ORIGINAL RESEARCH ARTICLE

Modifications of medical treatment and outcome after percutaneous correction of secondary mitral regurgitation

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Abstract

Aims   The optimization of guideline-directed medical therapy (GDMT) in reduced ejection fraction heart failure (HFrEF) is associated with improved survival and can reduce the severity of secondary mitral regurgitation (SMR). Highest tolerated doses should be achieved before percutaneous mitral valve repair (pMVR) and drugs titration further pursued after procedure. The degree of GDMT titration in patients with HFrEF and SMR treated with pMVR remains unexplored. We sought to evaluate the adherence to GDMT in HFrEF in patients undergoing pMVR and to explore the association between changes in GDMT post-pMVR and prognosis.

Methods and results   We included all the patients with HFrEF and SMR ≥ 3 + treated with pMVR between 2012 and 2019 and with available follow-up. GDMT, comprehensive of dosages, was systematically recorded. The study endpoint was a composite of death and heart transplantation. Among 133 patients successfully treated, 121 were included (67 ± 12 years old, 77% male patients). Treatment rates of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor neprilysin inhibitor (ACEIs/ARBs/ARNI), beta-blockers, and mineralcorticoid receptor antagonist at baseline and follow-up were 73% and 79%, 85% and 84%, 70% and 70%, respectively. At baseline, 33% and 32% of patients were using >50% of the target dose of ACEI/ARB/ARNI and beta-blockers. At follow-up (median time 4 months), 33% of patients unchanged, 34% uptitrated, and 33% of patients downtitrated GDMT. Downtitration of GDMT was independently associated with higher risk of death/heart transplantation (hazard ratio: 2.542, 95%confidence interval: 1.377–4.694, *P* = 0.003).

Conclusions   Guideline-directed medical therapy is frequently underdosed in HFrEF patients with SMR undergoing pMVR. Downtitration of medications after procedure is associated with poor prognosis.

Keywords   Reduced ejection fraction heart failure; Mitral regurgitation; Guideline-directed medical therapy; Percutaneous mitral valve repair

Introduction

In patients with heart failure (HF) and reduced ejection fraction (HFrEF), the progressive dilatation of the left ventricle may determine the geometric dislocation of the papillary muscles and mitral apparatus, impairing the coaptation of the mitral leaflets and resulting in secondary mitral regurgitation (SMR).[1] SMR increases the severity of volume overload and has been largely associated with worst symptoms, higher rate of HF-related hospitalizations, and worst survival.[2,3]

In recent years, percutaneous mitral valve repair (pMVR) has become available for the treatment of mitral regurgitation (MR)

in surgical high-risk patients.[4] Large registries attested the high rate of success and the safety of pMVR in patients with SMR, promoting an improvement in symptoms and quality of life after the reduction of SMR.[5–7] Two randomized trials recently reported the effects of pMVR for SMR in HFrEF patients with contrasting results.[8,9] In the Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients with Severe Secondary Mitral Regurgitation (MITRA-FR) trial, the combined risk of death or hospitalization for HF was not reduced by SMR correction.[8] Conversely, the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial demonstrated a reduction in all-cause mortality and in combined risk of death or hospitalization for HF with pMVR.[9] One of the likely explanations for these opposing results concerns the differences in medical therapy between the two studies.

Heart failure drugs may improve the severity of SMR in HFrEF,[10–12] and uptitration of HF medications should be further pursued after the procedure.[13] Complete optimization of guideline-directed medical therapy (GDMT) before pMVR was required for eligibility in both trials.[8,9] However, optimization criteria were more stringent in the COAPT and adjustments during follow-up were also different in the two studies.[8,9] Despite these hypotheses, the management of HF medications following pMVR of SMR has not been directly explored in the setting of randomized clinical trials and observational data from registries are lacking. In the present study, we therefore sought to assess the adherence to currently recommended GDMT for HF at the time of pMVR and the changes in medication regimens after pMVR in a cohort of patients with HFrEF and severe SMR undergoing pMVR.

Furthermore, the association between modifications in GDMT after pMVR and prognosis was also investigated.

Methods

Study population

From April 2012 to April 2019, all the patients with SMR and HFrEF undergoing successful (final MR grade ≤ 2+) pMVR with the MitraClip System (Abbott Vascular, Santa Clara, CA) in two third-level Italian referral centres for HF (University Hospital of Trieste and University Hospital 'St. Orsola-Malpighi' of Bologna) were consecutively included in a prospective registry.

Patients were considered eligible for the procedure after Heart Team discussion, in the presence of high-grade SMR (≥3+), symptomatic HF [New York Heart Association (NYHA) class ≥2], and significant left ventricular (LV) dysfunction (ejection fraction <40%), refractory to currently recommended HF therapy, including cardiac resynchronization therapy if indicated. Before the procedure, patients underwent

complete clinical evaluation, laboratory tests, and transthoracic and transesophageal echocardiography in order to assess feasibility or rule out any contraindications. HF aetiology (ischaemic vs. non-ischaemic) was systematically determined based on previous clinical history (known coronary artery disease, previous revascularization, or myocardial infarction), and coronary angiography was repeated if progression of coronary artery disease was suspected. Success of the procedure was defined as the implantation of at least one clip and reduction of severity of SMR to grade 2+ or less.[14] After pMVR, patients underwent a periodical complete clinical and echocardiographic revaluation.

