European Perspective of Percutaneous Mitral Leaflet Repair

An overview of the EVEREST trials and the MitraClip system used to treat mitral regurgitation.

BY OLAF FRANZEN, MD; SVEN MEYER, MD; STEPHAN BALDUS, MD; ANJELIKA COSTARD-JÄCKLE, MD; AND THOMAS MEINERTZ, MD

Endovascular mitral repair is an emerging option for selected patients with mitral regurgitation (MR), especially those with high morbidity and mortality risk related to mitral valve surgery.[1] Several percutaneously implantable devices have been developed, some of which are still in preclinical trials, and one that has already proven initial safety and efficacy and has completed enrollment in a pivotal randomized controlled trial.[2] In addition to percutaneous annuloplasty devices[3-5] and minimally invasive implantable ventricular reshaping devices,[1,6-10] a third category of devices, which mimics double-orifice surgical repair, has already entered the postmarket clinical arena in Europe.[11] This article focuses on the evidence that is currently available and our perspective with percutaneous mitral valve repair using the MitraClip system (Evalve, Inc., Menlo Park, CA) in Europe.

TREATING MR

Despite the complex and different etiologies of MR that affect the function of the valve leaflets, mitral annulus, subvalvular apparatus, or the left ventricular myocardium solely or in combination, the common natural course of MR ultimately leads to increased volume overload, severe symptoms, and an increased risk of death.[12,13] That is why, according to the latest guidelines, patients with symptomatic severe MR or asymptomatic severe MR with evidence of LV dysfunction or dilation are currently recommended for surgery.[14]

> "In need of an alternative, less-invasive treatment option, interventional cardiologists have been striving for direct percutaneous repair of the mitral valve."

Although surgical procedures, preferably repair, are often very effective,[15,16] surgery may be delayed or not an option for some patients due to the inherent morbidity and mortality risk related to major open chest cardiopulmonary bypass surgery.[17-19] In need of an alternative, less-invasive treatment option, interventional cardiologists have been striving for direct percutaneous repair of the mitral valve.[11] The most advanced percutaneous technique is repair with the MitraClip system.[20-22] It uses a repositionable, polyester-covered mechanical clip device to grasp and coapt mitral valve leaflets via a standard atrial transseptal approach, avoiding the need for cardiopulmonary bypass surgery and thoracotomy or sternotomy. Animal studies have demonstrated the feasibility and durability of endovascular mitral repair by clip implantation.[23-25]

THE EVEREST TRIAL

Since this technology passed the preclinical trial stages, the MitraClip has been subject to two major controlled trials in the United States: the EVEREST

(Endovascular Valve Edge-to-Edge Repair Study) I and II studies. The phase 1 clinical trial (EVEREST I) was successfully completed after enrollment of 55 patients, demonstrating feasibility and initial safety of the device with a reduction in MR in a significant proportion of patients.[21] In the pivotal phase 2 clinical trial (EVEREST II), safety and efficacy are being assessed with 24-month follow-up to monitor the longer outcome.[26] EVEREST II consists of a randomized arm and a high-risk registry arm. The randomized arm provides 2:1 randomization against surgical mitral valve repair. The high-risk registry arm evaluates safety and efficacy in patients with predicted excessive perioperative risk related to cardiac surgery. The inclusion criteria of the randomized arm of EVEREST II demand that study subjects have to be candidates for mitral valve repair or replacement surgery, including cardiopulmonary bypass. A diverse set of anatomical and clinical eligibility criteria provide investigators with a solid foundation for patient selection during the investigation. Patients are excluded from the randomized arm of EVEREST II if they have an ejection fraction (EF) of < 25% and/or an end-systolic dimension of > 55 mm, and from the high-risk registry arm if they have EF < 20% and/or an end-systolic dimension of > 60 mm. Enrollment in the high-risk arm necessitates screening but indicates ineligibility for the randomized arm of EVEREST II. As far as it is currently known, the majority of patients from the randomized arm of EVEREST II had degenerative MR; however, approximately 46 patients in the high-risk registry had functional MR. Enrollment in EVEREST II has successfully been completed, and results are expected in 2010.

When the MitraClip device received CE Mark approval in March 2008 in Europe, as could be expected, clinical application started mainly using the EVEREST II criteria, especially considering echocardiographic anatomic eligibility. The final EVEREST II trial results are still pending. The only currently accepted treatment for significant MR remains surgical repair or valve replacement. Thus in Europe, the early clinical application of percutaneous mitral repair will likely focus on patients with a high predicted perioperative morbidity and mortality risk calculated by the STS or EuroSCORE, as well as, similar to the high-risk registry population of the EVEREST II trial, patients with a specific surgical risk, such as porcelain aorta, previous chest surgeries, etc. In Europe, patients have already been treated whose risk profile was even beyond what was defined for the high-risk registry of EVEREST II. So far, there are no published data on the European experience.

