left atrial area (from 16 [± 4] to 4 [±1], P 5 .052).

The device was first tested in humans by Joa Chim Schofer in Hamburg, Germany. Acute results from a European phase I safety and efficacy trial, Carillon Mitral Annuloplasty Device European Union Study (AMADEUS), were reported (52). The study included patients with congestive heart failure, greater than or equal to 2 + functional MR, and depressed left ventricular systolic function (ejection fraction <40 %). Successful implantation occurred in 70 % of the patients (30 of 43) and resulted in improved functional class and MR severity of at least 11 in 80 % of the cases. Those who benefited most had evidence of congestive heart failure and greater than or equal to 2+ centric MR secondary to mitral annulus dilation. Major adverse events at 1-month follow-up included two myocardial infarctions, two coronary sinus perforations, one dissection, one anchor displacement, one contrast nephropathy, and one death. The device crossed the coronary arteries 84 % of the time; however, left circumflex flow compromise was seen in only six patients (14 %) in whom the device was immediately recaptured. Additional studies on the efficacy of the Carillon device in the treatment of patients with heart failure and functional MR include the Titan and Titan II trials (53,54).

The Viacor Percutaneous Transvenous Mitral Annuloplasty device

The Percutaneous Transvenous Mitral Annuloplasty (PTMA) device (Viacor) consists of a 7F polytetrafluoroethylene catheter through which different rigid elements are introduced into the coronary sinus from the right jugular or subclavian vein. Up to three rods of varying stiffness and length are inserted behind the P2 segment of the posterior mitral valve leaflet depending on the tension required to shorten the septal-lateral annular dimension (Figure 8 C). The device may be retrieved in the absence of efficacy or in the presence of arterial compromise. Preliminary studies in sheep models were highly encouraging and resulted in decrease MR severity (from 3-4 + to 1 +, P<.03) and associated with significant reductions in septal-lateral mitral annular dimensions (from 30 ± 2.1] mm to 24 ± 1.7] mm, P<.03).49 The first feasibility and safety study in humans was reported by Dubreuil and colleagues in 2007 and included four patients with ischemic MR and NYHA class II or III requiring surgical mitral annuloplasty. In this study, the device was temporally implanted, adjusted, and subsequently removed. The investigators report substantial reductions in regurgitant volumes (45.5 [±24.4] to 13.3 [±7.3] mL) due to the mechanically induced anterior-posterior diameter reduction (40.75 [±4.3] to 35.2 [± 1.6] mm) in three patients. In one patient, the device could not be deployed due to extreme angulated anatomy. The study represents a small sample and reported Canadian and European phase I Percutaneous

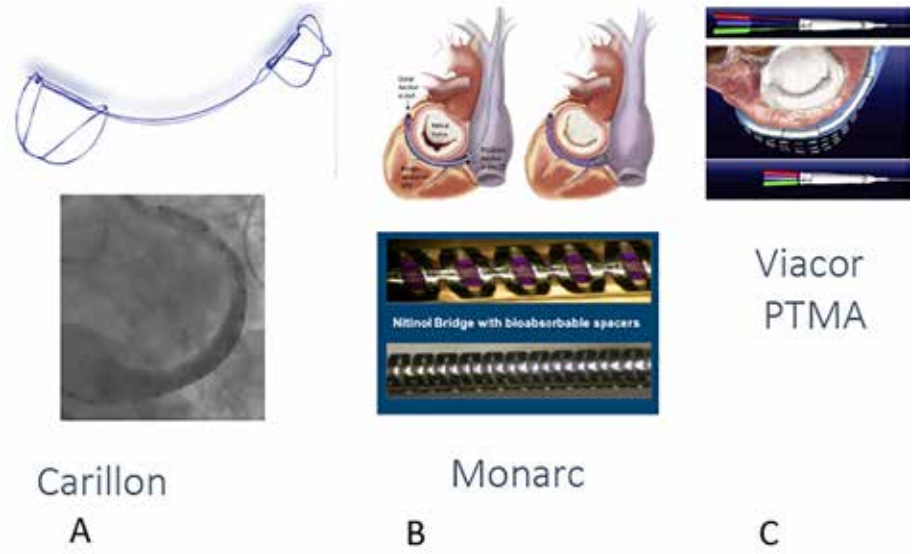


Figure 8. Coronary sinus cinching devices: Carillon (A), Monarc (B) and Viacor (C).