Demographic, clinical, echocardiographic, and procedural data were entered into a dedicated anonymous computerized database. Informed consent was obtained under the institutional review board policies of hospital administration. The study complied with the Declaration of Helsinki.

Echocardiographic analysis

Echocardiograms were recorded on digital media storage at the echocardiographic core laboratories of our institutions and analysed offline. SMR was graded by a multiparametric approach, based on transthoracic and transesophageal echocardiography, according to the current recommendations.[15] In particular, the vena contracta width was measured at the narrowest point of the regurgitant jet and the effective regurgitant orifice area was calculated from the proximal isovelocity surface area. The effective regurgitant orifice area assessment has been considered the preferred method for MR quantification. Cardiac chamber quantification and the evaluation of systolic function and diastolic function were performed according to international guidelines.[16,17]

Medical therapy

Guideline-directed medical therapy, comprehensive of dosages, was systematically recorded at the time of procedure and at follow-up and included angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptors blockers (ARBs)/angiotensin receptor neprilysin inhibitor (ARNI), evidence-based beta-blockers, and mineral receptor antagonists (MRAs). The percentage of the target dose of each individual drug (Supporting Information, *Table S1*[18]) was calculated, and patients were divided into groups according to prescribed dose: patients not receiving medication, patients treated with <25%, 25% to <50%, 50% to <75%, and 75% to 100% of the target dose. Downtitration of GDMT at follow-up was defined as drug discontinuation or dose reduction to lower quartiles, while uptitration was defined as drug starting or dose increased to higher quartiles. Finally, patients were divided into two groups: unchanged/uptitrated

GMDT included patients with unchanged or uptitrated ACEI/ARB/ARNI and/or beta-blockers; downtitrated GDMT included patients who downtitrated ACEI/ARB/ARNI and/or beta-blockers. Patients who uptitrated one class of drugs (ACEI/ARB/ARNI or beta-blockers) and downtitrated the other class were included in the unchanged/uptitrated GMDT group. Use and dosage of loop diuretics (expressed as furosemide equivalent) were also recorded.

Study endpoints

The primary study endpoint was a composite of death and heart transplantation. Follow-up ended on 31 June 2019 or at the time of the study endpoint.

Information regarding the endpoint was obtained from the patients or relatives, their physician, or the registers of death of the municipalities of residence.

Statistical analysis

Summary statistics of clinical and laboratory variables were expressed as mean ± standard deviation (for normally distributed continuous variables) or median and interquartile range (for non-normally distributed continuous variables) or counts and percentage (for nominal variables). Cross-sectional comparisons between groups were made by the ANOVA test on Gaussian-distributed continuous variables, using the Brown–Forsythe statistic when the assumption of equal variances did not hold, or the non-parametric median test when necessary. The χ^2 or Fisher's exact tests were calculated for discrete variables. Univariable Cox regression models were estimated to evaluate associations between demographic, clinical, echocardiographic, and therapeutic parameters assessed at first clinical post-procedural evaluation and the study endpoint. Therapeutic variables, inclusive of data on target doses, were specifically tested to evaluate their association with the study endpoints. Starting from the list of significant parameters at univariable analyses, a penalized multivariable Cox model was estimated to identify independent predictors of composite outcome of death and heart transplantation. Taking into account the low event rate, a combination of L1-lasso and L2-ridge penalties was applied; the optimal values of the penalties were determined using cross-validation.[19] Cumulative event-free survival estimates were plotted using the Kaplan–Meier technique. Differences between the survival curves were tested with the log–rank test. A *P* value <0.05 was considered to indicate statistical significance. IBM SPSS Statistics software (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp) was used for analysis and GraphPad Prism, Version 7 (GraphPad Software, La Jolla, CA, USA) for

illustrations. The R statistical package, library 'penalized' was used to fit the multivariable Cox model.

Results

During the study period, a total of 133 patients underwent successful pMVR. Among them, 121 had available clinical follow-up after procedure (median time at first post-pMVR evaluation 4 months, interquartile range: 2–6) and were included in the study. Twelve patients were excluded because they died before clinical follow-up (*n* = 2), had no information on GDMT (*n* = 3), or were lost to follow-up (*n* = 7). Procedural data and main characteristics of the study population at baseline and follow-up are summarized in *Table 1*. The mean age was 67 ± 12 years, 77% were male patients, median plasma B-type natriuretic peptide was 648 (354–1652) pg/mL, baseline mean LV ejection fraction (LVEF) was 30.8 ± 7.3% and baseline LV end-diastolic volume was 213.7 ± 68 mL, and all the patients had MR ≥ 3+. At follow-up, mean LVEF and mean LV end-diastolic volume were 28.5 ± 8.9% and 201.5 ± 72.5 mL, respectively, and 29% of patients had MR ≥ 3 + .

