Current Status and Future Direction of Transcatheter Mitral Valve Replacement

Zhen Meng, Er-Li Zhang, Yong-Jian Wu

Coronary Intervention Center, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China

Valvular heart disease (VHD) refers to the disorder of cardiac valves leading to valvular regurgitation or stenosis. Severe VHD will result in chronic heart failure and cardiac death. The only large population-based epidemiologic study involving echocardiography was performed in the United States in 2006. In this study, the prevalence of VHD in the United States was estimated to be 2.5%.[1] As a developing country, VHD caused by rheumatic heart disease is still a huge burden in China. It is estimated that there were around 7.07 million patients with rheumatic heart disease in China in 2015.[2] In addition, as life expectancy increases, the prevalence of the degenerative valvular disease increases sharply according to a regional survey in Xinjiang, which reported that the prevalence of degenerative valvular disease in Han elderly (mean age 67.7 years old) was 30.2%. Hence, due to Chinese socioeconomic characters, both rheumatic heart disease and degenerative valve disease contribute to the high burden of VHD in China. However, there is no national cross-sectional study to uncover the epidemiologic features of VHD in China. Our group is currently conducting the first degenerative valve disease cross-sectional study in China, aiming to provide a demographic profile of degenerative mitral valve disease nationwide. On this basis, a national multicenter registry will be started to build an adult severe VHD database in China.

Mitral valve disease, including mitral regurgitation (MR) and mitral stenosis (MS), is the most prevalent type of VHD.[3] In the past, surgery was regarded as the standard therapy of MR.[4,5] However, up to 50% of hospitalized-patients with severe MR are unsuitable for surgery, mainly due to increasing risk with advanced age, left ventricular dysfunction, and comorbidities.[6] In MS, percutaneous mitral commissurotomy is an effective treatment. However, it is not suitable for patients with moderate-to-severe MR.[4] As an emerging technique, transcatheter mitral valve replacement (TMVR) is a promising modality to treat mitral valve diseases with several advantages such as less invasive, versatility, and durable elimination of MR.

Although mitral valvular disease has a higher prevalence, transcatheter valve replacement was applied in aortic valvular more extensively due to the relatively simple anatomic feature. The recommendation of transcatheter aortic valve replacement (TAVR) expanded to symptomatic patients with severe AS (Stage D) and an intermediate surgical risk according to 2017 American College of Cardiology/American Heart Association Task Force guidelines.[7] The development of TAVR indicates advantages of transcatheter valve replacement. Nevertheless, TMVR was confronted with more challenges in anatomy and pathophysiology. The anatomic structure of mitral valve is complicated, and several important structures are adjacent to mitral valve apparatus, including coronary sinus, circumflex coronary artery, atrioventricular node, and left ventricular outflow tract.[8] In addition, pathogens and course of mitral valvular disease are diverse.[9] All these factors add technical difficulties to TMVR.

In general, TMVR is currently used in patients who were judged inoperable or at high surgical risk with the following conditions: (1) severe primary/functional MR; (2) once undergoing surgical replacement or annuloplasty, but the valve has degenerated (valve-in-valve and valve-in-ring implantation); or (3) severe MS caused by mitral annular calcification (MAC).[10]

To standardize the assessment of transcatheter mitral valve repair and replacement, the mitral valve academic research

Address for correspondence: Prof. Yong-Jian Wu, Coronary Intervention Center, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China
E-Mail: aricho1985@163.com

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.226080

Received: 31-12-2017 **Edited by:** Xin Chen
How to cite this article: Meng Z, Zhang EL, Wu YJ. Current Status and Future Direction of Transcatheter Mitral Valve Replacement. Chin Med J 2018;131:505-7.

consortium including representatives from the United States Food and Drug Administration published a consensus document to provide recommendations for the clinical trial design and endpoint definition in 2015. The definition of technical and device success in this editorial is according to the Mitral Valve Academic Research Consortium criteria.[11,12]