Transvenous Mitral Annuloplasty (PTOLEMY) trial included 27 patients with NYHA functional class II or III and moderate to severe functional MR reported by Sack and colleagues.51 Successful implantation was performed in 19 of the 27 patients. The remainder were excluded due to unsuitable coronary sinus anatomy. Of those who underwent successful implantation, 13 had a reduction in MR severity, and in six, the device was ineffective. Device removal was required in four patients due to fracture or device migration or diminished efficacy. Long-term success in MR reduction was seen in only 18.5 % of the patients. The phase II PTOLEMY trial is currently under way in Europe, Canada, and the United States and is expected to enroll 60 patients with moderate to severe MR, class II to IV heart failure, and left ventricular dysfunction (ejection fraction 25 % to 50 %) (55). A fatal migration of Viacor Percutaneous Mitral Annuloplasty Device resulting in Distal Coronary Venous Perforation was reported (58). The Company went out of business.

Remodeling of the Mitral Valvular Complex

An interesting group of transcatheter devices are those currently being developed to improve the paravalvular geometric distortion that is universally encountered in patients with nonorganic or functional MR. As discussed previously, functional MR is best defined a disease of the left ventricle that results in secondary mitral insufficiency and frequently seen in patients with dilated cardiomyopathies. Unfortunately, medical treatment options provide only minimal improvement in MR and the remaining mechanical treatments fall only within the realm of open-heart surgery, including annuloplasty repair or prosthetic MVR.

The Percutaneous Septal Sinus Shortening System

The Percutaneous Septal Sinus Shortening system, also known as PS3 (Ample Medical) and ARTO is a sophisticated transcatheter atrial/mitral annulus remodeling device that integrates several concepts and consists of three basic elements: (1) an atrial septal occluder, (2) an interconnecting cinching wire, and (3) permanent small coronary sinus T-bar element positioned behind P2. The interatrial occluder serves as a pivotal anchor and allows cinching to occur from the posterior annulus to the superior medial interatrial septum (55,56) (Figure 9). The concept was developed based on the premise that previous animal studies showed unequivocal increase in posterior wall to interatrial septum dimensions in

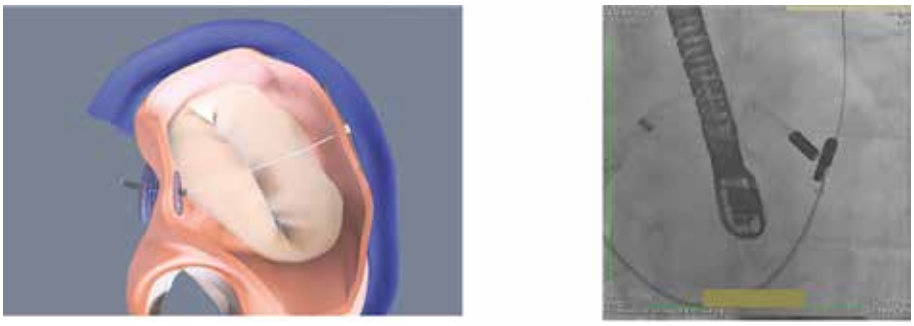


Figure 9. The PS3 or ARTO device.

functional MR. The authors' initial experience with the PS3 device was first reported in 23 sheep with dilated cardiomyopathy and functional MR (58). Immediate and midterm results at 30 days revealed reductions in septal to lateral dimensions and MR severity (58). Coronary arterial impingement was not observed, and the great cardiac vein was patent in all animals during follow-up histopathologic examination. Significant hemodynamic improvements and a drop-in brain natriuretic peptide levels were observed. Finally, there was no evidence of device migration, erosion, or intra-atrial bridge thrombosis. The feasibility and safety of this technique was first confirmed in two patients undergoing temporary implantation of the PS3 system before clinically indicated mitral valve repair surgery (59). In the first patient, the PS3 resulted in a relative change of 29 % in septal-lateral dimension and was associated with a 11 decrease in MR severity. The MR severity in the second patient decreased from 13 to 11 after a 31 % relative change in septal-lateral dimension. No procedural complications were reported. The CAFE ´ trial was an ongoing phase I safety and feasibility study developed to test the safety and efficacy of the chronic PS3 implant in humans with heart failure and severe functional MR. Promising preliminary results were presented by Cubeddu at the transcatheter therapeutic meeting in San Francisco, CA in September 2009. The multicenter, single-arm MAVERIC study assessed efficacy and safety of the transcatheter annular reduction therapy for functional MR using the ARTO system (MVRx) in 45 patients in at sites in Australia and Europe. The ARTO system works by shortening the minor axis of the mitral valve through the implantation of an adjustable bridge anchored between the lateral wall and the septum, which can be sized to reshape the mitral annulus to achieve the desired reduction in MR (60). MR grade was moderate to severe or severe in nearly three-quarters of patients before the procedure. At 6 months, however, MR grade had been reduced to mild or less in 87 % of patients, and trace or less in 58 % of patients. Moreover, MR improvement observed at 30 days persisted through 6 months. Safety at 6 months, defined as a composite of death, stroke, MI, cardiac tamponade, device-related cardiac surgery, or renal failure, was low at 16 %. Three CV-related deaths occurred (7.2 %), but no deaths were attributed to the device or the procedure. Improvements in NYHA class were also apparent at 6 months, with78 % of patients in NYHA class I or II, compared with 71 % in NYHA class ≥ III at baseline. Functional improvement was observed early and persisted during follow-up. Additionally, the rate of hospitalization for heart failure was low at 9.3 %. Additional data showed reduced volumes and indices at 6 months. The ARTO system yielded 100 % device success (60).