Medical therapy

At baseline, 88 (73%) and 103 (85%) patients used ACEI/ARB/ARNI and beta-blockers, respectively, while at follow-up, 95 (79%) patients used ACEI/ARB/ARNI and 102 (84%) patients used beta-blockers. Rate of MRA administration was 70% (*n* = 85) at baseline and 70% (*n* = 85) at follow-up. Mean dose of loop diuretics was 179 ± 136 and 159 ± 132 mg at baseline and follow-up, respectively, with 26% of patients who reduced and 38% who increased the diuretic dose at follow-up (*Table 1*).

Figure 1 shows the quartile distribution of target doses for ACEI/ARB/ARNI (upper panels) and beta-blockers (lower panels). At baseline, 12% (*n* = 14) were in the <25%, 28% (*n* = 34) were in the 25% to <50%, 21% (*n* = 25) were in the 50% to <75%, and 12% (*n* = 15) were in the 75% to <100% of target dose quartile of ACEI/ARB/ARNI, whereas at follow-up, 21% (*n* = 25) were in the <25%, 32% (*n* = 39) were in the 25% to <50%, 17% (*n* = 20) were in the 50% to <75%, and 9% (*n* = 11) were in the 75% to <100% of target dose quartile of ACEI/ARB/ARNI. Quartile distribution of beta-blockers administration at baseline was 17% (*n* = 21) of patients in the <25%, 36% (*n* = 43) in the 25% to <50%, 20% (*n* = 24) in the 50% to <75%, and 12% (*n* = 15) in the 75% to <100% of target dose quartile. At follow-up, 21% (*n* = 26) of patients were in the <25%, 37% (*n* = 45) were in the 25% to <50%, 16% (*n* = 19) were in the 50% to <75%, and 10% (*n* = 12) were in the 75% to <100% of target dose quartile of beta-blockers.

Table 1 Baseline and follow-up main demographic, clinical, echocardiographic, and therapeutic characteristics of the total study population

Population	Baseline (*n* = 121)	Follow-up (*n* = 121)
Age (years)	67 ± 12	67 ± 12
Male gender (%)	77	—
BMI (kg/m^2)	25.7 ± 4.3	—
Logistic Euroscore (%)	20 ± 16	—
N° CLIPS ≥ 2 (%)	65	—
COPD (%)	16	—
Diabetes (%)	34	—
Hypertension (%)	59	—
PAD (%)	26	—
IHD (%)	55	—
Previous HF hospitalization (%)	70	—
NYHA Class ≥3 (%)	90	31
NYHA class (%)		
I	1	8
II	9	61
III	68	25
IV	22	6
HR (bpm)	69 ± 13	72 ± 14
SBP (mmHg)	111 ± 17	110 ± 16
DBP (mmHg)	67 ± 8	66 ± 7
BNP (pg/mL)	648 (354–1652)	818 (345–1306)
GFR (mL/min/m^2)	50 (37–74)	48 (32–70)
GFR < 60 mL/min/m^2 (%)	65	61
Hb (g/dL)	11.9 ± 2	—
History of AF (%)	46	—
LVEDD (mm)	67 ± 12	66 ± 10
LVEDV (mL)	213.7 ± 68	201.5 ± 72.5
LVESV (mL)	149 ± 56	143 ± 63
LVEF (%)	30.8 ± 7.3	28.5 ± 8.9
LAA (cm^2)	36 ± 12	34.4 ± 9.7
PASP (mmHg)	49 ± 14	41 ± 13
RV dysfunction (%)	57	41
TR ≥ 2+ (%)	41	22
MR severity (%)		
1+ o 0	0	24
2+	0	47
3+	29	21
4+	71	8
Medical therapy/device		
ACEI/ARB/ARNI (%)	73	79
ACEI/ARB/ARNI quartile of target dose (%)		
<25%	12	21
25% to <50%	28	32
50% to <75%	21	17
75% to 100%	12	9
Beta-blockers (%)	85	84
Beta-blockers quartile of target dose (%)		
<25%	17	21
25% to <50%	36	37
50% to <75%	20	16
75% to 100%	12	10
MRA (%)	70	70
Loop diuretics (%)	100	100
Mean furosemide-equivalent dose (mg)	179 ± 136	159 ± 132
Reduced diuretic dose at follow-up (%)	—	26
Increased diuretic dose at follow-up (%)	—	38
No change in diuretic dose at follow-up (%)	—	36
ICD (%)	71	76
CRT (%)	39	40

ACEI, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor neprlisyn inhibitors; BMI, body mass index; BNP, B-type natriuretic peptide; bpm, beats per minute; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; GFR, glomerular filtration rate; Hb, haemoglobin; HF, heart failure; HR, heart rate; ICD, implantable cardioverter defibrillator; IHD, ischaemic heart disease; LAA, left atrial area; LVEDD, left ventricle end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; MRA mineral corticoid antagonists; NYHA, New York Heart Association; PAD, peripheral artery disease; PASP pulmonary artery systolic pressure; RV, right ventricle; SBP systolic blood pressure; TR, tricuspid regurgitation.

