Editorial Commentary

Transcatheter edge-to-edge mitral valve repair in functional mitral regurgitation: patient selection according to MITRA-FR and COAPT

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Functional mitral regurgitation (MR) is frequent in patients with a diseased left ventricle (1) and contributes to worse prognosis (2,3). Pharmacotherapy and—if indicated—cardiac resynchronization therapy according to current guidelines (4) build the basis of treatment in such patients. The third column of therapy might evolve as transcatheter edge-to-edge mitral valve repair (TMVR). Up-to date over 90,000 patients with severe symptomatic MR were treated with the most widely used device MitraClip© (Abbott, Santa Clara, CA, USA) applying the edge-to-edge repair technique according to Alfieri´s stich with an extremely high safety profile even in patients with low left ventricular ejection fraction (5).

The first randomized Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation (MITRA-FR) was published in December 2018 (6). The number of randomized patients was 304. The results were negative and very disappointing. The combined primary endpoint of rehospitalization for heart failure and all-cause death at 1 year was 54.6% in the intervention group and 51.3% in the control group (P=0.53). The rate of death from any cause was 24.3% in the intervention group and 22.4% in the control group.

In the second randomized Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation trial (COAPT, 614 randomized patients) the primary endpoint hospitalizations due to heart failure within 24 months was significantly lower in the TMVR group (35.8%) compared to the control group receiving only optimal medical therapy (67.9%, P<0.001) (7). In addition, Stone *et al.* presented a significant reduced all-cause mortality in the TMVR group compared to the medical group at 24 months (29.1% *vs.* 46.1%, P<0.001).

Why these discrepancies?

It was in 2001 when Grigioni *et al.* published their trial on long-term outcome of patients after myocardial infarction in the presence or absence of ischemic functional MR (8). The authors showed a poor outcome of only 38% 5-year survival in patients with MR compared to a favourable 61% 5-year survival in the absence of MR (P<0.001). What they also showed was that an effective regurgitant orifice area (EROA) ≥20 mm² was an independent predictor of 5-year mortality [2.23 (1.31–3.79), P=0.003]. Although this was a relatively small trial investigating outcome in 194 patients with ischemic MR the European Society of Cardiology (ESC) guidelines on valvular heart disease (9) adopt this finding in classifying a functional MR as severe when an EROA ≥20 mm² is detected in echocardiography whereas American guidelines did not. This is important to understand why both trials use different cut-off values for

EROA in MR classification.

Two key aspects regarding mitral regurgitation and left ventricular dimension

In MITRA-FR—since it is a European trial—the inclusion cut-off for EROA of MR was above 20 mm² according to European guidelines (9) whereas in COAPT the cut-off started at 30 mm² which lead to an accumulation of patients with less severe MR in MITRA-FR (52% with EROA <30 mm² and only 16% with EROA >40 mm²) compared to COAPT (only 14% with EROA <30 mm² and 41% with EROA >40 mm²) (10). Regarding left ventricular ejection fraction there was no difference between both trials but left ventricular dimensions were different. MITRA-FR patients presented with already more dilated ventricles at inclusion compared to COAPT patients (left ventricular end diastolic volume index (LVEDVI), 135 mL/m² in MITRA-FR *vs.* 101 mL/m² in COAPT). As a direct consequence COAPT accumulates patients with more severe MR and smaller ventricles (10) compared to MITRA-FR. This difference is in accordance with a sub-analysis from COAPT by Stone *et al.* (presented at Trans-Catheter-Therapeutics 2018) showing no difference in terms of the primary endpoint in patients with EROA ≤30 mm² and LVEDVI >96 mL/m² which constitutes a subgroup which is more "MITRA-FR" like (10).

Key aspects regarding patient selection

The ratio between screened patients and randomized patients was much lower in MITRA-FR than in COAPT illustrated by the fact that out of 15 patients screened approximately 10 were randomized in MITRA-FR compared to only 6 in COAPT. Furthermore, MITRA-FR had less strict inclusion criteria than COAPT. Patients—constituting a subgroup with a naturally very restricted life expectancy—with heart failure stage D according to American College of Cardiology/American Heart Association guidelines (11) [non-ambulatory New York Heart Association (NYHA) Functional Class IV], a left ventricular end-systolic diameter above 70 mm, a right-sided congestive heart failure with moderate or severe right ventricular dysfunction, an estimated pulmonary artery pressure in excess of 70 mmHg, a chronic obstructive pulmonary disease with home oxygen therapy or chronic outpatient oral steroid use were excluded from COAPT but could be theoretically included in MITRA-FR.

Safety and efficacy issues

MITRA-FR had a higher complication rate and lower success rate than COAPT. MITRA-FR reported 14.6% device related complications whereas COAPT did only 8.5% when adjusted to MITRA-FR definition of complications (10). In the interventional arm, the number of patients without clip implantation (9.2% *vs.* 5%) and the number of patients with remaining moderate-to-severe and severe MR was higher in MITRA-FR compared to COAPT at discharge (8% *vs.* 5%) as well as 1 year (17% *vs.* 5.2%).

Number needed to treat

Of course, there is no number needed to treat (NNT) in MITRA-FR due to negative results. The NNT of COAPT to save one life within 24 months is 5.9. Compared to previous studies which showed a survival benefit of heart failure therapy, this is very efficient. For instance, in the multicenter, randomized trial comparing the efficacy and safety of angiotensin receptor-neprilysin inhibitor Sacubitril/Valsartan versus Enalapril, 36 patients need to be treated over 27 months to save one life (12).

Proof of concept—treating functional MR improves outcome and functional capacity in COAPT

The lesson learned from COAPT is that TMVR might be able to decelerate left ventricular disease progression and improve prognosis. In contrast to the optimal medical group where left ventricular dimensions increased by 17%—the left ventricular end-diastolic volume even declined in the TMVR group (–3.7%). The same observation was made on functional capacity showing a 60% decrease in 6-minute walking distance in the optimal medical treatment group versus a solidification in the TMVR group (–2.2%) at 1 year.

To summarize both trials provide physicians with complementary knowledge for patient selection demonstrating that more MR and less left ventricular dilation is necessary to benefit from TMVR when guideline directed optimal medical treatment on highest tolerable dosis is not relieving symptoms anymore. The ongoing RESHAPE-HF2 trial (Clinical Evaluation of the Safety and

Effectiveness of the MitraClip System in the Treatment of Clinically Significant Functional Mitral Regurgitation 2) will provide further information on optimal patient selection assessing a primary endpoint of cardiovascular mortality at 24 month between patients treated with TMVR versus optimal medical therapy in the future (ClinicalTrials.gov Identifier: NCT02444338, last update January 2019).

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Footnote

Conflicts of Interest: M Orban has received speaker honoraria from SedanaMedical and AstraZeneca. J Hausleiter received speaker honoraria from Abbott Vascular and Edwards LifeSciences. Another author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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