The iCoapsys

The iCoapsys (Myocor) left ventricular reshaping device was, until recently, a promising alternative percutaneous strategy developed to treat functional MR. Although no longer in use, the strategy represents a concept that is worthy of mention and may one day re-emerge through improved concepts. The iCoapsys transventricular system consists of an anterior

and posterior epicardial pad tethered together by a subvalvular transventricular chord that travels through the left ventricle and between the papillary muscles. Conformational changes are intended to reorient the papillary muscles and reduce left ventricle geometric distortion, resulting in decrease in regurgitant orifice and MR severity. Promising results were reported from the early animal experience (61). Unfortunately, the Food and Drug Administration– approved Valvular and Ventricular Improvement Via iCoapsys Delivery (VIVID) feasibility study in humans was prematurely discontinued due to the inherent technical difficulties during device implantation, and suboptimal patient applicability.

PERIVALVULAR PROSTHETIC MITRAL REGURGITATION

Percutaneous repair of perivalvular prosthetic MR has evolved to become yet another attractive alternative strategy. Paravalvular MR is a well- recognized dreadful complication that may be seen in up to 7 % of patients after prosthetic heart valve surgery (62). Although the majority of affected patients are asymptomatic, heart failure, hemolytic anemia, or infective endocarditis may be seen in high-risk patients, redo operations are commonly challenging and associated with significantly increased procedural mortality (63,64). Nevertheless, a series of percutaneous endovascular devices have been explored and used off-label with promising results (65-69). Among them are the Amplatzer Vascular Plug, Amplatzer Septal Occluder, and Amplatzer Duct Occluder from AGA Medical (Golden Valley, Minnesota).

The percutaneous treatment of paravalvular mitral leaks is particularly challenging, one of the most difficult in interventional cardiology, mainly because of the increased need for catheter manipulation after transseptal puncture. Consequently, the use of steerable, bidirectional tip catheters often becomes necessary to identify and cross the regurgitant defect. In other instances, it is necessary to create an arteriovenous rail using a snaring catheter antegradely or retrogradely. In rare instances, a left ventricular apical puncture is required. The Amplatzer Duct Occluder is the most commonly used device. Oversizing of the device by 2 to 3 mm is typically recommended. Nevertheless, implantation of two or possibly three devices may be necessary. In the authors' experience, simultaneous 3-D transesophageal echocardiogram imaging should be encouraged in all cases, as it provides optimal information during device implantation (62-64). Although the feasibility and effectiveness of these techniques have been reported, it should be remembered that these devices were not specifically designed for this indication. Nevertheless, the authors are hopeful that the encouraging results will prompt the development of transcatheter-specific paravalvular closure techniques and are confident that these advances, and those related to intraoperative imaging (ie, 4-D TEE), will ultimately result in improved technical success and long-term clinical outcome.

Transcatheter mitral valve replacement (PMVR) has recently emerged as an exciting new frontier in the field of cardiac structural interventions. Although transcatheter aortic valve replacement (TAVR) is a well-established treatment option for patients with symptomatic severe calcific aortic stenosis, the experience with transcatheter MVR remains at an early stage. There have been important challenges in the development of this technology, including the complexity of the mitral valve anatomy involving a saddle oval shape, the subvalvular apparatus, the interaction with the left ventricular outflow tract (LVOT) and the aortic valve, as well as the large size of transcatheter MVR devices and large catheters for implantation. Patients with failed surgical mitral bioprostheses or rings have been treated with the off-label use of standard aortic transcatheter heart valve devices. Transcatheter mitral valve-in-valve and valve-in-ring have been successfully performed with aortic transcatheter heart valve in hundreds of patients worldwide. The most frequently used transcatheter heart valves have been the Edwards SAPIEN family of valves (Edwards Lifesciences; Irvine, CA) (Figure 10) (70). The Medtronic Intrepid™ transcatheter heart valve (Medtronic; Minneapolis, MN) has a self-expandable nitinol outer stent, which provides fixation and sealing, and a circular inner stent, which houses a 27-mm tri-leaflet bovine pericardium valve with an effective orifice area of 2.4 cm^2 (Figure 11). The valve is implanted via transapical access; a transseptal delivery approach is being developed.