Figure 1 Use and dosing of ACEI/ARB/ARNI (upper panels) and betablockers (lower panels) at baseline (left panels) and follow-up (right panels) in the overall study cohort. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor.
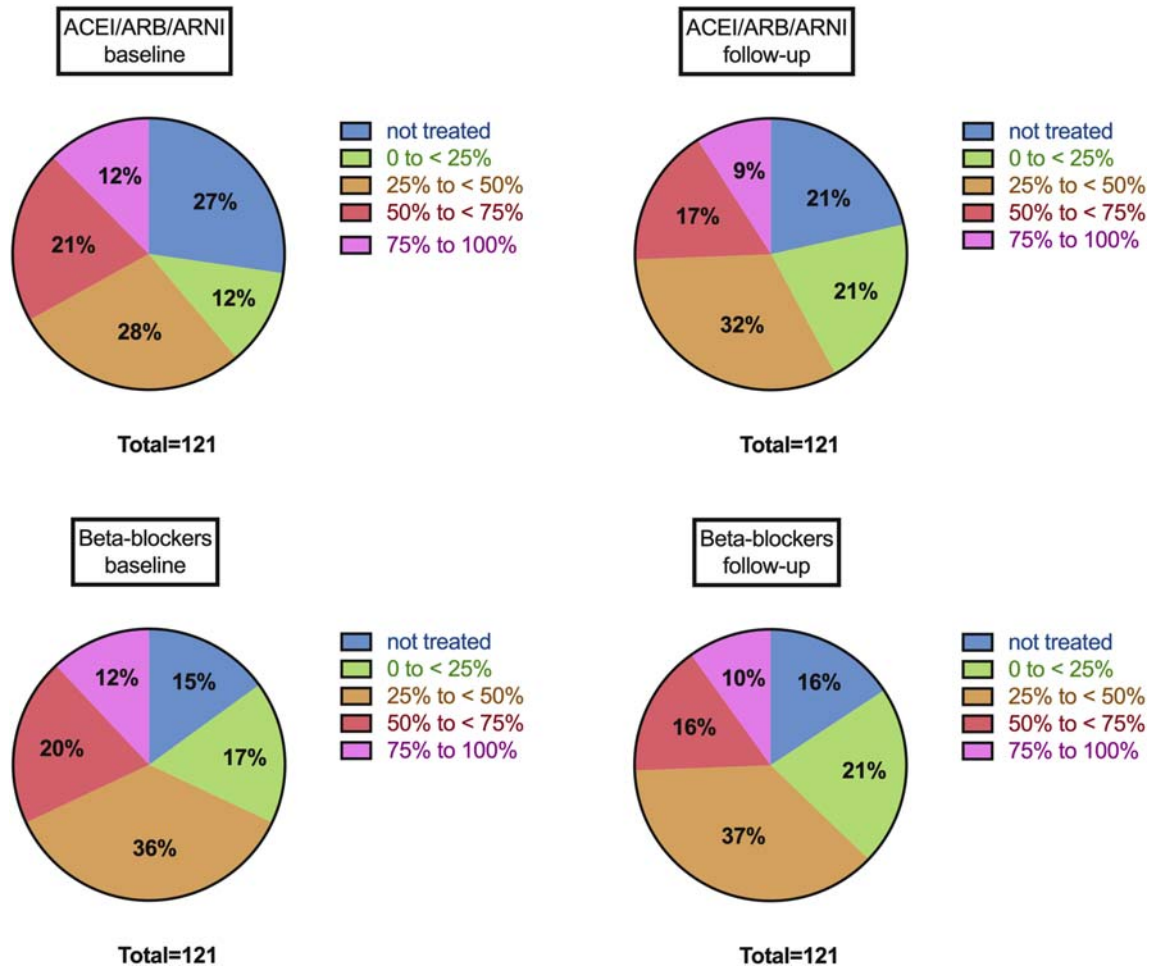
In total, 81 patients (67%) unchanged/uptitrated GDMT at follow-up (40 unchanged and 41 uptitrated GDMT, Supporting Information, *Table S2* for main characteristics), whereas 40 patients (33%) downtitrated GDMT. *Table 2* shows the main characteristics of the unchanged/uptitrated vs. downtitrated GDMT groups at baseline and follow-up. Noteworthy, at baseline, more patients in the downtitration group were at target dose of ACEI/ARB/ARNI as compared with patients with unchanged/uptitrated GDMT. As shown in *Table 2* and *Figure 2*, despite no differences in symptoms and MR severity at baseline, at follow-up, patients who downtitrated GDMT were more symptomatic (43% in NYHA class ≥3 vs. 25% in patients with unchanged/uptitrated GDMT, P = 0.049) and had larger LV end-systolic volume (162 ± 79 vs. 133 ± 51 mL, P = 0.040) and numerically higher recurrence of MR grade ≥ 3+ compared with patients with unchanged/uptitrated GMDT (40% vs. 23%, P = 0.078).

Association between changes in guideline-directed medical therapy and mortality/heart transplantation

During a median follow-up of 25 months (interquartile range: 9.5–40.5), the primary outcome occurred in 45 (37%) patients (38 died and 7 underwent heart transplantation). At Kaplan–Meier survival analysis, patients who downtitrated GDMT had significantly higher risk of death/heart transplantation as compared with patients with unchanged/uptitrated GMDT (*Figure 3*). No differences were observed between unchanged vs. uptitrated GDMT patients (P = 0.357, Supporting Information, *Figure S1*).