Anatomic eligibility criteria are likely to be redefined in this subset of patients treated without the strict EVEREST protocols. It remains necessary to demonstrate safety and efficacy for the MitraClip device, especially in this vulnerable cohort of patients, and considerably more data are needed to aid in the appropriate selection of patients. Special consideration has to be given to heart failure patients with severe LV dysfunction (ie, an LVEF that is even lower than 20%, secondary functional MR, and a substantially dilated ventricle). The relatively noninvasive characteristic of the MitraClip approach, in comparison to surgical approaches, may encourage broader application of this treatment option for this subset of patients. This might be facilitated by the fact that surgical approaches have not clearly demonstrated any long-term survival benefit in this population.[27] For patients with advanced heart failure, the optimal management of relevant MR is still a subject of debate and controversy. The current European Society of Cardiology's guidelines recommend mitral valve surgery in patients with heart failure whenever they have to get revascularized and only in selected patients with severe functional MR and severely depressed LV function, who remain symptomatic despite optimal medical therapy (IIb, level C recommendation).[28] It seems that elective surgical procedures for mitral repair are mainly necessitated by the heavy symptomatic burden of these patients. Thus, lacking a clear indication for surgical repair in high-risk surgical candidates, the MitraClip therapy might be an attractive less invasive option for these patients with a major unmet clinical need.

CONCLUSION

If the clip implantation proves to be feasible in high-risk and heart failure patients with severe LV dysfunction, even in those who do not match EVEREST or high-risk registry criteria because of low LVEF or large dimensions, and eventually, in patients that are not responding to cardiac resynchronization therapy, it could help to solve an important clinical problem. In those patients apart from absolute reduction of MR, a maintenance goal of sufficient relative reduction of MR might translate into symptomatic relief. In addition to issues such as safety, predicting response to therapy with emphasis on ischemic MR, indirect effects on annular dimensions or papillary muscle displacement, performance in concert with cardiac resynchronization therapy, durability, and major pathophysiological effects such as remodeling—much remains to be elucidated and will be addressed in larger prospective multicenter trials, which have already been planned. At the moment, the MitraClip device therapy appears to be a promising treatment option in patients with a clear indication for mitral repair.

According to orally communicated initial European data, it also seems appropriate for heart failure patients with severe LV dysfunction, secondary functional MR, and a substantially dilated ventricle. Numerous issues need to be better understood before the approach can be accepted as the therapy of choice for functional MR in those end-stage patients or high-risk surgical candidates. The results of the EVEREST studies and further adequately designed and powered clinical trials are needed to define the value of intervention in subpopulations with an unmet clinical need. ■

Olaf Franzen, MD, is Senior Interventionalist Structural Heart Disease, Department of General and Interventional Cardiology, University Heart Center Hamburg in Hamburg, Germany. He has disclosed that he receives grant/research funding from Evalve. Dr. Franzen may be reached at +49 (40)7410-52966; svmeyer@uke.uni-hamburg.de.

Sven Meyer, MD, is with the Department of General and Interventional Cardiology, Senior Staff, Heart Failure and Transplantation Unit, University Heart Center Hamburg in Hamburg, Germany. He has disclosed that he receives grant/research funding from Evalve. Dr. Meyer may be reached at +49 (40) 7410-53471; svmeyer@uke.uni-hamburg.de.

Stephan Baldus, MD, is Head Senior Physician, Department of General and Interventional Cardiology, University Heart Center Hamburg in Hamburg, Germany. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein. Dr. Baldus may be reached at +49 (40)7410-55320; baldus@uke.uni-hamburg.de.

Angelika Costard-Jäckle, MD, is HF Program Director, Department of General and Interventional Cardiology, Heart Failure and Transplantation Unit, University Heart Center Hamburg in Hamburg, Germany. She has disclosed that she receives grant/research funding from Evalve. Dr. Costard-Jäckle may be reached at +49 (40) 7410-56466; herzambulanz@uke.uni-hamburg.de.

Thomas Meinertz, MD, is Medical Director, Department of General and Interventional Cardiology, University Heart Center Hamburg in Hamburg, Germany. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein. Dr. Baldus may be reached at +49 (40)7410-53972; meinertz@uke.uni-hamburg.de.