Thirty-eight patients have been treated in a pilot study (71). The valve was successfully deployed in 35 patients, and there were 4 procedure-related deaths. MR severity was reduced to 1(+) in 3 and 0 in 32 patients, resulting in improvement of symptoms of 1 or more functional class in 21 of 25 patients with clinical follow-up data available. A clinical trial has been initiated (70-71).

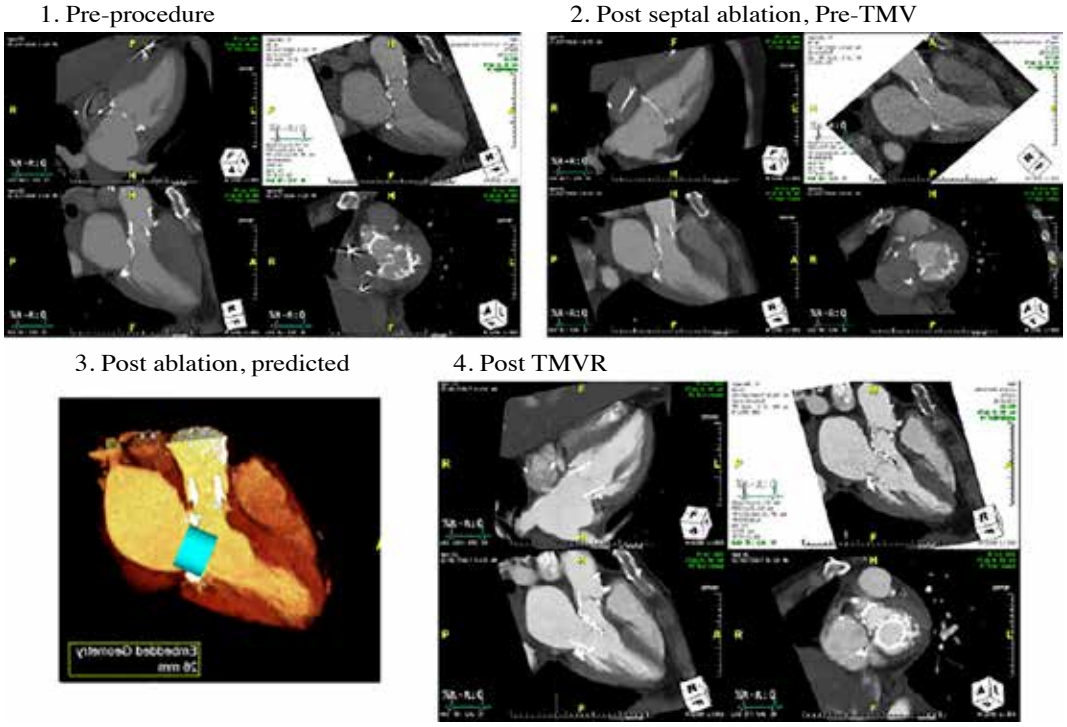


Figure 10. Percutaneous Transseptal Mitral Valve Replacement using a 26 mm Edwards Sapien Valve.

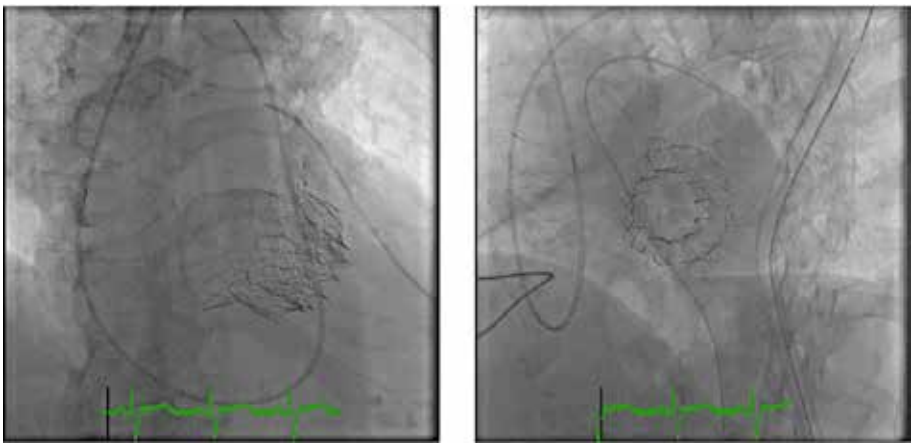


Figure 11. Percutaneous transapical Mitral Valve Replacement using a 46 mm Medtronic Intrepid Valve as part of the Apollo Trial.