Univariate and multivariate analyses for death/heart transplantation are reported in *Table 3*. After adjustment for other significant covariates, including quartiles of target dose of ACEI/ARB/ARNI and beta-blockers, downtitration of GDMT

Table 2 Baseline and follow-up main demographic, clinical, echocardiographic, and therapeutic characteristics according to GDMT changes

	Baseline			Follow-up		
	GDMT downtitrated (*n* = 40, 33%)	GDMT uptitrated/ unchanged (*n* = 81, 67%)	*P* value	GDMT downtitrated (*n* = 40, 33%)	GDMT uptitrated/ unchanged (*n* = 81, 67%)	*P* value
Age (years)	65 ± 14	68 ± 11	0.166	65 ± 14	68 ± 11	0.170
Male gender (%)	78	77	0.907	—	—	—
BMI (kg/m^2)	25.3 ± 4.3	25.9 ± 4.3	0.459	—	—	—
Logistic Euroscore (%)	17 ± 16	21 ± 16	0.147	—	—	—
N° CLIPS ≥ 2 (%)	68	63	0.624	—	—	—
COPD (%)	18	15	0.703	—	—	—
Diabetes (%)	28	37	0.297	—	—	—
Hypertension (%)	48	64	0.060	—	—	—
PAD (%)	23	27	0.581	—	—	—
IHD (%)	48	59	0.221	—	—	—
Previous HF hospitalization (%)	70	70	0.967	—	—	—
NYHA class ≥3 (%)	85	93	0.189	**43**	**25**	**0.049**
NYHA class (%)						
I	0	0	0.480	5	9	0.483
II	15	7	0.112	52	66	0.140
III	58	74	0.065	32	21	0.189
IV	27	19	0.258	11	4	0.156
HR (bpm)	68.8 ± 14	68.8 ± 12.8	0.998	71 ± 14	72 ± 15	0.739
SBP (mmHg)	112 ± 15	11 ± 18	0.726	108 ± 19	110 ± 14	0.380
DBP (mmHg)	67 ± 8	67 ± 9	0.734	66 ± 8	67 ± 7	0.478
BNP (pg/mL)	1054 (489–1684)	528 (319–1510)	0.665	818 (341–1257)	638 (328–1596)	0.943
GFR (mL/min/m^2)	52 (40–78)	48 (33–70)	0.437	56 (37–73)	46 (30–68)	0.207
GFR < 60 mL/min/m^2 (%)	63	67	0.651	54	65	0.285
Hb (g/dL)	11.6 ± 2.5	12 ± 1.7	0.315	—	—	—
History of AF (%)	55	42	0.176	—	—	—
LVEDD (mm)	67 ± 14	67 ± 11	0.961	67.5 ± 10	65.2 ± 10	0.284
LVEDV (mL)	213.7 ± 74.2	213.7 ± 64.5	0.999	216 ± 89	195 ± 63	0.160
LVESV (mL)	150 ± 63	149 ± 53	0.883	**162 ± 79**	**133 ± 51**	**0.040**
LVEF (%)	30.7 ± 7.5	30.9 ± 7.3	0.922	26.7 ± 10.6	29.3 ± 7.9	0.152
LAA (cm^2)	34.3 ± 13	36.4 ± 11	0.514	34.7 ± 11	34.3 ± 9.3	0.881
PASP (mmHg)	49 ± 14.2	48 ± 12.5	0.749	42 ± 13.2	40.6 ± 12	0.450
RV dysfunction (%)	65	53	0.213	39	46	0.564
TR ≥ 2+ (%)	40	42	0.836	30	17	0.267
MR severity (%)						
1+	0	0	N.C.	20	27	0.470
2+	0	0	N.C.	40	50	0.331
3+	28	30	0.808	26	19	0.650
4+	72	70	0.808	14	4	0.058
Medical therapy/device						
Furosemide dose (mg)	195 ± 148	170 ± 129	0.361	157 ± 134	160 ± 130	0.899
Loop diuretics (%)	100	100	N.C	100	100	N.C
Reduced diuretic dose at follow-up (%)	—	—	—	24	27	0.680
Increased diuretic dose at follow-up (%)	—	—	—	42	37	0.551
No change in diuretic dose at follow-up (%)	—	—	—	34	36	0.821
Beta-blockers (%)	80	88	0.266	**73**	**90**	**0.013**
Beta-blockers quartile of target dose (%)						
<25%	20	12	0.266	**26**	**9**	**0.012**
25% to <50%	**5**	**24**	**0.012**	21	23	0.833
50% to <75%	35	36	0.931	37	39	0.803
75% to 100%	40	28	0.199	16	29	0.118
ACEI/ARB/ARNI (%)	83	68	0.090	73	83	0.192
ACEI/ARB/ARNI quartile of target dose (%)						
<25%	17	32	0.090	30	17	0.109
25% to <50%	5	15	0.112	25	19	0.407
50% to <75%	30	27	0.744	33	32	0.965
75% to 100%	**48**	**26**	**0.018**	**12**	**32**	**0.020**
MRA (%)	67	78	0.220	65	73	0.375
ICD (%)	73	70	0.808	80	74	0.473
CRT (%)	38	39	0.854	40	39	0.935

ACEI, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor neprlisyn inhibitors; BMI, body mass index; BNP, B-type natriuretic peptide; bpm, beats per minute; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; GDMT, guideline-directed medical therapy; GFR, glomerular filtration rate; Hb, haemoglobin; HF, heart failure; HR, heart rate; ICD, implantable cardioverter defibrillator; IHD, ischaemic heart disease; LAA, left atrial area; LVEDD, left ventricle end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; MRA mineral corticoid antagonists; NYHA, New York Heart Association; PAD, peripheral artery disease; PASP pulmonary artery systolic pressure; RV, right ventricle; SBP systolic blood pressure; TR, tricuspid regurgitation.
In bold are *P* values < 0.05.

