SHORT COMMUNICATION

Impact of improving severity of secondary mitral regurgitation on survival

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Abstract

Aims   Secondary mitral regurgitation (SMR) is frequent in patients with heart failure with reduced ejection fraction (HFrEF) and portends detrimental prognosis. Despite interventions addressing the mitral valve (MV) have been proven effective to improve survival, an important knowledge gap exists regarding the role of medical therapy (MT) in this context. Thus, we aimed at investigating the role of MT optimization in patients with SMR and HFrEF.

Methods and results   A total of 435 patients with SMR and HFrEF were retrospectively evaluated. Of those, 158 with severe SMR were finally included, with 63 (40%) managed with MT alone and 96 (60%) with MV intervention plus MT. Echocardiography was performed after 30 days of MT optimization or MV intervention. Responders were patients with a final mitral regurgitation (MR) grade of ≤2+. Survival data were gathered through the National Database Index and patient chart review. MR severity improved in 131 patients (100% MV intervention; 57% MT) but stayed the same or worsened in 27 patients. Responders and non-responders were similar for baseline characteristics. Overall, long-term survival of responders was significantly higher than non-responders [hazard ratio (HR) 0.55, 95% confidence interval (CI) (0.32–0.96), $P = 0.032$]. No difference in survival was observed when evaluated by intervention type in the overall population (MT alone, $n = 63$; MV intervention plus MT, $n = 95$) [HR 0.77, 95% CI (0.48–1.26), $P = 0.3$], nor within responder group (MT alone, $n = 36$; MV intervention plus MT, $n = 95$) [HR 1.03, 95% CI (0.56–1.89), $P = 0.94$].

Conclusions   MT reduces SMR severity in 57% of the patients with severe SMR. A final SMR grade of ≤2+ is linked to improved survival, independently of the type of treatment they receive.

Background

Any degree of secondary mitral regurgitation (SMR) is associated with a worse prognosis in patients with heart failure with reduced ejection fraction (HFrEF) compared with patients with no SMR.[1] Clinical trials of medical therapy (MT) with neurohormonal antagonists have reported improvement in SMR severity, although trials were focused on treatment of HFrEF rather than SMR.[2] In fact, data on the effectiveness of MT on SMR reduction and clinical outcomes are lacking. The COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial investigators did not keep a log of screen fails due to improved mitral regurgitation (MR) following MT, and in the MITRA-FR (Multicentre Randomized Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) study, optimization of MT was left to the physician decision and has not been published so far. To this extent, we have previously showed that MT effectively reduces SMR in roughly 57% of patients with SMR.[3]

Aims

This report is now focused on evaluating whether MT-induced SMR reduction is associated with improved survival compared with mitral valve (MV) intervention.

Methods

To address this question, we retrospectively studied 435 patients evaluated for possible MV intervention between April 2013 and February 2019.[3] Of these, 177 were excluded for MR severity < 3+; 100 were excluded for various reasons (lost to follow-up, incomplete echocardiographic data, cardiac resynchronization therapy, or advanced HF therapies). MR severity was adjudicated based on a multi-parametric approach, as recommended by current guidelines, which relied upon quantitative and qualitative data.[4] Thus, 159 patients were evaluated for possible MV intervention. Of these, 63 (40%) were managed with MT alone and 96 (60%) with MV intervention plus MT. As per guidelines, patients with persistent >3+ MR despite the use of stable maximal doses of guideline-directed medical therapy (GDMT) were considered eligible to MV intervention (Supporting Information,

Table S1). Echocardiography was performed after 30 days of MT or MV intervention. Survival data were gathered through the National Database Index (43 exact matches) and patient chart review (115 patients). The study was approved by the Baylor Institutional Review Board.

Patients with a final MR grade of ≤2+ after 30 days of MT or MV intervention plus MT were considered responders. Long-term survival of responders was compared with non-responders in both MT and MV intervention plus MT groups. Continuous variables were summarized as mean ± SD or as median and interquartile range (IQR) as appropriate and were compared using Student's *t*-test or the Kruskal–Wallis test. Categorical variables were compared using χ^2 test. P-value of <0.05 was considered statistically significant. Detailed statistical method has been previously described.[3] Cox proportional hazard analysis was performed to evaluate the association of effective regurgitant orifice area and the left ventricular end-diastolic volume (EROA/LVEDV) with survival.

