JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2014 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 64, NO. 17, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.06.1208

Short-Term Results of Transapical Transcatheter Mitral Valve Implantation for Mitral Regurgitation

Anson Cheung, MD,* John Webb, MD,† Stefan Verheye, MD, PhD,‡ Robert Moss, MD,† Robert Boone, MD,† Jonathan Leipsic, MD,§ Ron Ree, MD,‖ Shmuel Banai, MD¶

ABSTRACT

BACKGROUND Mitral regurgitation (MR) is the most common valvular heart disease, and mitral valve surgery is the gold standard therapy for severe MR. Many patients with severe MR are not referred for surgery because of old age, comorbidities, or severe left ventricular dysfunction. Transcatheter mitral valve implantation may be a better therapeutic option for these high-risk patients with severe symptomatic MR.

OBJECTIVES This study sought to describe the first-in-man series of transapical mitral valve implantation for mitral regurgitation with the TIARA device.

METHODS Extensive preclinical ex vivo and animal studies were conducted with the transapical mitral valve implantation of the Tiara system. The first 2 cases of human implantation were successfully performed in a 73-year-old man and a 61-year-old woman with severe functional MR. Both patients were in New York Heart Association class IV heart failure with depressed left ventricular ejection fraction, pulmonary hypertension, and additional comorbidities.

RESULTS The valve was implanted uneventfully in both patients. General anesthesia and transapical access were used. Patients were hemodynamically stable with no need for cardiopulmonary bypass. Immediately after implantation, systemic arterial pressure and stroke volume increased and pulmonary pressure decreased dramatically. There were no intraoperative complications, and both patients were extubated in the operating room. Post-procedural echocardiograms at 48 h, 1 month, and 2 months demonstrated excellent prosthetic valve function with a low transvalvular gradient and no left ventricular outflow tract obstruction. There was a trivial paravalvular leak in the first patient at 48 h, which was completely resolved at subsequent studies; no paravalvular leak occurred in the second patient.

CONCLUSIONS Transapical transcatheter mitral valve implantation is technically feasible and can be performed safely. Early hemodynamic performance of the prosthesis was excellent. Transcatheter mitral valve implantation may become an important treatment option for patients with severe MR who are at high operative risk. (J Am Coll Cardiol 2014;64:1814–9) © 2014 by the American College of Cardiology Foundation.

Mitral regurgitation (MR) is the most prevalent valvular heart disease and is a major contributor to congestive heart failure and death. Conventional surgical repair or replacement remains the treatment of choice for symptomatic patients with severe MR. Operative mortality and morbidity remain high in the elderly and in patients with left ventricular (LV) dysfunction or significant comorbidities, leading to under-referral of patients for mitral surgery (1,2). The search for new transcatheter mitral valve therapies is driven by preclusion of high-risk patients from surgical mitral

From the *Division of Cardiothoracic Surgery, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada; †Division of Cardiology, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada; ‡Interventional Cardiology, ZNA Middelheim Hospital, Antwerp, Belgium; §Department of Radiology, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada; ‖Department of Anesthesiology and Pharmacology, St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada; and ¶Interventional Cardiology, Tel Aviv Medical Center, Tel Aviv, Israel. Dr. Cheung is a consultant for Neovasc Inc. Dr. Banai is the medical director of Neovasc Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received April 9, 2014; revised manuscript received June 17, 2014, accepted June 24, 2014.

valve repair or replacement. Percutaneous mitral valve repair therapy with the MitraClip (Abbott Laboratory, Abbott Park, Illinois) has been well studied and is becoming an established option for a subset of patients with MR (3–6); however, secondary to various anatomical restrictions, many patients are not candidates. Novel catheter-based technologies intended to treat mitral valve disease percutaneously or minimally invasively without the aid of cardiopulmonary bypass are currently under development (7–10). Transcatheter aortic valve replacement (TAVR) has revolutionized the management of valvular aortic stenosis by providing a safe and efficacious alternative to surgical valve replacement. TAVR is currently reserved for patients with severe aortic stenosis who are at high risk for surgical valve replacement due to comorbid conditions, thus increasing their operative risk for major complications and death. Consequently, an explosive adoption of TAVR has occurred (11–13). It is reasonable to suggest that the next "revolution" may take place in the field of transcatheter therapies for patients with severe MR and at high surgical risk.