To date, dozens of delivery systems and prosthesis have been designed and developed for TMVR. Accesses have been proposed to deliver mitral valve prosthesis including transapical, transseptal, and transatrial. The mainstream approach is transapical because mitral prosthesis is larger than aortic prosthesis which can be delivered through femoral artery. A few of them including Tendyne valve (Abbott Vascular, Santa Clara, CA, USA), Tiara transcatheter mitral valve system (Neovasc Inc., Vancouver, BC, Canada), CardiAQ transcatheter mitral valve implantation system (CardiAQ Valve Technologies Inc., Irvine, CA, USA), Intrepid TMVR system (Medtronic Inc., Inneapolis, MN, USA), and caisson are undergoing clinical trials. Ongoing clinical trials are all nonrandomized, single group-assigned and open-label to demonstrate the safety and feasibility of device. All inclusion criteria contain prohibitive or high risk of open surgery. Early results of Tendyne valve (NCT02321514) were published in 2017. It was a global feasibility trial involving 30 patients with Grade 3 or 4 MR and showed that there were no acute deaths, strokes, or myocardial infarctions. After 30-day follow-up, successful device implantation free of cardiovascular mortality, stroke, and device malfunction was 86.6%.[13] Until now, it is the only device with satisfying early result. On the contrary, a multicenter registry involving 13 patients with severe MR to determine long-term outcomes following TMVR with the FORTIS transcatheter valve system, demonstrated that technical success was achieved in 10 patients. At 2-year follow-up, all-cause mortality was up to 54%. The Edwards Lifesciences halted the FORTIS valve program in May 2015 because of the high-rate of thrombosis.[14]

While devices especially designed for TMVR are developing, transcatheter aortic prosthesis has been wildly applied in TMVR. The main situations using aortic devices are dysfunctional mitral bioprostheses or annuloplasty rings and MS with MAC. Mitral bioprostheses, annuloplasty rings, and calcified mitral annulus can provide landmark and support structure to position and anchor the device. Aortic devices used in mitral replacement include Sapien XT, Sapien3, lotus valve system, and direct flow medical aortic valve prosthesis, *etc*. Yoon *et al*.[15] created an international multicenter registry involving 248 patients to evaluate the outcomes of TMVR in patients with failed mitral bioprosthetic valves and annuloplasty rings, and the results showed that overall technical and device success rates were 92.3% and 85.5%, respectively, indicating that TMVR had acceptable outcomes in high-risk patients with degenerated bioprostheses or failed annuloplasty rings. The placement of AoRTic TraNscathetER Valves (PARTNER II, NCT03222141) trial is a clinical trial to assess the safety and effectiveness of the SAPIEN 3 transcatheter heart valve in patients with a failing mitral bioprosthetic valve. Guerrero *et al*.[16] conducted a global multicenter registry involving 64 patients to evaluate the outcomes of the early experience of TMVR with SAPIEN, SAPIEN 3, SAPIEN XT, and Inovare in patients with severe MAC. Technical success was achieved in 46 (72%) patients. Thirty-day all-cause mortality was 29.7%, indicating that TMVR in patients with severe MAC is feasible but may be associated with significant adverse events. MITRAL (NCT02370511) is a clinical trial to establish the safety and feasibility of the Edwards SAPIEN XT and SAPIEN 3 device and delivery systems in patients with severe symptomatic calcific mitral valve disease and severe MAC who are not candidates for standard mitral valve surgery. A case report that aortic devices were performed in native MR was published recently in 2017. At 2-month follow-up, the patient survived in the New York Heart Association functional Class II. Echocardiography showed minimal anterior paravalvular leaks. Further studies are required in more patients to confirm the feasibility of this technique.[17,18]

Main complications observed in clinical practice of TMVR are left ventricle outflow tract obstruction, thrombus, paravalvular leak and hemolysis, anatomic structure injury, migration and malposition. Methods to reduce the occurrence of complication include accurate geometrical appraisal of mitral annulus apparatus to choose appropriate valve prosthesis size, advanced imaging techniques used to detect complications, careful operation, and optimum valve design and further research to standardize the procedure.[19]

In summary, mitral valve disease is still a heavy burden in China. Considering the complicated pathophysiology of MR, treatment should be individualized to cope with specific type. As an emerging technique, TMVR may benefits patient who are unsuitable for other treatments. However, optimization of device designs and development of new materials are required to further reduce in-plant complications and improve delivery efficiency. More clinical trials are warranted to find the optimum indications for TMVR.

