International Journal of Cardiology 288 (2019) 57–58

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Editorial

Transcatheter treatment of functional mitral regurgitation after MITRA-FR and COAPT – Patient selection is most important

Martin Orban *, Jörg Hausleiter

Medizinische Klinik und Poliklinik I, Ludwig-Maximilians-Universität München, Munich, Germany

ARTICLE INFO

Article history:
Received 16 November 2018
Accepted 22 November 2018
Available online 24 November 2018

Keywords:
Valvular heart disease
Functional mitral regurgitation
Secondary mitral regurgitation
Percutaneous edge-to-edge mitral valve repair
Transcatheter edge-to-edge mitral valve repair
MitraClip

Behind aortic stenosis mitral regurgitation is the second most frequent valvular heart disease. Mitral regurgitation is classified as primary (degenerative) or secondary (functional). Secondary MR is a consequence of a diseased left ventricle – either ischemic or non-ischemic – which leads to left ventricular dilatation and restricted leaflet motion, while the leaflets and the sub-valvular apparatus are mostly preserved. Prognosis of these patients is determined by the left ventricular dysfunction. The cornerstone of treatment in these patients is optimal guideline directed pharmacotherapy at maximal tolerated doses and – if applicable – cardiac resynchronization therapy [1]. In end stage heart failure, heart transplantation or implantation of left ventricular assist devices (LVAD) – as destination therapy – is the last resort in highly selected patients. As secondary severe MR in heart failure patients worsens prognosis and accelerates left ventricular failure in a vicious circle treating MR is reasonable. Surgical therapies of secondary MR have not proven beneficial in terms of prognosis [2].

Due to the considerably lower peri- and post-procedural risk compared to surgical procedures transcatheter mitral valve repair (TMVR) – which evolved in the last decade – might be the treatment of choice in this patient population. By mimicking Alfieri's stich TMVR – using the mitral clip approach (MitraClip®, Abbott Vascular, Santa Clara, California) –has evolved as the most applied alternative non-surgical treatment option for patients with symptomatic MR who were judged inoperable by the heart team. Latest European guidelines implemented this therapy option as recommendation for the treatment of secondary MR ([3] recommendation class IIb, level of evidence C) while American guidelines still do not.

In this issue of *The Journal of International Cardiology* Gallasso [4] investigates predictors of outcomes in patients with functional MR undergoing TMVR. Although the study population is small the authors performed a systematic determination of peak VO_2 during cardiopulmonary exercise test pre-procedural in 74 patients and identified a cut-off value of 10 ml/kg/min via Receiver Operating Characteristic as best predictor of all three study endpoints cardiac and all-cause death as well as rehospitalization for heart failure. Moreover the study confirms previous published data that atrial fibrillation is a predictor of mortality [5,6].

Hence, a pre-procedural performed cardiopulmonary exercise test could discriminate patients with potential prognosis from patients without reasonable prognosis after TMVR. This result is of great value since the only two finished randomized studies on this field, the Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation (MITRA-FR) and the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation trial (COAPT) were recently presented a few months ago but showed differing results. Key aspects of both trials are displayed in Table 1.

Transcatheter mitral valve repair for functional mitral regurgitation — conflicting results in MITRA-FR vs. COAPT

At the European Society of Cardiology (ESC) congress 2018 in August this year the MITRA-FR trial which randomly compared optimal medical therapy (OMT) vs. OMT plus TMVR showed no difference in the primary endpoint which was a composite of rehospitalization and all-cause death after 1 year [7]. Patient number was 304. Compared to MITRA-FR double as much patients were randomized in the COAPT trial which was published at the Trans-Catheter-Therapeutics (TCT) congress 2018 in September this year [8]. In large contrast to MITRA-FR, COAPT showed a significant reduction in the primary endpoint (hospitalizations due to heart failure within 24 months) in the TMVR group compared to OMT. Moreover the authors presented a significant reduction of all-cause mortality in the TMVR group compared to the

Abbreviations: MR, mitral regurgitation; OMT, optimal medical therapy; TMVR, transcatheter edge-to-edge mitral valve repair.

DOI of original article: https://doi.org/10.1016/j.ijcard.2018.06.041.

* Corresponding author at: Medizinische Klinik und Poliklinik I, Klinikum der Universität München, Campus Großhadern, Ludwig-Maximilians-Universität München, Marchioninistr. 15, 81377 München, Germany.
E-mail address: MartinOrban@gmail.com (M. Orban).

https://doi.org/10.1016/j.ijcard.2018.11.112
0167-5273/

Table 1
Overview of three randomized clinical trials assessing safety and efficacy of TMVR in functional MR.