SEE PAGE 1820

The structure and function of the mitral valve are far more complex than the aortic valve. This complexity poses many barriers to the development of transcatheter mitral therapies: a D-shaped annulus; the lack of a fibrous annular structure; variability of leaflet and subvalvular apparatus anatomy; and proximity to the left ventricular outflow tract (LVOT), circumflex coronary artery, and coronary sinus (14).

The transapical mitral valve implantation (TAMI) of the Tiara system (Neovasc Inc., Richmond, British Columbia, Canada) is a novel, catheter-based technology for the treatment of severe MR, with published data from preclinical ex vivo, animal, and cadaveric experiments (15,16). The present article reports the first 2 cases of human transcatheter TAMI.

TAMI SYSTEM

The Tiara valve consists of a nitinol alloy–based, self-expanding frame and tri-leaflet bovine pericardium (**Figures 1A and B**). The valve is anatomically shaped to fit the asymmetric, D-shaped mitral annulus. Its atrial portion is designed to help seat the prosthesis onto the atrial portion of the mitral valve annulus. Ventricular anchoring structures are designed to secure the valve onto the fibrous trigons and posterior shelf of the annulus. These features firmly secure the valve, preventing migration and minimizing paravalvular leakage (PVL), LVOT obstruction, and coronary vessel encroachment. The valve is loaded into a 32-F delivery device just before the procedure. The delivery device comprises a self-dilating tip with a turn-knob mechanism and is designed to directly enter the LV apex without a delivery introducer sheath. Resheathing, repositioning, and retrieval of the prosthesis are possible until the final stage of deployment.

PATIENT #1. Patient #1 was a frail, 73-year-old man with previous myocardial infarction and stenting who developed severe ischemic cardiomyopathy and functional MR. He had had multiple previous admissions for heart failure and remained in New York Heart Association class IV despite optimal medical and cardiac resynchronization therapy. Comorbidities included: chronic renal insufficiency, requiring intermittent hemodialysis; severely impaired pulmonary function due to pulmonary fibrosis; systemic hypertension; dyslipidemia; and type 2 diabetes. An echocardiogram

ABBREVIATIONS AND ACRONYMS

LV = left ventricular

LVOT = left ventricular outflow tract

MR = mitral regurgitation

PVL = paravalvular leakage

TAMI = transapical mitral valve implantation

TAVR = transcatheter aortic valve replacement

TEE = transesophageal echocardiography

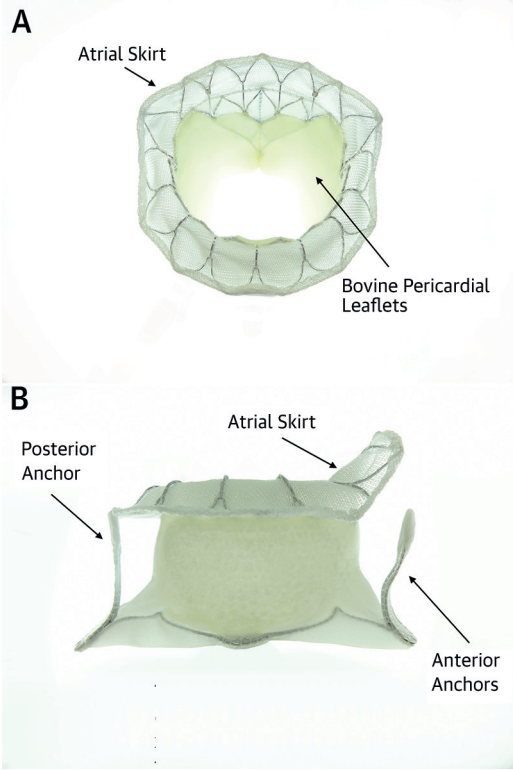


FIGURE 1 Transcatheter Mitral Valve Prosthesis and Delivery System

(A) Atrial view of the transcatheter mitral valve prosthesis. **(B)** Lateral profile of the transcatheter mitral valve prosthesis.