Results

MR severity improved in all MV intervention patients (*n* = 95; 1 lost to follow-up) and in 36 MT patients for a total of 131

Table 1 Baseline characteristics of the study population

	Non-responders (*N* = 27)	Responders (*N* = 131)	Total (*N* = 158)	*P*-value
Age (median [IQR])	71 [61.5–76]	73 [65–79]	72.5 [64–79]	0.44
Female	8 (29.6%)	53 (40.5%)	61 (38.6%)	0.29
Diabetes	10 (37.0%)	64 (48.9%)	74 (46.8%)	0.26
BMI (mean ± SD)	28.29 ± 10.32	28.14 ± 6.55	28.16 ± 7.16	0.94
HTN	23 (85.2%)	113 (86.3%)	136 (86.1%)	0.88
HLD	20 (74.1%)	91 (69.5%)	111 (70.3%)	0.63
Previous MI	19 (70.4%)	70 (53.4%)	89 (56.3%)	0.11
Previous CABG	12 (44.4%)	44 (33.6%)	56 (35.4%)	0.28
Previous stroke or TIA	5 (18.5%)	22 (16.8%)	27 (17.1%)	0.83
PAD	8 (29.6%)	19 (14.5%)	27 (17.1%)	0.06
COPD	6 (22.2%)	30 (22.9%)	36 (22.8%)	0.94
Afib	15 (55.6%)	69 (52.7%)	84 (53.2%)	0.78
CKD	15 (55.6%)	61 (46.6%)	76 (48.1%)	0.39
MR grade				0.46
3	4 (20%)	19 (13.8%)	23 (14.6%)	
4	16 (80%)	119 (86.2%)	135 (85.4%)	
LVEF (%)				0.24
Mean ± SD	38.09 ± 15.06	41.8 ± 14.22	41.17 ± 14.38	
LVESV				0.05
Mean ± SD	119.74 ± 49.17	98.72 ± 49.48	102.31 ± 49.90	
LVEDV				**0.02**
Mean ± SD	194.20 ± 57.77	163.82 ± 61.92	169.01 ± 62.12	
EROA/LVEDV ratio				0.07
Mean ± SD	0.27 ± 0.37	0.20 ± 0.12	0.21 ± 0.19	
EROA				**<0.01**
Mean ± SD	0.40 ± 0.30	0.29 ± 0.17	0.31 ± 0.20	
Reg volume				**0.04**
Mean ± SD	57.86 ± 36.34	45.10 ± 26.52	47.29 ± 28.73	

Afib, atrial fibrillation; BMI, body mass index; CABG, coronary artery bypass graft; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; EROA, effective regurgitant orifice area; HLD, hyperlipidaemia; HTN, hypertension; IQR, interquartile range; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MI, myocardial infarction; MR, mitral regurgitation; PAD, peripheral arterial disease; TIA, transient ischaemic attack.
P-values in bold are significant at <0.05.