SUMMARY: Over the past 10 years, novel nonsurgical strategies for the treatment of valvular heart disease have opened new options in patient care. Animal and early human studies indicate that many of these techniques are safe effective and feasible. Several clinical studies are currently under way and will likely determine the benefits of transcatheter mitral valve therapy. It is apparent, given the complexity of the mitral valve apparatus and its subvalvular structure, that a single device to treat all forms of MR is unlikely to be developed. The encouraging results of the MitraClip suggest, however, that this technique may eventually play a role in the treatment of organic MR. Furthermore, this technique has recently been applied successfully in several patients with functional MR (45). The role for isolated coronary sinus devices remains uncertain, however, and limited by the variable relationship between the coronary sinus and the mitral valve annulus. Ultimately, although the role of transcatheter left ventricular remodeling to treat functional MR is ideal, this strategy remains in the infancy of its development. Despite the substantial technical and financial efforts invested in transcatheter mitral valve therapy, most of the emerging devices remain early in their development and will ultimately need to be proven effective when compared to the gold standard open surgical repair. Finally, the applicability of many of these percutaneous interventions will require advanced training of highly qualified operators and interventional standards to prevent the widespread discriminant use of these techniques.

REFERENCES

1. Mozzaffarian D, Benjamin EJ, Go AS, Blaha MJ. Heart Disease and Stroke Statistics – 2015 Update: A report from the American Heart Association. Writing Group members. Circulation 2015;131:e29- e322.
2. Wang DD, Eng MH. Mitral Valve Replacement for Post-Surgical Mitral Failures. Interventional Cardiology Reviews. 2018;13:77-80.
3. Marcus RH, Sarell P, Pococwa, et al. THe spectrum of sevre rheumatic mitral valve disease in a developing country. Correlations among clinical presentation, surgical pathological findings and hemodynamic sequelae. Ann Intern Med 1994;120:177-183.
4. Guidelines Baumgarten H, Falk V, Box JJ, et al, for the ESC Scientific Document Group 2017 ESC/ EACTS guidelines for the management of valvular heart disease. Eur Heart J. 2017;38:2739-2791.
5. Winderich NC, Beigel R, Siegel RJ. Management of Mitral Stenosis using 2 D and 3D echo-Doppler imaging. JACC Cardiovascular Imaging. 2013;6:1191-1205.
6. Cubeddu RJ, Palacios IF. Percutaneous Techniques for Mitral Valve Disease. Cardiol Clinic. 2010;28:139-153.
7. Inoue K, Owaki T, Nakamura T, et al. Clinical application of transvenous mitral commissurotomy by a new balloon catheter. J Thorac Cardiovasc Surg. 1984;87(3):394-402.
8. Lock JE, Khalilullah M, Shrivastava S, et al. Percutaneous catheter commissurotomy in rheumatic mitral stenosis. N Engl J Med. 1985;313(24):1515-1518.
9. Palacios I, Block PC, Brandi S, et al. Percutaneous balloon valvotomy for patients with severe mitral stenosis. Circulation 1987;75(4):778-784.
10. Al Zaibag M, Ribeiro PA, Al Kasab S, et al. Percutaneous double-balloon mitral valvotomy for rheumatic mitral-valve stenosis. Lancet. 1986;1(8484):757-761.
11. Vahanian A, Michel PL, Cormier B, et al. Results of percutaneous mitral commissurotomy in 200 patients. Am J Cardiol 1989;63(12):847-852.
12. McKay RG, Lock JE, Safian RD, et al. Balloon dilation of mitral stenosis in adult patients: postmortem and percutaneous mitral valvuloplasty studies. J Am Coll Cardiol. 1987;9(4):723-731.
13. McKay CR, Kawanishi DT, Rahimtoola SH. Catheter balloon valvuloplasty of the mitral valve in adults using a double-balloon technique. Early hemodynamic results. JAMA. 1987;257(13):1753-1761.
14. Abascal VM, Wilkins GT, O'Shea JP, et al. Prediction of successful outcome in 130 patients undergoing percutaneous balloon mitral valvotomy. Circulation. 1990;82(2):448-456.
15. Herrmann HC, Wilkins GT, Abascal VM, et al. Percutaneous balloon mitral valvotomy for patients with mitral stenosis. Analysis of factors influencing early results. J Thorac Cardiovasc Surg. 1988;96(1):33-38.
16. Rediker DE, Block PC, Abascal VM, et al. Mitral balloon valvuloplasty for mitral restenosis after surgical commissurotomy. J Am Coll Cardiol. 1988;11(2):252-256.
17. Palacios IF, Block PC, Wilkins GT, et al. Follow-up of patients undergoing percutaneous mitral balloon valvotomy. Analysis of factors determining restenosis. Circulation 1989;79(3):573-579.
18. Abascal VM, Wilkins GT, Choong CY, et al.