References

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M, *et al.* Burden of valvular heart diseases: A population-based study. Lancet 2006;368:1005-11. doi: 10.1016/s0140-6736(06)69208-8.
2. Watkins DA, Johnson CO, Colquhoun SM, Karthikeyan G, Beaton A, Bukhman G, *et al.* Global, regional, and national burden of rheumatic heart disease, 1990-2015. N Engl J Med 2017;377:713-22. doi: 10.1056/NEJMoa1603693.
3. Iung B, Vahanian A. Epidemiology of acquired valvular heart disease. Can J Cardiol 2014;30:962-70. doi: 10.1016/j.cjca.2014.03.022.
4. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, *et al.* 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739-91. doi: 10.1093/eurheartj/ehx391.
5. Jiang ZL, Feng XY, Ma N, Zhu JQ, Zhang L, Ding FB, *et al.* Comparison of the outcomes of modified artificial chordae technique for mitral regurgitation through right minithoracotomy or median sternotomy.

Chin Med J 2016;129:2153-9. doi: 10.4103/0366-6999.189917.
6. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, *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. doi: 10.1016/S0195-668X(03)00201-X.
7. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, *et al.* 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135:e1159-95. doi: 10.1161/cir.0000000000000503.
8. Van Mieghem NM, Piazza N, Anderson RH, Tzikas A, Nieman K, De Laat LE, *et al.* Anatomy of the mitral valvular complex and its implications for transcatheter interventions for mitral regurgitation. J Am Coll Cardiol 2010;56:617-26. doi: 10.1016/j.jacc.2010.04.030.
9. Maganti K, Rigolin VH, Sarano ME, Bonow RO. Valvular heart disease: Diagnosis and management. Mayo Clin Proc 2010;85:483-500. doi: 10.4065/mcp.2009.0706.
10. Partida RA, Elmariah S. Transcatheter mitral valve interventions: Current therapies and future directions. Curr Treat Options Cardiovasc Med 2017;19:32. doi: 10.1007/s11936-017-0538-2.
11. Stone GW, Vahanian AS, Adams DH, Abraham WT, Borer JS, Bax JJ, *et al.* Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: Part 1: Clinical trial design principles: A Consensus document from the mitral valve academic research consortium. J Am Coll Cardiol 2015;66:278-307. doi: 10.1016/j.jacc.2015.05.046.
12. Stone GW, Adams DH, Abraham WT, Kappetein AP, Généreux P, Vranckx P, *et al.* Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: Part 2: Endpoint definitions: A consensus document from the mitral valve academic research consortium. J Am Coll Cardiol 2015;66:308-21. doi: 10.1016/j.jacc.2015.05.049.
13. Muller DW, Farivar RS, Jansz P, Bae R, Walters D, Clarke A, *et al.* Transcatheter mitral valve replacement for patients with symptomatic mitral regurgitation: A global feasibility trial. J Am Coll Cardiol 2017;69:381-91. doi: 10.1016/j.jacc.2016.10.068.
14. Regueiro A, Ye J, Fam N, Bapat VN, Dagenais F, Peterson MD, *et al.* 2-year outcomes after transcatheter Mitral valve replacement. JACC Cardiovasc Interv 2017;10:1671-8. doi: 10.1016/j.jcin.2017.05.032.
15. Yoon SH, Whisenant BK, Bleiziffer S, Delgado V, Schofer N, Eschenbach L, *et al.* Transcatheter mitral valve replacement for degenerated bioprosthetic valves and failed annuloplasty rings. J Am Coll Cardiol 2017;70:1121-31. doi: 10.1016/j.jacc.2017.07.714.
16. Guerrero M, Dvir D, Himbert D, Urena M, Eleid M, Wang DD, *et al.* Transcatheter mitral valve replacement in native mitral valve disease with severe mitral annular calcification: Results from the first multicenter global registry. JACC Cardiovasc Interv 2016;9:1361-71. doi: 10.1016/j.jcin.2016.04.022.
17. Kar B, Nascimbene A, Gregoric ID, Patel M, Loyalka P. Transcatheter mitral valve replacement with the Edwards Sapien 3 valve. Tex Heart Inst J 2017;44:269-73. doi: 10.14503/thij-16-5823.
18. Wang Y, Gao CQ, Shen YS, Wang G. Echocardiographic follow-up of robotic mitral valve repair for mitral regurgitation due to degenerative disease. Chin Med J 2016;129:2199-203. doi: 10.4103/0366-6999.189909.
19. Regueiro A, Granada JF, Dagenais F, Rodés-Cabau J. Transcatheter mitral valve replacement: Insights from early clinical experience and future challenges. J Am Coll Cardiol 2017;69:2175-92. doi: 10.1016/j.jacc.2017.02.045.