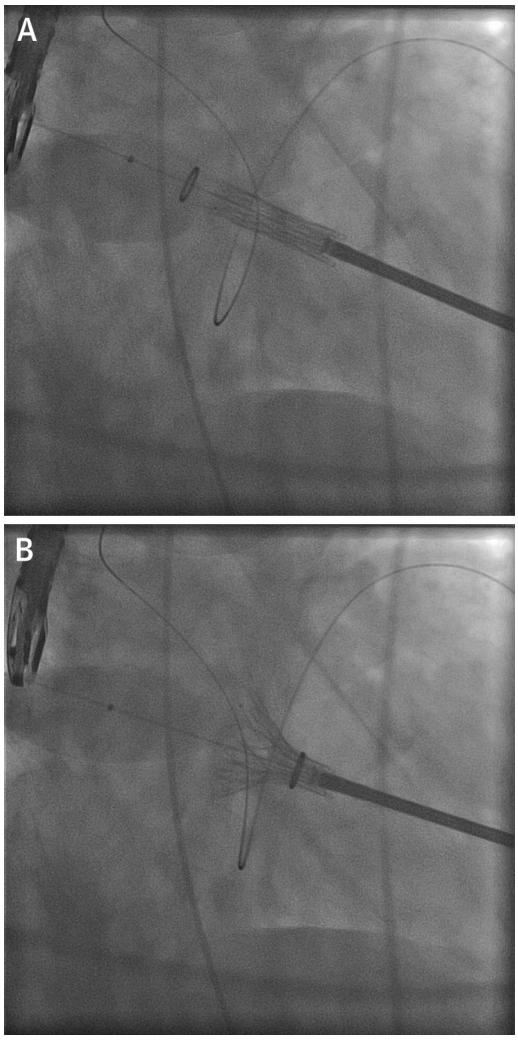


FIGURE 2 Transapical Mitral Valve Implantation Procedure

(A) Advancement of the transapical mitral valve implantation system across the mitral valve into the left atrium. **(B)** Full deployment of the atrial portion of the bioprosthesis in the left atrium.

documented severe LV dysfunction and dilation. The LV ejection fraction was 15% to 20%, LV end-diasystolic diameter was 76 mm, and he had an estimated pulmonary arterial systolic pressure of 60 mm Hg. There was severe functional MR with restriction of both anterior and posterior leaflets. The calculated Society of Thoracic Surgeons' risk of mortality for mitral valve replacement was 47.7%, and the Logistic EuroSCORE II was 24.7%.

PATIENT #2. Patient #2 was a 61-year-old woman with ischemic cardiomyopathy and severe functional MR secondary to old inferior myocardial infarction.

TABLE 1 Pre-Operative Echocardiographic Characteristics of the Patients

	LA Diameter (mm)	LVEDD (mm)	Vena Contracta (cm)	EROA (cm^2)	MR Grade	LVEF
Patient #1	5.6	76	0.64	0.59	Severe	15%
Patient #2	5.4	62	0.71	0.62	Severe	25%

EROA = effective regurgitant orifice area; LA = left atrium; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; MR = mitral regurgitation.

She had heart failure with New York Heart Association classes III to VI symptoms and was referred for cardiac transplantation. Comorbidities included systemic hypertension, dyslipidemia, chronic obstructive lung disease, chronic atrial fibrillation, and liver cirrhosis. Coronary angiography showed a patent right coronary stent and nonobstructive coronary atherosclerosis. Echocardiography revealed severe functional mitral and tricuspid regurgitation with an LV ejection fraction of 25%, LV end-diasystolic diameter of 62 mm, and pulmonary hypertension. Her Society of Thoracic Surgeons' risk score and logistic EuroSCORE II were 4.5% and 9.1%, respectively. She was deemed too high risk for surgical mitral valve replacement and not a good candidate for the MitraClip secondary to poor coaptation height by the heart team. Detailed preoperative echocardiographic characteristics of both patients are listed in Table 1.