Echocardiographic evaluation of mitral valve structure and function in patients followed for at least 6 months after percutaneous balloon mitral valvuloplasty. J Am Coll Cardiol. 1988;12(3):606-615.

19. Block PC, Palacios IF, Block EH, et al. Late (two-year) follow-up after percutaneous balloon mitral valvotomy. Am J Cardiol. 1992;69(5):537-541.
20. Nobuyoshi M, Hamasaki N, Kimura T, et al. Indications, complications, and short-term clinical outcome of percutaneous transvenous mitral commissurotomy. Circulation. 1989;80(4):782-792.
21. Wilkins GT, Weyman AE, Abascal VM, et al. Percutaneous balloon dilatation of the mitral valve: An analysis of echocardiographic variables related to outcome and the mechanism of dilatation. Br Heart J. 1988;60(4):299-308.
22. Tuzcu EM, Block PC, Griffin BP, et al. Immediate and long-term outcome of percutaneous mitral valvotomy in patients 65 years and older. Circulation. 1992;85(3):963-971.
23. Palacios IF, Sanchez PL, Harrell LC, et al. Which patients benefit from percutaneous mitral balloon valvuloplasty? Prevalvuloplasty and postvalvuloplasty variables that predict long-term outcome. Circulation. 2002;105(12):1465-1471.
24. Cruz-Gonzalez I, Sanchez-Ledesma M, Sanchez PL, et al. Predicting success and long-term outcomes of percutaneous mitral valvuloplasty: A multifactorial score. Am J Med. 2009;122(6):581. e11–89.
25. Chen CR, Cheng TO, Chen JY, et al. Long-term results of percutaneous mitral valvuloplasty with the Inoue balloon catheter. Am J Cardiol. 1992;70(18):1445-1448.
26. Hung JS, Chern MS, Wu JJ, et al. Short- and long-term results of catheter balloon percutaneous transvenous mitral commissurotomy. Am J Cardiol. 1991;67(9):854-862.
27. Cribier A, Eltchaninoff H, Koning R, et al. Percutaneous mechanical mitral commissurotomy with a newly designed metallic valvulotome: Immediate results of the initial experience in 153 patients. Circulation. 1999;99(6):793-799.
28. Leon MN, Harrell LC, Simosa HF, et al. Comparison of immediate and long-term results of mitral balloon valvotomy with the double-balloon versus Inoue techniques. Am J Cardiol. 1999;83(9):1356-1363.
29. Turi ZG, Reyes VP, Raju BS, et al. Percutaneous balloon versus surgical closed commissurotomy for mitral stenosis. A prospective, randomized trial. Circulation. 1991;83(4):1179-1185.
30. Reyes VP, Raju BS, Wynne J, et al. Percutaneous balloon valvuloplasty compared with open surgical commissurotomy for mitral stenosis. N Engl J Med. 1994;331(15):961-967.
31. Ben Farhat M, Ayari M, Maatouk F, et al. Percutaneous balloon versus surgical closed and open mitral commissurotomy: Seven-year follow-up results of a randomized trial. Circulation. 1998;97(3):245-250.
32. Nkomo VT, Gardin JM, Skelton TN, et al. Burden of valvular heart diseases: A population-based study. Lancet. 2006;368(9540):1005-1011.
33. Robbins JD, Maniar PB, Cotts W, et al. Prevalence and severity of mitral regurgitation in chronic systolic heart failure. Am J Cardiol. 2003;91(3):360-362.
34. Bursi F, Enriquez-Sarano M, Nkomo VT, et al. Heart failure and death after myocardial infarction in the community: The emerging role of mitral regurgitation. Circulation. 2005;111(3):295-301.
35. McGee EC, Gillinov AM, Blackstone EH, et al. Recurrent mitral regurgitation after annuloplasty for functional ischemic mitral regurgitation. J Thorac Cardiovasc Surg. 2004;128(6):916-924.
36. Alfieri O, Maisano F, De Bonis M, et al. The double-orifice technique in mitral valve repair: A simple solution for complex problems. J Thorac Cardiovasc Surg. 2001;122(4):674-681.
37. Maisano F, Caldarola A, Blasio A, et al. Midterm results of edge-to-edge mitral valve repair without annuloplasty. J Thorac Cardiovasc Surg. 2003;126(6):1987-1997.
38. Maisano F, Vigano G, Calabrese C, et al. Quality of life of elderly patients following valve surgery for chronic organic mitral regurgitation. Eur J Cardio Thorac Surg. 2009;36(2):261-266.
39. Condado JA, Acquatella H, Rodriguez L, et al. Percutaneous edge-to-edge mitral valve repair: 2-year follow-up in the first human case. Catheter Cardiovasc Interv. 2006;67(2):323-325.
40. Feldman T, Wasserman HS, Herrmann HC, et al. Percutaneous mitral valve repair using the edge-to- edge technique: Six-month results of the EVEREST Phase I Clinical Trial. J Am Coll Cardiol. 2005;46(11):2134-2140.
41. Feldman T, Foster E, Glower D, et al., on behalf of the EVEREST II Investigators. Percutaneous repair or surgery for mitral regurgitation. N Engl J Med. 2011;364:1395-1406.
42. Feldman T, Kar S, Elmariah S, Smart SC, Trento A, Siegel RJ, et al, and EVEREST II Investigators. Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation: 5-Year Results of EVEREST II. J Am Coll Cardiol. 2015;66:2844-2854.
43. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, et al; COAPT investigators. Transcatheter Mitral-Valve Repair in Patines with Heart Failure. N Eng J Med. 2018; 0a1806640 (Epub ahead of print).
44. Naqvi TZ, Buchbinder M, Zarbatany D, et al. Beating-heart percutaneous mitral valve repair using a transcatheter endovascular suturing device in an animal