1. Fukamachi K. Percutaneous and off-pump treatments for functional mitral regurgitation. J Artif Organs. 2008;11:12-18.
2. Mack MJ. Percutaneous mitral valve repair: a fertile field of innovative treatment strategies. Circulation. 2006;113:2269-2271.
3. Dubreuil O, Basmadjian A, Ducharme A, et al. Percutaneous mitral valve annuloplasty for ischemic mitral regurgitation: first in man experience with a temporary implant. Catheter Cardiovasc Interv. 2007;69:1053-1061.
4. Siminiak T, Firek L, Jerzykowska O, et al. Percutaneous valve repair for mitral regurgitation using the Carillon Mitral Contour system. Description of the method and case report. Kardiol Pol. 2007;65:272-278; discussion 279.
5. Kaye DM, Byrne M, Alferness C, et al. Feasibility and short-term efficacy of percutaneous mitral annular reduction for the therapy of heart failure-induced mitral regurgitation. Circulation. 2003;108:1795-1797.
6. Inoue M, McCarthy PM, Popovic ZB, et al. Mitral valve repair without cardiopulmonary bypass or atriotomy using the Coapsys device: device design and implantation procedure in canine functional mitral regurgitation model. Heart Surg Forum. 2004;7:E117-E121.
7. Fukamachi K, Inoue M, Popovic ZB, et al. Off-pump mitral valve repair using the Coapsys device: a pilot study in a pacing-induced mitral regurgitation model. Ann Thorac Surg. 2004;77:688-692; discussion 692-693.
8. Fukamachi K, Popovic ZB, Inoue M, et al. Changes in mitral annular and left ventricular dimensions and left ventricular pressure-volume relations after off-pump treatment of mitral regurgitation with the Coapsys device. Eur J Cardiothorac Surg. 2004;25:352-357.
9. Inoue M, McCarthy PM, Popovic ZB, et al. The Coapsys device to treat functional mitral regurgitation: in vivo long-term canine study. J Thorac Cardiovasc Surg. 2004;127:1068-1076; discussion 1076-1077.
10. Pedersen WR, Block P, Leon M, et al. iCoapsys mitral valve repair system: percutaneous implantation in an animal model. Catheter Cardiovasc Interv. 2008;72:125-131.
11. Mack M. Percutaneous mitral valve therapy: when? Which patients? Curr Opin Cardiol. 2009;24:125-129.
12. Carabello BA. The current therapy for mitral regurgitation. J Am Coll Cardiol. 2008;52:319-326.
13. Block PC. Percutaneous transcatheter repair for mitral regurgitation. J Interv Cardiol. 2006;19:547-551.
14. American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Society of Cardiovascular Anesthesiologists; Society for Cardiovascular Angiography and Interventions; et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. Circulation. 2006;114:e84-231.
15. Bach DS, Bolling SF. Early improvement in congestive heart failure after correction of secondary mitral regurgitation in end-stage cardiomyopathy. Am Heart J. 1995;129:1165-1170.
16. Gillinov AM, Cosgrove DM, Blackstone EH, et al. Durability of mitral valve repair for degenerative disease. J Thorac Cardiovasc Surg. 1998;116:734-743.
17. Ambler G, Omar RZ, Royston P, et al. Generic, simple risk stratification model for heart valve surgery. Circulation. 2005;112:224-231.
18. STS U.S. Cardiac Surgery Database. Mitral valve repair and replacement patients: incidence of complications summary. www.sts.org. Accessed July 14, 2009.
19. Jamieson WR, Edwards FH, Schwartz M, et al. Risk stratification for cardiac valve replacement. National Cardiac Surgery Database. Database Committee of the Society of Thoracic Surgeons. Ann Thorac Surg. 1999;67:943-951.
20. Feldman T. EVEREST registry (Endovascular Valve Edge-to-Edge Repair Studies) reduction in mitral regurgitation 12 months following percutaneous mitral valve repair. Clin Cardiol. 2007;30: 416-417.
21. 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;46:2134-2140.
22. Herrmann HC, Rohatgi S, Wasserman HS, et al. Mitral valve hemodynamic effects of percutaneous edge-to-edge repair with the MitraClip device for mitral regurgitation. Cathet Cardiovasc Interv. 2006;68:821-828.
23. Luk A, Butany J, Ahn E, et al. Mitral repair with the Evalve MitraClip device: histopathologic findings in the porcine model. Cardiovasc Pathol. 2008. In press.
24. St Goar FG, Fann JI, Komtebedde J, et al. Endovascular edge-to-edge mitral valve repair: short-term results in a porcine model. Circulation. 2003;108:1990-1993.
25. Fann JI, St Goar FG, Komtebedde J, et al. Beating heart catheter-based edge-to-edge mitral valve procedure in a porcine model: efficacy and healing response. Circulation. 2004;110:988-993.
26. Feldman T, Glower D Jr. EVEREST II. Pivotal Study of a Percutaneous Mitral Valve Repair System. http://clinicaltrials.gov/ct2/show/NCT00209274?term=EVEREST+II&rank=1. Accessed July 14, 2009.
27. Wu AH, Aaronson KD, Bolling SF, et al. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. J Am Coll Cardiol. 2005;45:381-387.
28. Dickstein K. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: application of natriuretic peptides. Eur Heart J. 2008;10:933-989.