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Should MitraClip also be used in less severe functional mitral regurgitation? The RESHAPE-HF2 study

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Transcatheter edge-to-edge repair (TEER) is currently indicated in symptomatic patients with severe functional mitral regurgitation (MR) who are not eligible for surgery and who have a high likelihood of responding to treatment. This recommendation is based on two randomized trials suggesting that the benefits of TEER may be limited to patients with severe MR, defined by an effective regurgitant orifice area (EROA) $\geq$0.40 cm^2, and a non-excessively remodelled left ventricle. The randomized RESHAPE-HF2 study recently showed that compared to medical therapy alone, treatment with TEER by MitraClip in patients with symptomatic heart failure and less severe functional MR, with lower EROA (mean 0.23 cm^2), is associated with a significant reduction in hospitalizations for heart failure, and an improvement in symptoms and quality of life, without a clear benefit on mortality. However, within the cohort of patients with less severe MR enrolled in the RESHAPE-HF2 study, the benefits of MitraClip compared to medical therapy alone seem more significant in selected patients with characteristics associated with a higher risk of heart failure exacerbation, suggesting the importance of careful selection of patients with symptomatic heart failure and MR who could benefit from TEER.

Treatment of functional mitral regurgitation

Functional mitral regurgitation (MR) is a frequent finding in patients with left ventricular systolic dysfunction and is associated with worsening symptoms and prognosis of heart failure.[1] Management of symptomatic patients with heart failure and functional MR includes optimization of guideline-recommended medical therapy and, if indicated, cardiac resynchronization therapy.[2] After this first-line approach, surgical or transcatheter treatment is recommended only in patients with severe functional MR who remain symptomatic despite optimal medical therapy, and the indication for such invasive treatment must be established by the Heart Team.[3] According to European guidelines,[3] transcatheter edge-to-edge repair (TEER) of the mitral valve should be considered in symptomatic patients with severe functional MR who are not eligible for surgery and meet criteria associated with a high probability of responding to treatment (Class IIB). This latter recommendation is based on two randomized clinical trials, MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) and COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation), which showed conflicting results on the efficacy of TEER with the MitraClip system compared to optimal medical therapy alone in patients with symptomatic heart failure and severe functional MR.[4-7] The MITRA-FR trial enrolled 304 patients with heart failure and a left ventricular ejection fraction (LVEF) of 15–40%, symptomatic in NYHA (New York Heart Association) Class II–IV and with severe MR defined by an EROA (effective regurgitant orifice area) >20 mm^2 and a regurgitant volume >30 mL. This study, over 24 months, did not show any benefit of MitraClip compared to optimal medical therapy alone either in terms of

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Table 1 Results of the three co-primary endpoints of the REHAPE-HF2 trial

Endpoint	TEER + optimal medical therapy	Optimal medical therapy	Rate ratio/mean difference (95% CI)
Hospitalization for heart failure or cardiovascular death during 24 months, incidence per 100 patient-years	37.0	58.9	Rate ratio 0.64 (0.48–0.85)
Hospitalization for heart failure during 24 months, incidence per 100 patient-years	26.9	46.6	Rate ratio 0.59 (0.42–0.82)
Mean change in the KCCQ-OS score from baseline to 12 months	+21.6 punti	+8 punti	Differenza media 10.9 punti (6.8–15)

TEER, transcatheter edge-to-edge repair; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary.

mortality and hospitalizations or in terms of improvement of symptoms and quality of life.[4,5]