model. Catheter Cardiovasc Interv. 2007;69(4):525-531.

45. Tibayan FA, Rodriguez F, Liang D, et al. Paneth suture annuloplasty abolishes acute ischemic mitral regurgitation but preserves annular and leaflet dynamics. Circulation. 2003;108(Suppl 1):II128-133.
46. Sisminiak T, Dankowski R, Baezco A, Lee C, Firek L, Kalmuchi P, et al. Percutaneous direct mitral annuloplasty using the Mitralign Bident system: Description of the method and a case report. Kardiol Pol. 2013;71:1287-1292.
47. Gooley RP, Meredith IT. The Accucinch Transcatheter Direct Mitral Valve Annuloplasty System. Eurointervention 2015;11:W60-W61.
48. Maselli D, Guarracino F, Chiaramonti F, et al. Percutaneous mitral annuloplasty: An anatomic study of human coronary sinus and its relationship with mitral valve annulus and coronary arteries. Circulation. 2006;114(5):377–80. (6):851-855.
49. RR, Witzel T, Dickens D, et al. Percutaneous treatment for mitral regurgitation: The QuantumCor system. J Interv Cardiol. 2008;21(2):178-182.
50. Webb JG, Harnek J, Munt BI, et al. Percutaneous transvenous mitral annuloplasty: Initial human experience with device implantation in the coronary sinus. Circulation. 2006;113.
51. Harnek J, Web JG, Kuch KH, Tschope C, Vahanian A, Buller CE, et al. Transcatheter Implanttaion of the Monarc coronary sinus device for mitral regurgitation: 1-year results from the Evolution phase 1 study (clinical Evaluation of the Edwards Lifesciences Percutaneous Mitral Annuloplasty System for the treatment of Mitral Regurgitation. JACC Cardiovascular Interv. 2011;4:115-122.
52. Sisminiak T, Hoppe UC, Schofer J, Haude M, Herrman JP, Vainer J, et al. Effectiveness and safety of percutaneous coronary sinus-based mitral valve repair in patients with dilated cardiomyopathy (from the AMADEUS trial). Am J Cardiol. 2009;104:565-570.
53. Siminiak T, Wu JC, Haude M, Hoppe UC, Sadowski JL, Fajadet J, et al. Treatment of functional mitral regurgitation by percutaneous annuloplasty: Results of the TITAN Trial. European Journal of Heart Failure Advance Access. 2012;14:931-938.
54. Lipiecki J, Siminiak T, Sievert H, Muller-Ehmesen J, Degen H, Wu JC, et al, for the TITAN II Investigators. Open Heart 2016; 3: e000411.
55. Maniu CV, Patel JB, Reuter DG, et al. Acute and chronic reduction of functional mitral regurgitation in experimental heart failure by percutaneous mitral annuloplasty. J Am Coll Cardiol. 2004;44(8):1652-1661.
56. Machaalany J, Bilodeau L, Hoffman R, Sack S, Sievert H, Kautzner J, et al. Treatment of functional mitral valve regurgitation with the permanent percutaneous transvenous mitral annuloplasty system: Results of the multicenter International Percutaneous Transvenous Mitral Annuloplasty system to reduce Mitral Valve Regurgitation in patients with heart failure trial. (PTOLEMY - 2 trial). Am Heart J. 2013;165 761-769.