PRE-OPERATIVE ASSESSMENTS. Cardiac-gated multislice computed tomography imaging was performed

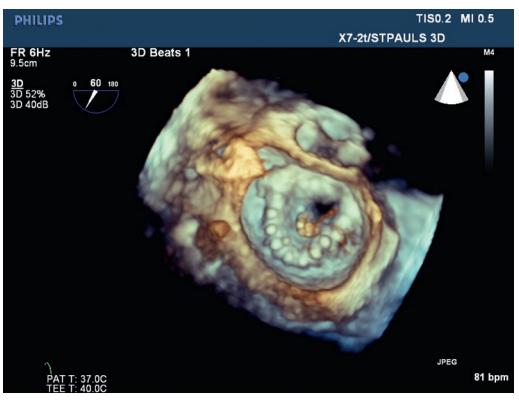


FIGURE 3 Three-Dimensional TEE Confirmation of Coaxial Position and Correct Orientation of the Mitral Valve Prosthesis Within the D-Shaped Native Mitral Annulus

TEE = transesophageal echocardiography.

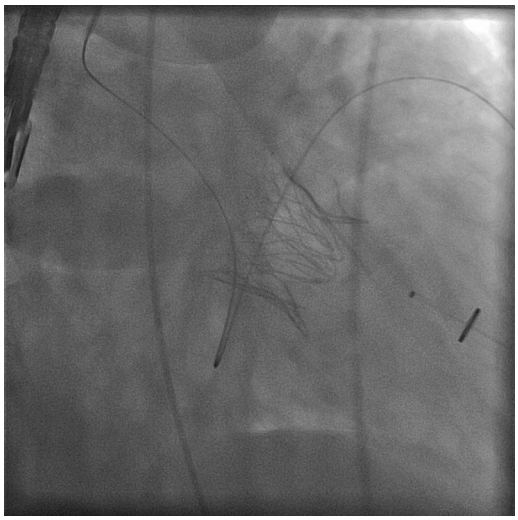


FIGURE 4 Full Deployment of the Bioprosthesis and Full Resheathing of the Delivery Catheter

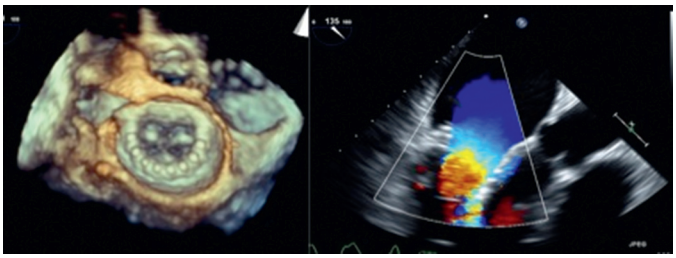


FIGURE 5 TEE Showing a Normally Functioning Mitral Valve Prosthesis With no Significant Paravalvular Leak, a Low Transvalvular Gradient, and no LV Outflow Obstruction

LV = left ventricular; TEE = transesophageal echocardiography.

to delineate mitral valve structures and facilitate the pre-operative planning of fluoroscopic implant angles. Both patients were assessed by the multidisciplinary heart team, with a consensus that the risk with conventional mitral valve surgery was prohibitive. MitraClip was considered as an option for both patients; however, both patients were believed to be poor candidates secondary to inadequacy in coaptation depth. Permission to proceed with transcatheter mitral valve replacement by using the Tiara TAMI system was granted on compassionate grounds by the Health Canada Special Access Programme. Informed consent forms for first-in-human implantations were obtained from both patients.