Figure 2 Distribution of NYHA class (left panel) and MR severity (right panel) at baseline and follow-up in the unchanged/uptitrated GDMT group as compared with the downtitrated GDMT group. F-up, follow-up; GDMT, guideline-directed medical therapy; MR, mitral regurgitation; NYHA, New York Heart Association.
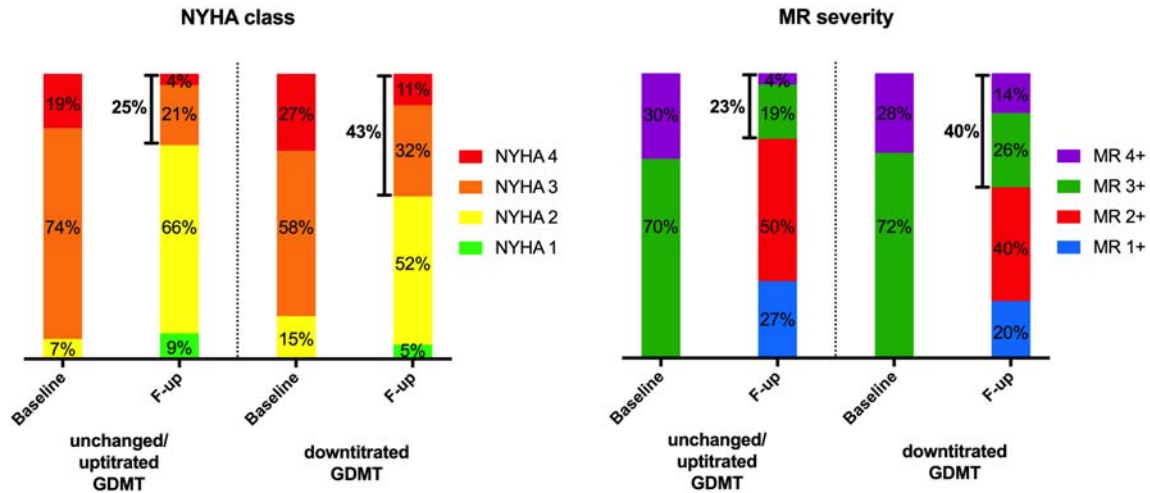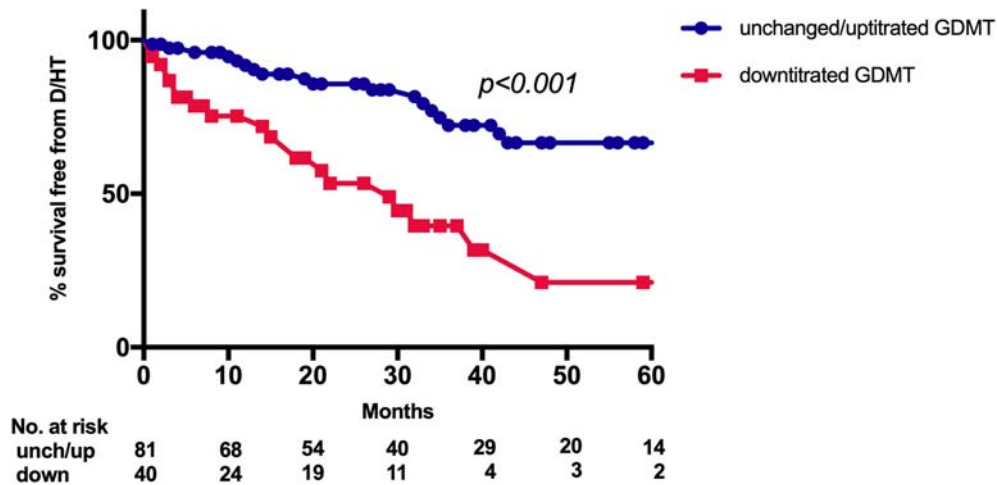

Figure 3 Kaplan–Meier curves showing the survival free from heart transplantation in patients with unchanged/uptitrated GDMT (blue line) vs. patients with downtitrated GDMT (red line). D/HT, death/heart transplantation; GDMT, guideline-directed medical therapy.

at follow-up remained significantly associated with higher risk of death/heart transplantation (hazard ratio: 2.542, 95% confidence interval: 1.377–4.694, $P = 0.003$) along with NYHA class (hazard ratio: 2.809, 95% confidence interval: 1.712–4.609, $P < 0.001$).