	MITRA-FR[7]	COAPT[8]	RESHAPE-HF2
Sponsor	IIT	Industry	IIT
Patients randomized	304	614	420*
Patients screened (percentage of randomized patients)	452 (159%)	1576 (257%)	
recruitment	2013-2017	2012-2017	2015-ongoing
centers	37	78	
participating countries	France	US, Canada	Europe
EROA inclusion criterion (mm^2)	**>20**	**>30**	
baseline EROA (mm^2)	**31**	**41**	
baseline LVEDVindex (ml/m^2)	**135**	**101**[9]	
baseline LV-EF	33	31	
MR grade ≤1 postprocedurally (%)	76	82	
MR grade ≤1/2 postprocedurally (%)	92	95	
device-related complications	15	3	
Follow-up of the primary endpoint	1 year	2 years	2 years

Key differences are displayed in bold red. IIT, investigator initiated trial; US, United States. *estimated enrollment. EROA, effective regurgitation orifice area; LVEDV, left ventricular enddiastolic volume; LV-EF, left ventricular ejection fraction; MR, mitral regurgitation.

OMT group (29.1% vs. 46.1%, HR 0.62 [0.46–0.82], $p < 0.001$). How can one understand these serious outcome differences between the two trials? One explanation is the relevant differences in MR grade and left ventricular dimensions at inclusion. Simply, COAPT included patients with more severe MR and less dilated ventricles [9] (see Table 1, key differences in bold red). According to a subgroup analysis from Stone et al. presented at TCT 2018 the patient cohort with EROA ≤30 mm^2 and LVEDVI >96 ml/m^2 did not profit in terms of the primary endpoint which constitutes a subgroup which is more or less "MITRA-FR" like. As shown in COAPT TMVR might be able to stabilize the left ventricular and valvular disease. While the 6 minute walking distance (MWD) declines by 60% in the medical treatment group at 12 months, the 6 MWD in the interventional group remains stable (−2.2%). Moreover LVEDV increased by 17% in the medical treatment group while it remains stable in the interventional group (−3.7%) [9].

Maybe the results of A Clinical Evaluation of the Safety and Effectiveness of the MitraClip System in the Treatment of Clinically Significant Functional Mitral Regurgitation 2 trial (RESHAPE-HF2, Table 1) will serve as a referee in this issue. The primary endpoint will be cardiovascular mortality at 24 months but results will not be available before September 2019 according to ClinicalTrials.gov (Identifier: NCT02444338).

It becomes more and more clear that patient selection – after a strict guideline directed medical therapy on highest tolerable doses – is needed and the results in this issue of the *International Journal of Cardiology* could help to do so.

Conflicts of interest

M.O. has no conflict of interest. J.H. received speaker honoraria from Abbott Vascular and Edwards LifeSciences.

References

[1] P. Ponikowski, A.A. Voors, S.D. Anker, H. Bueno, J.G. Cleland, A.J. Coats, et al., 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC, Eur. Heart J. 37 (2016) 2129–2200.
[2] D. Goldstein, A.C. Gelijns, A.J. Moskowitz, Surgery for severe ischemic mitral regurgitation, N. Engl. J. Med. 374 (2016) 1992–1993.
[3] H. Baumgartner, V. Falk, J.J. Bax, M. De Bonis, C. Hamm, P.J. Holm, et al., 2017 ESC/EACTS guidelines for the management of valvular heart disease, Eur. Heart J. 38 (2017) 2739–2791.
[4] G. Gallasso, Predictors of outcome in heart failure patients with severe functional mitral regurgitation undergoing MitraClip treatment, Int. J. Cardiol. (2018).
[5] A. Jabs, R.S. von Bardeleben, P. Boekstegers, M. Puls, E. Lubos, R. Bekeredjian, et al., Effects of atrial fibrillation and heart rate on percutaneous mitral valve repair with MitraClip: results from the TRAnscatheter Mitral valve Interventions (TRAMI) registry, EuroIntervention 12 (2017) 1697–1705.
[6] C. Godino, A. Scotti, M. Taramasso, M. Adamo, M. Russo, M. Chiarito, et al., Two-year cardiac mortality after MitraClip treatment of functional mitral regurgitation in ischemic and non-ischemic dilated cardiomyopathy, Int. J. Cardiol. 269 (2018) 33–39.
[7] J.F. Obadia, D. Messika-Zeitoun, G. Leurent, B. Iung, G. Bonnet, N. Piriou, et al., Percutaneous repair or medical treatment for secondary mitral regurgitation, N. Engl. J. Med. 379 (2018 Aug 27) 2297–2306.
[8] G.W. Stone, J. Lindenfeld, W.T. Abraham, S. Kar, D.S. Lim, J.M. Mishell, et al., Transcatheter mitral-valve repair in patients with heart failure, N. Engl. J. Med. 379 (2018 Sep 23) 2307–2318.
[9] G. Stone, COAPT: a randomized trial of transcatheter mitral valve leaflet approximation in patients with heart failure and secondary mitral regurgitation, Congress Presentation TCT 2018, 2018.