RESULTS

Procedures were performed in a hybrid operating room under general anesthesia with endotracheal intubation. Invasive systemic arterial and pulmonary arterial monitoring was initiated. Implantations were performed by a multidisciplinary team consisting of an interventional cardiologist and a cardiac surgeon, and were guided by simultaneous transesophageal echocardiography (TEE) and high-definition fluoroscopy. Patients were positioned supine. A 4-cm mini-anterior thoracotomy was performed to access the LV apex with the placement of 2 octagonal pledgeted sutures securing the LV apex. Systemic heparinization was initiated to achieve an activated clotting time >300 s. Needle puncture of the LV apex was performed, followed by the introduction of a 0.035-inch J-wire across the mitral valve into the left atrium under TEE and fluoroscopic guidance. A 7-F sheath was then used to introduce a 0.035-inch Amplatz extra-stiff wire (Boston Scientific Corp., Marlborough, Massachusetts). The delivery system was directly inserted into the left ventricle and across the mitral valve into the mid-left atrium. This action was followed by release of the atrial portion (Figures 2A and B). Orientation of the flat portion of the D-shaped valve to the LVOT, coaxiality, and alignment were confirmed with three-dimensional TEE in the mid-left atrium (Figure 3). After full deployment of the atrial skirt, the valve was rotated until the flat portion of the D-shaped frame corresponded with the LVOT. Seating of the valve onto the atrial annulus

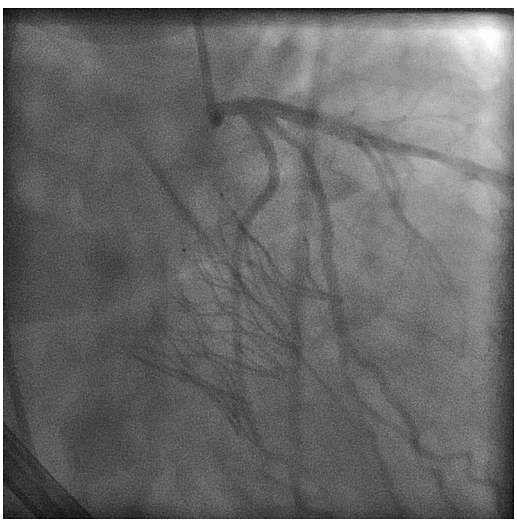


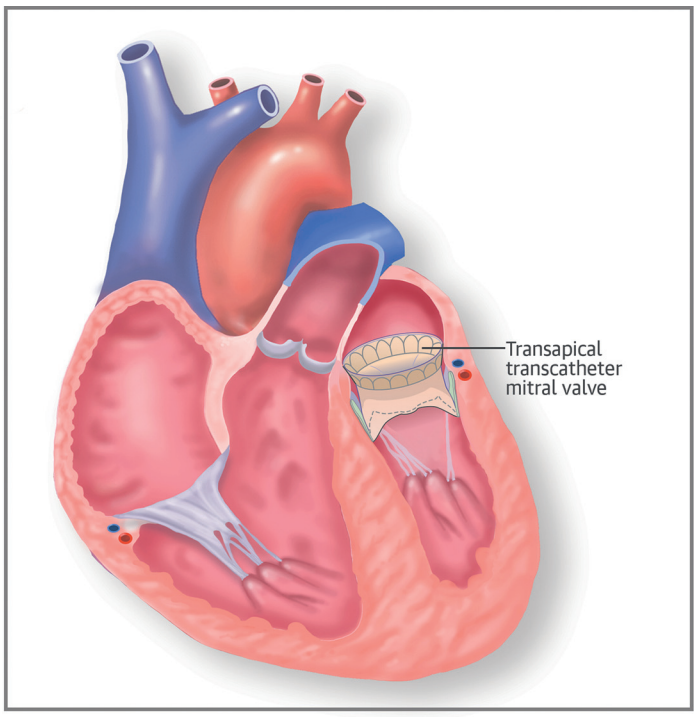
FIGURE 6 Selective Left Coronary Angiogram Showing a Patent and Uncompressed Circumflex Artery