Discussion

The key findings of our study are that among patients with HFrEF and severe SMR treated with pMVR, optimization of GDMT before procedure was partial, with less than 50% of

the overall population using >50% of the target dose of ACEI/ARB/ARNI and/or beta-blockers. After pMVR, 67% of patients had unchanged/uptitrated GDMT vs. 33% that downtitrated ACEI/ARB/ARNI and/or beta-blockers. In this real-world cohort, downtitration of GDMT at clinical follow-up was strongly associated with poor survival, free from heart transplantation.

Optimization of GDMT in HFrEF is a major goal for HF specialists, as recommended by current guidelines.[18] Moreover, it reduces the severity of SMR.[10,11] Nevertheless, data from real-world largest registries report a low rate of full therapeutic titration in HFrEF patients, which is only partially explained by the side effects of antineurohormonal drugs.[20,21]

In the Change the Management of Patients with Heart Failure, <75% of the eligible patients were treated with ACEI/ARB/ARNI, beta-blockers, and/or MRA, despite <2% having absolute contraindications to treatment. Less than 25% simultaneously received all the three evidence-based classes of drug. Underdosing was similarly reported, with major proportions of patients using <50% of target doses.[20] Higher rates of treatment were reported in the European Society of Cardiology Heart Failure Long-Term Registry, but again, only 30% of patients received the target dose of GDMT. In one-third of this population, a reason for not achieving the recommended dose was not reported.[21]

Percutaneous mitral valve repair has been demonstrated to be safe and effective for the correction of SMR in HFrEF. Large registries confirmed the potential benefit obtained in relief of symptoms and reduction in HF hospitalizations.[5–7] Two randomized studies recently brought contradictory results with the MITRA-FR trial not demonstrating any reduction in all-cause mortality/hospitalization for HF at 12 months vs. the COAPT trial that demonstrated a reduction in HF hospitalizations at 24 months and in the composite of death and HF hospitalization at 1 year.[8,9]

One of the potential explanations for such controversy was the different strategy of intensification of medical therapy before randomization. In the COAPT trial, the status of GDMT was evaluated centrally in order to guarantee the maximal optimization before implantation and to minimize changes in medications after procedure, whereas in the MITRA-FR, judgement of medical therapy was demanded to local centres and modifications allowed 'per real-world practice'.[8,9]

Current guidelines invite to consider pMVR in HFrEF with SMR as a second-step option if the patient remains symptomatic despite the highest tolerated doses of HF drugs,[18] emphasizing the need of the maximal effort by clinicians in order to obtain the full maximization of treatment. In the

two randomized studies, the rates of ACEI/ARB/ARNI, beta-blockers, and MRA were ~70%, 90%, and 50%, respectively, with a higher proportion of patients in the treatment arm vs. the GDMT-only arm on ACEI/ARB/ARNI (72 vs. 62%, $P = 0.02$) in the COAPT study.[8,9] No further information was available on medications' dosages at baseline. In our experience that collected patients from two third-level referral centres for HF and cardiomyopathies, 73%, 85%, and 70% of patients were treated with ACEI/ARB/ARNI, beta-blockers, and MRA, respectively, thus similar to the populations from randomized clinical trials. However, only 33% and 32% were using >50% of the target dose of ACEI/ARB/ARNI and beta-blockers, attesting the difficulty in achieving the maximal optimization of GDMT in clinical practice. Specific reasons for the lacking titration were not available. Chronic obstructive pulmonary disease affected 16% of the cohort, and kidney function was moderately impaired. However, patients downtitrating vs. stable/uptitrating GDMT had similar rates of diabetes and chronic obstructive pulmonary disease with borderline lower rates of hypertension, suggesting that other reasons are probably implicated in the different therapeutic management. Intolerance to dose titration might be a further explanation and can be due to the advanced disease, as our patients presented with advanced symptoms, large LV remodelling, low LVEF, pulmonary hypertension, and more than 50% with right ventricular dysfunction.

Changes in guideline-directed medical therapy after percutaneous mitral valve repair and association with outcomes

Data from large US registries highlighted the lacking progress in the proportion of patients obtaining the full titration of HF drugs.[22] As expected, medical reasons such as worsening HF

Table 3 Univariate and multivariate Cox regression analysis and variables associated with the primary endpoint of death/heart transplantation at follow-up

	Unadjusted			Adjusted		
	HR	95% CI	P	HR	95% CI	P
NYHA class[a]	3.138	1.930–5.103	<0.001	2.809	1.712–4.609	<0.001
LVEF[a]	0.940	0.906–0.975	0.001			
RV dysfunction[a]	2.199	1.146–4.219	0.018			
MR ≥ 3+ at follow-up[a]	3.333	1.777–6.287	<0.001			
ACEI/ARB/ARNI	0.518	0.265–1.013	0.055			
ACEI/ARB/ARNI quartile of target dose[a]	0.788	0.614–1.011	0.061			
Beta-blockers	0.542	0.272–1.080	0.082			
Beta-blockers quartile of target dose[a]	0.763	0.583–0.999	0.050			
MRA	1.195	0.624–0.288	0.590			
Loop diuretics	1.001	0.999–1.003	0.310			
Furosemide dose equivalent	1.000	0.998–1.003	0.823			
Downtitrated GDMT[a]	2.846	1.569–5.165	0.001	2.542	1.377–4.694	0.003