In contrast, the COAPT trial enrolled 614 patients with the following inclusion criteria: moderate-to-severe MR (3+), defined as an EROA between 0.30 and 0.39 cm^2, or severe MR (4+), defined as an EROA $\geq$0.40 cm^2; NYHA Class II–IV; and LVEF 20–50%. In this study, patients who underwent TEER with MitraClip showed a significant reduction in 24-month hospitalizations for heart failure and all-cause mortality compared with the group treated with medical therapy alone. The divergence in results between those two studies has been attributed to differences in study design, use of medical therapy, procedural factors, and, most importantly, to the severity degree of MR and the extent of ventricular dysfunction of included patients. Indeed, based on the American definitions of severe MR (EROA $\geq$0.40 cm^2), patients enrolled in the COAPT showed on average a greater severity of MR, and a lesser left ventricular dilation compared to those included in the MITRA-FR trial, in which severe MR was defined as an EROA $\geq$0.20 cm^2, according to the European criteria.[8,9] These observations suggested the importance of an accurate selection of the population that could benefit from TEER and contributed to support the idea that treatment with MitraClip should be considered in selected patients with severe MR who fulfil as much as possible the COAPT inclusion criteria. However, it remains undetermined whether the positive effects of MitraClip shown in the COAPT study can be replicated in other settings, and the selection of the population with functional MR who could benefit most from TEER is still a matter of debate. The randomized RESHAPE-HF2 (Randomized Investigation of the MitraClip Device in Heart Failure: Second Trial in Patients with Clinically Significant Functional Mitral Regurgitation) trial recently provided further evidence on the clinical impact of the MitraClip compared to medical therapy alone in patients with symptomatic heart failure and moderate-severe or severe MR.[10]

RESHAPE-HF2: design and results

RESHAPE-HF2 is an investigator-initiated clinical trial including 505 patients with heart failure and functional MR enrolled in 30 centres in 9 European countries and randomized (1:1) to receive MitraClip or optimal medical therapy alone. The study included patients with moderate-severe or severe (EROA $\geq$20 mm^2) functional MR who were not eligible for surgery, with an LVEF 15–40%, in NYHA Class II–IV despite optimized medical therapy, and who have had at least one hospitalization for heart failure in the previous 12 months or an increase in atrial natriuretic peptides in the 90 days before randomization.

The study population had a median LVEF of 31% [interquartile range (IQR) 25–37%], a median left ventricular end-diastolic volume of 205 mL (IQR 157–250), a median EROA of 0.23 cm^2 (IQR 0.20–0.29), and a median regurgitant volume of 36 mL (IQR 29–43). The MR was classified as severe of grade 4+ in 44% of patients. A total of 65.9% of enrolled patients had at least one hospitalization for heart failure in the previous 12 months, and 75% were in NYHA Class III/IV. Finally, the median KCCQ-OS (Kansas City Cardiomyopathy Questionnaire-Overall Summary) score was 43 points.

The three co-primary endpoints of the study are shown in *Table 1*. Treatment with MitraClip compared with optimal medical therapy alone was associated with a significant 36% relative reduction in the composite of cardiovascular mortality or heart failure hospitalization through 24 months, which was driven predominantly by a lower incidence of hospitalizations. There were no significant differences in the cumulative incidence of cardiovascular mortality at 24 months [17.8% vs. 20.4%; hazard ratio 0.84, 95% confidence interval (CI) 0.55–1.28, $P = 0.43$]. Furthermore, the annualized incidence (number of events/total number of patients-years) of all-cause mortality was not significantly different between the two groups (17% vs. 18.6%; hazard ratio 0.90, 95% CI 0.71–1.13, $P = 0.37$).

Patients undergoing TEER compared to those treated with medical therapy alone reported a significant improvement in quality of life, with an increase in the mean KCCQ-OS score. Functional capacity also improved in the MitraClip group, within which, after 12 months, a greater proportion of patients in NYHA Class I and II (74.5% vs. 58.5%, $P < 0.001$) and a higher mean change in the distance covered in the 6-min walk test (34.0 ± 105.9 m vs. 5.1 ± 97.6 m, $P = 0.05$) were observed compared to the group assigned to medical therapy alone. Finally, at 12 months, an MR with a severity grade $\leq$2 was observed in 90.4% of patients treated with MitraClip compared to 36.1% of those in the medical therapy group. It is important to note that out of 43 patients in the medical therapy group in whom an MR with a severity grade $\leq$2 was observed at 12 months, 15 of them underwent treatment with MitraClip.