Figure 1 Kaplan–Meier curves for survival in patients with secondary mitral regurgitation and heart failure with reduced ejection fraction. (A) Survival difference by response (responders vs. non-responders). (B) Survival difference by treatment type. CI, confidence interval; HR, hazard ratio; MV, mitral valve.
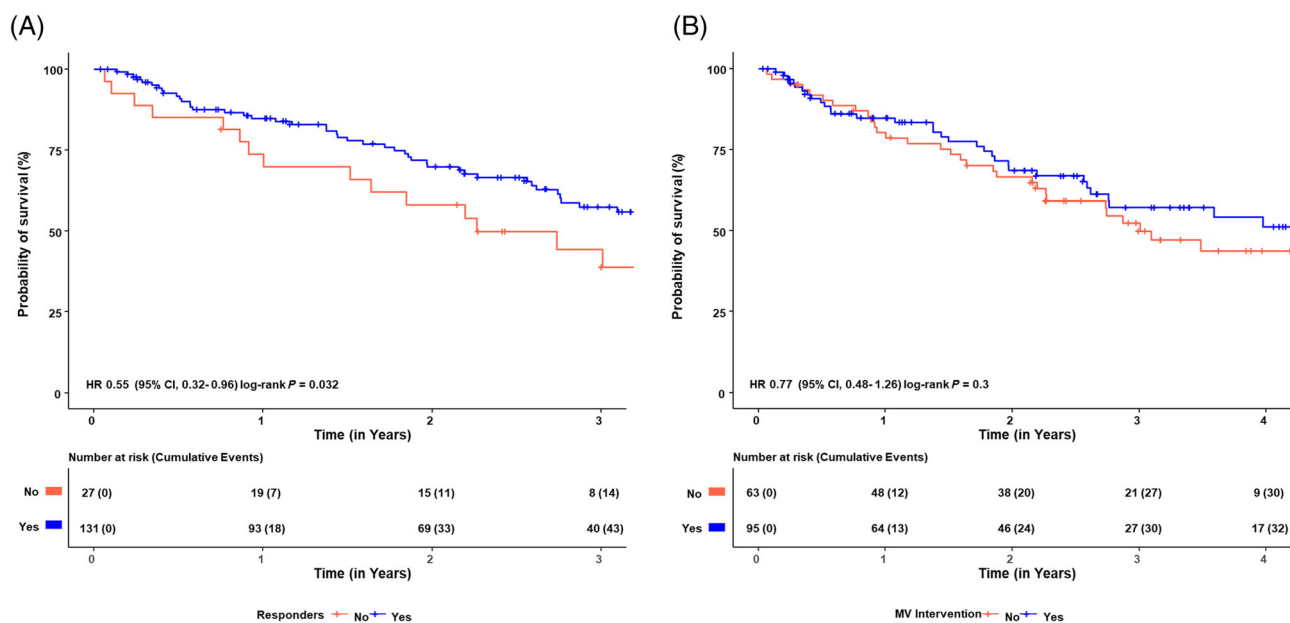
patients (responders) but stayed the same or worsened in 27 patients (non-responders, all within the MT alone group). The 27 patients with persistent 3–4+ MR after MT did not undergo MV intervention due to randomization to MT (*n* = 4), hospice (*n* = 14), anatomic exclusions to MV intervention with prohibitive risk for surgery (*n* = 6), or death (*n* = 3). Overall, median follow-up was 3.19 years [IQR (2.16–4.59)], without significant difference between groups. Responders and non-responders were similar for baseline characteristics (*Table 1*). Non-responders had larger left ventricular (LV) volumes [LVEDV: 194.20 ± 57.77 vs. 163.82 ± 61.92, *P* = 0.02; left ventricular end-systolic volume (LVESV): 119.7 ± 41.2 vs. 98.7 ± 49.5, *P* = 0.049] and larger EROA (0.40 ± 0.30 vs. 0.29 ± 0.17, *P* < 0.01). Baseline and study entry medication did not differ among groups, except for aldosterone antagonists, which were more often prescribed in the non-responder group (at baseline, 48.1% vs. 22.9%, *P* < 0.01; study entry, 48.1% vs. 24.4%, *P* = 0.01; Supporting Information, *Table S1*).

Overall, long-term survival of responders was significantly higher than non-responders [hazard ratio (HR) 0.55, 95% confidence interval (CI) (0.32–0.96), *P* = 0.032] (*Figure 1A*). Interestingly, no difference in survival was observed when evaluated by intervention type (MT alone, *n* = 63; MV intervention plus MT, *n* = 95) [HR 0.77, 95% CI (0.48–1.26), *P* = 0.3] (*Figure 1B*). Similarly, within responder group (MT alone, *n* = 36; MV intervention plus MT, *n* = 95), survival difference was not statistically significant [HR 1.03, 95% CI (0.56–1.89), *P* = 0.94]. No significant relation was found

between the EROA/LVEDV ratio and survival [HR 1.2, 95% CI (0.50–2.88), *P* = 0.68].

Conclusions

Despite the limitation of a retrospective registry with a relatively small population, the results of this study confirm that the final MR grade, rather than the way it was achieved, determines prognosis of patients with SMR and HFrEF. This is identical to a recent report from the COAPT trial.[5] Our data suggest a potential explanation for the discordant results of the two large, randomized trials of MV intervention vs. MT. In COAPT, MT was optimized prior to randomization, whereas in MITRA-FR, patients were randomized prior to optimization of MT. Our data indicate that severe SMR improves in many patients treated with MT including novel drugs and that this is associated with long-term survival similar to patients treated with MV intervention. Of note, we observed a low proportion of patients being on renin-angiotensin-aldosterone system (RAAS) (including sacubitril/valsartan), without significant difference between responders and non-responders. This is, however, somewhat in line with what has been previously described in the literature.[6] Non-responders were characterized by larger LV volumes and EROA; thus, possibly, a more advanced stage of the disease could explain their lack of response to GDMT as well as worse clinical outcomes. In our population, the baseline

EROA/LVEDV ratio (marker of proportionality/disproportionality) was not a predictor of survival (although it did predict 1+ MR after MT only) possibly due to the small population size. It remains challenging to predict which patients are likely to respond to MT alone. Recently, rapid initiation/titration of MT has been proposed.[6] Patients with severe SMR that persist after MT and otherwise meet COAPT entry criteria should be offered MV intervention as such patients have dramatic improvement in outcomes.

In conclusion, MT is effective in reducing MR grade in 57% of patients with severe SMR. Importantly, survival of SMR patients is not dictated by the type of treatment they receive but rather by its effectiveness in improving MR grade.

Conflicts of interest

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Medical therapy at baseline and study-entry of the study population.

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