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor neprilsyn inhibitors; CI, confidence interval; GDMT guideline-directed medical therapy; HR, hazard ration; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA mineral corticoid antagonists; NYHA, New York Heart Association; RV, right ventricle.
[a]Variables included in the penalized multivariable Cox model.

symptoms/HF hospitalizations, drug intolerance, or worsening kidney function are the most common underlying reasons for downtitration. Oppositely, younger and less sick patients are more likely to initiate/increase HF medications. However, lacking case management by HF specialists was a further reason for failing GDMT optimization.[22]

Interventional procedures in HFrEF patients, in particular pMVR, cannot be systematically considered as curative, because the underlying structural myocardial disease dominates in the genesis of the HF syndrome. GDMT thus remains the cornerstone of disease management. Moreover, in the specific setting of SMR, the positive effect of GDMT on the entity of regurgitation is an additional reason that supports high-intensity medical treatment of HFrEF after pMVR.[10–12] In the COAPT trial, background therapy was intensified to a greater degree in patients who had the procedure, as compared with the control group. Uptitration of GDMT may promote the stability of LV reverse remodelling, aiding the closing action of the mitral valve clips. In the COAPT trial, the low incidence of recurrent MR can be partly explained by the higher intensification in the procedural arm, as compared with the control group.[9,13]

In our cohort, at first clinical evaluation after pMVR, despite a slightly higher proportion of patients treated with ACEI/ARB/ARNI compared with baseline, we did not observe a significant increase in the rate of patients achieving the target dose of GDMT. In the controlled setting of the COAPT trial, the 12 month rates of >50% dose reduction/discontinuation of ACEI/ARB/ARNI and beta-blockers were both ~5%.[9] In our study, downtitration of GDMT occurred in 33% of patients and was strongly associated with worst outcome. Interestingly, the 24 month rate of death/heart transplantation in patients downtitrating GDMT was 47%, in overlap with the survival proportion of the medical treatment arm of the COAPT trial and higher than the total MITRA-FR study population.[8,9] Patients with unchanged/uptitrated GDMT, instead, appeared to gain the largest benefit from the procedure, with less recurrence of MR ≥ 3+, larger reduction in LV end-systolic volume, and lower NYHA class at follow-up. Furthermore, the 24 month mortality free from heart transplantation was better in comparison with the device arm of the COAPT trial.[9] Ours is the first report specifically focused on the medical management of patients undergoing pMVR and strongly supports the importance of a careful approach to the medical management of HF along with the interventional strategy for the correction of SMR.

The reasons for changes made in medications were not available. Baseline characteristics of patients with unchanged/uptitrated GDMT were similar to patients with downtitration of GDMT, with the exception of an unexpected higher rate of patients at target dose of ACEI/ARB/ARNI and a larger, but not significant, proportion of patients in NHYA class IV in the downtitration group. Systemic blood pressure and heart rate were not different between groups. Therefore, comorbidities and intolerance to medications unlikely explained the dose reduction. We cannot exclude that a worsening in HF symptoms may have led to GDMT downtitration, because these patients presented a worst functional class at follow-up. Further possible reasons for therapeutic modification not related to medical condition have been reported, such as low compliance by the patients, the erroneous feeling that pMVR may be curative, or lacking knowledge by providers and general practitioners,[22,23] attesting the importance of the systematic care by HF specialists for these patients after the procedure.

Limitations

As in all observational studies, the present study suffers from the common bias of different selection criteria and treatments. The relatively small sample size and the retrospective nature of the study may limit the strength of our findings. However, it remains the first study specifically investigating the impact of changes in GDMT on the prognosis of HFrEF with SMR corrected percutaneously. Larger prospective studies are advocated to explore the impact of GDMT management in patients undergoing pMVR. The data were collected from two different third-level referral centres for HF. Although the two samples were largely comparable in terms of clinical characteristics, treatments, procedure, and outcome, a potential bias due to the variability in local practice and clinical selection criteria across institutions is still possible. Medication changes were not managed as time-dependent variables across the whole follow-up. However, this is beyond the aims of the present study and needs to be explored in larger cohorts. Specific reasons for treatment modifications were not systematically available, and in particular, adverse effects (e.g. coughs, symptomatic hypotension, etc.) might have been missed.

Conclusions

In HFrEF patients with SMR, the maximal effort should be made to achieve the complete optimization of GDMT before pMVR. The present study demonstrated that complete optimization of GDMT remains insufficient. Moreover, because the correction of SMR is not curative in these patients, maintaining or preferably uptitrating neurohormonal drugs after the procedure should be encouraged during the follow-up to gain the larger and more stable benefit from the procedure, whereas downtitration or discontinuation of GDMT may be harmful and should be avoided.

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Conflict of interest

None declared.

Supporting information

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

Figure S1. Kaplan–Meier curves showing the survival-free from heart transplantation in patients with uptitrated GDMT (orange line) vs patients with unchanged GDMT (light blue line).

Table S1. Guideline recommended agents and doses.

Table S2. Baseline and follow-up main characteristics of the subgroup of patients with unchanged/uptitrated GDMT divided according to uptitrating or unchanging GDMT.

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