was achieved by gentle traction toward the left ventricle. Rapid ventricular pacing at 180 beats/min was initiated, and the ventricular anchoring mechanism was released with capture of the anterior and posterior native mitral leaflets (Figure 4). A post-implant LV angiogram showed no significant MR, and invasive pressure measurement confirmed an unobstructed LVOT. TEE revealed secure seating of the prosthesis with normal valvular function, trivial PVL, and a transvalvular gradient of 2 to 3 mm Hg (Figure 5). Selective left coronary injection showed a patent and uncompressed circumflex artery (Figure 6). Both patients were hemodynamically stable throughout the procedure. There were no LV apical access issues, and blood transfusion was not required. Patients were extubated in the operating room and transferred in stable condition to the post-surgical intensive care unit. An increase in systemic pressure and a reduction of pulmonary pressure were evident post-implantation.

Patient #1 was transferred to the ward on day 4 for convalescence and rehabilitation. On post-operative day 21, he experienced a post-hemodialysis hypotensive episode requiring cardiopulmonary resuscitation and reintubation, which was further complicated by right lower lobe pneumonia and sepsis. The patient was treated medically, had a remarkable recovery, and was discharged 5 weeks' post-implant. At 2 months, the patient had recurrent heart failure requiring readmission. Repeat transthoracic echocardiogram confirmed poor LV function with a well-functioning prosthesis. Despite a well-functioning prosthesis and elimination of MR, Patient #1 experienced refractory end-stage cardiac failure. Palliative care was initiated, and the patient died on day 69 post-implant.

Patient #2 had a uneventful recovery and was discharged 5 days' post-implant. Significant symptomatic and functional improvements were noted at 2 months, with New York Heart Association functional class II symptoms, reduction in brain natriuretic peptide, and improvement in the 6-min walk test. Repeat transthoracic echocardiograms in both patients on day 4, and at 1 and 2 months' post-TAMI demonstrated normal valve function with no evidence of thrombus formation, PVL, or LVOT obstruction. The transvalvular gradient remained low, at 2 mm Hg (Central Illustration).

STUDY LIMITATIONS. Our study is limited by the low number of patients and the relatively short follow-up period. Ongoing compassionate implantation of the Tiara device and continuing follow-up of the treated patients will further define the safety and efficacy of this procedure.



CENTRAL ILLUSTRATION Implantation of the Transapical Transcatheter Mitral Valve

(Top) Demonstration of first-in-human cases in high-risk patients with end-stage ischemic cardiomyopathy and severe mitral regurgitation. **(Bottom)** Transthoracic echocardiography pre-implantation showing severe mitral regurgitation and at 2 months' post-implantation demonstrating a well-seated and functioning mitral prosthesis with no mitral regurgitation or paravalvular leak.

CONCLUSIONS

MR is the most common valvular pathology. Conventional surgical repair or replacement is used in

only a small proportion of affected patients. Transcatheter valve therapy has revolutionized the management of aortic stenosis patients and is now a well-established treatment. The development of catheter-based therapies for mitral valve disease is lagging as a consequence of the complexity of mitral valve anatomy and function.

The Tiara TAMI is a catheter-based mitral implantation system specifically designed to treat MR. This valve, with its self-expanding, nitinol alloy-based frame and bovine pericardial leaflets, has specific features that accommodate the complex structures of the mitral valve apparatus. The bioprosthesis is anatomically shaped, with atrial and ventricular anchoring mechanisms that secure the prosthesis, preventing migration, sealing paravalvular leaks, and allowing unobstructed blood flow across the LVOT. Capture of the mitral anterior leaflet may lower the risk of LVOT obstruction from the systolic anterior motion of the anterior leaflet. A potential added benefit of mitral leaflet and chordae captures is preservation of LV geometry, which may promote reverse remodeling.