57. MacHaalany JM, St-Pierre A, Senechal M, Larose E, Philippon F, Abdelaal E, et al. Fatal Late Migration of Viacor Percutaneous Transvenous Mitral Annuloplasty Device Resulting in Distal Coronary Venous Perforation. Canadian J Cardiol. 2013;29:130.e1-130.e4
58. MacHaalany JM, St-Pierre A, Senechal M, Larose E, Philippon F, Abdelaal E, et al. Fatal Late Migration of Viacor Percutaneous Transvenous Mitral Annuloplasty Device Resulting in Distal Coronary Venous Perforation. Canadian J Cardiol. 2013;29:130.e1-130.e4
59. Rogers JH, Macoviak JA, Rahdert DA, Takeda PA, Palacios IF, Low RI. Percutaneous septal sinus shortening: a novel procedure for the treatment of functional mitral regurgitation. Circulation. 2006;113(19):2329-2334.
60. Palacios IF, Condado JA, Brandi S, Rodriguez V, Bosh F, Silva G, et al. Safety and feasibility of acute percutaneous septal sinus shortening: First-in-human experience. Catheter Cardiovasc Interv. 2007;69(4):513-518.
61. Rogers JH, Thomas M, Morice MC, et al. Treatment of heart failure with associated functional mitral regurgitation using the ARTO system: Initial results of the first-in-human MAVERIC trial (Mitral Valve Repair Clinical Trial). JACC Cardiovasc Interv. 2015;8:1095-1104.
62. Pedersen WR, Block P, Leon M, et al. iCoapsys mitral valve repair system: Percutaneous implantation in an animal model. Catheter Cardiovasc Interv. 2008;72(1):125-131.
63. Jindani A, Neville EM, Venn G, et al. Paraprosthetic leak: a complication of cardiac valve replacement. J Cardiovasc Surg. 1991;32(4):503-538.
64. Safi AM, Kwan T, Afflu E, et al. Paravalvular regurgitation: A rare complication following valve replacement surgery. Angiology. 2000;51(6):479-487.
65. Echevarria JR, Bernal JM, Rabasa JM, et al. Reoperation for bioprosthetic valve dysfunction. A decade of clinical experience. Eur J Cardiothorac Surg. 1991;5(10):523–6 [discussion 527].
66. Pate GE, Al Zubaidi A, Chandavimol M, et al. Percutaneous closure of prosthetic paravalvular leaks: Case series and review. Catheter Cardiovasc Interv. 2006;68(4):528-533.
67. Kort HW, Sharkey AM, Balzer DT. Novel use of the Amplatzer duct occluder to close perivalvar

leak involving a prosthetic mitral valve. Catheter Cardiovasc Interv. 2004;61(4):548-551.

68. Webb JG, Pate GE, Munt BI. Percutaneous closure of an aortic prosthetic paravalvular leak with an Amplatzer duct occluder. Catheter Cardiovasc Interv. 2005;65(1):69-72.

69. Johri AM, Yared K, Durst R, et al. Three-dimensional echocardiography-guided repair of severe paravalvular regurgitation in a bioprosthetic and mechanical mitral valve. Eur J Echocardiogr. 2009;10(4):572-575.

70. Guerrero M, Urena M, Himbert D, WQang DD, Eleid M, Kodali S, et al. 1-Year Outcomes of Transcatheter Mitral Valve Replacement in Patients With Severe Mitral Annular Calcification. J Am Coll Cardiol. 2018;71:1841-1853.

71. Bapat V, Rajagopal V, Meduri C, Farivar S, Walton A, Duffy SJ, et al and for the Intrepid Global Pilot Study Investigators. Early Experience with New Transcatheter Mitral Valve Replacement. JACC. 2017.10.061