RESHAPE-HF2: analysis and interpretation of results

In the RESHAPE-HF2 trial, MitraClip treatment of functional MR compared to medical therapy alone in patients with symptomatic heart failure showed a reduction in hospitalizations for heart failure and an improvement in symptoms and quality of life. However, these positive effects were not associated with a benefit on mortality. The impact of MitraClip on outcomes observed in the RESHAPE-HF2 study compared to other trials is discussed below.

Impact of MitraClip on hospitalizations

The RESHAPE-HF2 trial showed that MitraClip compared to medical therapy alone significantly reduced hospitalizations for heart failure and for cardiovascular causes but had no significant impact on all-cause or fatal hospitalizations.[11] However, TEER reduced the number of days of hospitalization for heart failure (1067 vs. 1776 days), compared to the control group.

The significant reduction in hospitalizations for heart failure associated with MitraClip is consistent with what was observed in the COAPT study, with the novelty that the RESHAPE-HF2 study extends this benefit of MitraClip to a population with MR of lower severity than that shown by patients in the COAPT trial. Indeed, at baseline, the mean EROA was 0.23 cm^2 in RESHAPE-HF2 vs. 0.41 cm^2 in the COAPT study, and only 14% of patients in RESHAPE-HF2 had an EROA >0.40 cm^2 and 23% had an EROA <0.20 cm^2. However, in RESHAPE-HF2 the reduction in heart failure hospitalizations was more evident and significant in the subgroups that at the time of inclusion in the study had an NYHA Class III/IV, or had an ejection fraction <30%, or had a heart failure hospitalization in the previous 12 months.[11] About the latter aspect, the subgroup analysis showed that in patients with no history of hospitalization in the year before inclusion in the study, the effect of MitraClip on hospitalizations for heart failure was neutral (26.8% vs. 26.4%; rate ratio 1.01, 95% CI 0.54–1.91).[11] These data together suggest that in the RESHAPE-HF2 study the benefits of MitraClip in patients with less severe MR are more evident in patients at higher risk of heart failure exacerbation identified mainly by factors such as lower LVEF, greater severity of symptoms, and previous history of hospitalization for heart failure. Therefore, the identification of patients with characteristics associated with a high risk of heart failure exacerbation could be crucial to optimize the efficacy of TEER in patients with moderate-severe functional MR. Indeed, the RESHAPE-HF2 study showed that the reduction in heart failure hospitalizations with the MitraClip compared to medical therapy alone is more evident and significant in patients with severe MR of grade 4+ (22.7% vs. 56%; rate ratio 0.41, 95% CI 0.25–0.67), compared to those with moderate-severe MR of grade 3+ (30% vs. 39.7%; rate ratio 0.78, 95% CI 0.50–1.21), who could benefit from the MitraClip if additional risk factors for heart failure exacerbation are present.

The results of the RESHAPE-HF2 and COAPT trials differ from those of the MITRA-FR trial, which did not show a benefit on hospitalizations with MitraClip. These conflicting results could be explained by the fact that patients enrolled in the MITRA-FR, compared to those of the COAPT and RESHAPE-HF2 studies, had greater ventricular dilation (mean left ventricular end-diastolic volume 250 vs. 193 vs. 211 mL, respectively), in which the significant displacement of the subvalvular apparatus contributes more to the severity of MR, thus potentially limiting the effect of a leaflet-targeted treatment such as that offered by TEER.

Finally, the potential benefits of the MitraClip suggested by the RESHAPE-HF2 study must be interpreted in consideration that hospitalization by itself is an endpoint subject to possible bias resulting from the fact that physicians were aware of the assigned treatment. However, the magnitude of the 41% reduction in heart failure hospitalizations with MitraClip, together with the difference in mean days of hospitalization between the two groups, suggests that the influence on results of a possible different approach by the investigators depending on the treatment arm could be reasonably limited. Another potential influence on results to be considered is that due to the restricted use of the recommended four pillars of medical therapy.[2] In the RESHAPE-HF2 trial, SGLT2 inhibitors or angiotensin receptor neprilysin inhibitors were used at baseline in only ~9% and 13% of patients, respectively. Therefore, even with this additional study, the relative efficacy of MitraClip in a more contemporary setting with more frequent use of guideline-directed medical therapy remains undetermined.