Our first-in-human cases in 2 high-risk patients with end-stage ischemic cardiomyopathy and severe MR demonstrate the feasibility and potential safety of this procedure. The procedure was performed without hemodynamic compromise, was minimally invasive, and off-pump. Instant elimination of MR with normal valvular function, secure seating, low transvalvular and LVOT gradient, and the absence of significant PVL were achieved. Ongoing follow-up of patient clinical status and valvular function continues. Catheter-based mitral valve implantation is technically feasible and may present another chapter in the evolution in the treatment of valvular heart disease.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Anson Cheung, Division of Cardiothoracic Surgery, St. Paul's Hospital, 1081 Burrard Street, Vancouver, British Columbia V6Z 1Y6, Canada. E-mail: acheung@providencehealth.bc.ca.

PERSPECTIVES

COMPETENCY IN PATIENT CARE: Transcatheter mitral valve implantation is a less invasive alternative for patients with severe mitral regurgitation for whom the risks associated with surgical valve repair or replacement are prohibitive.

TRANSLATIONAL OUTLOOK: More experience with transcatheter mitral valve implantation and comparisons of this technology with intensive medical therapy or surgery in clinical trials are needed to establish the indications and limitations.

REFERENCES

1. Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. Eur Heart J 2003;24:1231–43.

2. Mirabel M, Iung B, Baron G, et al. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? Eur Heart J 2007;28:1358–65.

3. Nishimura RA, Otto CM, Bonow RO, et al., for the ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2438–44.

4. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC); European Association for Cardio-Thoracic Surgery (EACTS), Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J 2012;33:2451–96.

5. Feldman T, Mauri L, Kar S, et al., for the EVEREST II Investigators. Final results of the EVEREST II randomized controlled trial of percutaenous and surgical reduction of mitral regurgitation (abstr). J Am Coll Cardiol 2014;63:A1682.

6. Auricchio A, Schillinger W, Meyer S, et al., for the PERMIT-CARE Investigators. Correction of mitral regurgitation in nonresponders to cardiac resynchronization therapy by MitraClip improves symptoms and promotes reverse remodeling. J Am Coll Cardiol 2011;58:2183–9.

7. Chiam PT, Ruiz CE. Percutaneous transcatheter mitral valve repair: a classification of the technology. J Am Coll Cardiol Intv 2011;4:1–13.

8. Mauri L, Foster E, Glower DD, et al., for the EVEREST II Investigators. 4-Year results of a randomized controlled trial of percutaneous repair versus surgery for mitral regurgitation. J Am Coll Cardiol 2013;62:317–28.

9. Lozonschi L, Bombien R, Osaki S, et al. Transapical mitral valve stent implantation: a survival series in swine. J Thorac Cardiovasc Surg 2010;140:422–6.e1.

10. Schofer J, Siminiak T, Haude M, et al. Percutaneous mitral annuloplasty for functional mitral regurgitation: results of the CARILLON Mitral Annuloplasty Device European Union Study. Circulation 2009;120:326–33.

11. Makkar RR, Fontana GP, Jilaihawi H, et al., for the PARTNER Trial Investigators. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. N Engl J Med 2012;366:1696–704.

12. Kodali SK, Williams MR, Smith CR, et al., for the PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012;366:1686–95.

13. Rodés-Cabau J, Webb JG, Cheung A, et al. Long-term outcomes after transcatheter aortic valve implantation: insights on prognostic factors and valve durability from the Canadian multicenter experience. J Am Coll Cardiol 2012;60:1864–75.

14. Seeburger J, Borger MA, Mohr FW. Transcatheter mitral valve repair: a high mountain to climb. Eur Heart J Suppl 2010;12 Suppl E:E46–51.

15. Banai S, Jolicoeur EM, Schwartz M, et al. Tiara: a novel catheter-based mitral valve bioprosthesis: initial experiments and short-term pre-clinical results. J Am Coll Cardiol 2012;60:1430–1.

16. Banai S, Verheye S, Cheung A, et al. Transapical mitral implantation of the Tiara bioprosthesis: pre-clinical results. J Am Coll Cardiol Intv 2014;7:154–62.

KEY WORDS mitral regurgitation, mitral valve implantation, mitral valve replacement, transapical, transcatheter