Impact of MitraClip on mortality

In contrast to the results of the COAPT trial, in the RESHAPE-HF2 study, there were no significant differences in mortality between patients undergoing TEER and those who received medical therapy alone. This divergence could be due to differences in the selection of populations enrolled in the two studies. The COAPT study enrolled patients who on average had advanced MR, not proportionate to the relatively moderate left ventricular dilation.[12] Therefore, in the COAPT population, MR was the main factor responsible for heart failure. Therefore, TEER, by correcting the severe MR, allowed to effectively eliminate a significant load on the left ventricle that was of such extent as to worsen ventricular remodelling, thus leading to a significant impact on prognosis. On the contrary, the RESHAPE-HF2 study included patients with MR of less severity or even of moderate grade in a ventricle without excessive dilations on average, which may not have an unfavourable impact on ventricular remodelling and consequently may not be sufficient to modify prognosis during the same follow-up time. This hypothesis is also supported by the fact that 2-year mortality within the control arm assigned to medical therapy was higher in the COAPT study (46.1%) than that observed in RESHAPE-HF2 (29.6%). However, this notable difference could also be due to a more general low clinical risk profile of RESHAPE-HF2 patients or to the greater use of different heart failure drugs in the latter study. Indeed, the use of mineralocorticoid receptor antagonists and angiotensin receptor neprilysin inhibitors was more frequent in the RESHAPE-HF2 trial than in the COAPT trial, which, as demonstrated in several studies, may have caused a greater reduction in MR, thus attenuating the additional benefit of TEER over medical therapy on prognosis.[13] Furthermore, enrolment in RESHAPE-HF2 took

more than 8 years during which therapies changed and operators became more experienced. It remains unknown how the change in medications after enrolment may have influenced the results in RESHAPE-HF2.

The lack of benefit of the MitraClip on mortality observed in the RESHAPE-HF2 trial is consistent with that reported in the MITRA-FR trial. However, in the latter trial, the marked ventricular dilation observed in enrolled patients likely represented the determining factor in heart failure, making the patients less susceptible to the benefits of MR treatment. Therefore, the current body of evidence suggests that MitraClip would not add a mortality benefit in patients with an advanced left ventricular remodelling or in those with less severe MR treated with more robust medical therapy.

Impact of MitraClip on quality of life

An important aspect of the RESHAPE-HF2 trial is the significant improvement in quality of life and functional capacity reported by patients treated with MitraClip compared to those treated with medical therapy alone. This finding is consistent with what was observed in the COAPT trial. However, in RESHAPE-HF2 compared to the COAPT trial, enrolled patients were more commonly in NYHA Class III/IV and had a lower KCCQ-OS score indicating a worse quality of life. Greater impairment in quality of life may explain the benefits on functional capacity achieved with MitraClip in the RESHAPE-HF trial despite lower MR severity compared to the COAPT trial.

However, functional capacity endpoints may also have been influenced by awareness of the treatment received. Furthermore, the impact of MitraClip on symptoms and quality of life in the context of more robust use of currently recommended heart failure therapy remains not established.

Conclusions

The RESHAPE-HF2 study suggested that treatment with TEER could be extended to selected patients with less severe functional MR, but still with an EROA >0.20 cm^2, to reduce hospitalizations for heart failure and improve symptoms and quality of life. Patients with less severe MR benefiting from TEER maybe those at higher risk of heart failure exacerbation or with a relevant impairment of quality of life despite medical therapy at the maximum tolerated dose. These data are important considering that patients treated in clinical practice frequently have moderate-severe MR.[14,15] However, further data are needed to confirm trial results in the context of a more robust use of guideline-directed medical therapy. Furthermore, the extension of MitraClip to a cohort with moderate functional MR defined by an EROA <0.20 cm^2 must await the results of a dedicated randomized study focusing on this low-risk population.

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Data availability

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Disclaimer

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