JACC: HEART FAILURE
VOL. 5, NO. 9, 2017

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jchf.2017.06.015

Evolution of Functional Mitral Regurgitation and Prognosis in Medically Managed Heart Failure Patients With Reduced Ejection Fraction

Riwa Nasser, MD, Lauranne Van Assche, MD, Anne Vorlat, MD, PhD, Tom Vermeulen, MD, Emeline Van Craenenbroeck, MD, PhD, Viviane Conraads, MD, PhD, Vicky Van der Meiren, DBMS, Bharati Shivalkar, MD, PhD, Paul Van Herck, MD, PhD, Marc J. Claeys, MD, PhD

ABSTRACT

OBJECTIVES The purpose of this study was to assess whether medical management may alter the severity of functional mitral regurgitation (FMR) and its prognosis in patients who have heart failure with reduced ejection fraction (HFrEF).

BACKGROUND FMR in patients who have HFrEF is associated with a worse prognosis. It is uncertain to what extent medical management may alter the severity of FMR and its prognosis.

METHODS The extent of FMR was assessed at baseline and after a median follow-up period of 50 months in 163 consecutive HFrEF patients (left ventricular ejection fraction <40%). Severe FMR was defined as mitral regurgitation (MR) grade 3-4. All of the patients received the maximal tolerable doses of their heart failure (HF) medications. Major adverse cardiac events were defined as a composite of all-cause death and the need for heart transplantation or hospitalization for HF and/or malignant arrhythmias.

RESULTS A total of 50 (31%) patients had severe MR at baseline. During the follow-up period, 38% of the severe FMR patients showed an improvement to nonsevere FMR (MR grade <3), whereas 18% of the nonsevere FMR patients developed severe FMR despite optimal HF treatment. Cox regression analysis revealed that the presence of sustained severe FMR or worsening of FMR was the most important independent prognostic determinant with an adjusted odds ratio of 2.5 (95% confidence interval: 1.5 to 4.3, major adverse cardiac events 83% vs. 43%). In addition, those patients showed a 13% increase in left ventricular end-diastolic volume index (LVEDVI), whereas the patients with improvement in their severe MR showed a 2% decrease in LVEDVI ($p = 0.01$).

CONCLUSIONS Severe FMR was successfully treated with medication in almost 40% and was associated with prevention of left ventricular adverse remodeling and with an improved long-term prognosis.
(J Am Coll Cardiol HF 2017;5:652–9) © 2017 by the American College of Cardiology Foundation.

Functional mitral regurgitation (FMR) is a common finding in patients with underlying myocardial dysfunction and results from decreased left ventricular (LV) closing forces and from distortion of the LV geometry tethering the structurally normal mitral leaflets (1). Severe FMR has been shown to be associated with increased morbidity and mortality independent of both LV ejection fraction (LVEF) and clinical markers of heart failure (HF) (2-6). In the study by Bursi et al. (2), moderate or severe mitral regurgitation (MR) was observed in 12% of early post-myocardial infarction (post-MI) patients and was associated with a 3-fold increase in the risk of HF and a 1.6-fold increased risk of death during 5 years of follow-up. In a more recent study by Rossi et al. (3), severe FMR was

From the Department of Cardiology, Antwerp University Hospital, Antwerp, Belgium. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Nasser and Van Assche contributed equally to this work. Dr. Conraads is deceased.

Manuscript received May 18, 2017; revised manuscript received June 14, 2017, accepted June 25, 2017.

present in 24% of patients with systolic HF (both ischemic and nonischemic) and was related to a 2-fold increase in death and rehospitalization due to HF during an average of 3 years of follow-up. The negative impact of FMR on prognosis has been linked to progressive adverse LV remodeling due to ongoing volume overload, although this association is still controversial. Current therapies targeting pathological ventricular remodeling, such as the use of inhibitors of the renin-angiotensin-aldosterone axis and beta-blocking agents, have manifested significant effectiveness in reducing morbidity and mortality in patients with systolic HF (7–9), and there is some evidence from small-sized studies that those agents can reduce the severity of FMR in the short term (10). It is uncertain, however, to what extent optimal medical HF management may steadily improve the severity of FMR and its long-term prognosis in a general population of patients with systolic HF. This information is of paramount importance to optimize patient selection for surgical or percutaneous repair of severe FMR.

SEE PAGE 660

Therefore, the present study evaluated the evolution of FMR in HF patients with reduced ejection fraction (HFrEF) within a structured and standardized HF clinic and relates alterations in the severity of FMR to their long-term morbidity and mortality as well as to changes in LV volumes.

METHODS

PATIENT POPULATION. All of the HF patients with a LVEF ≤40% (HFrEF) who were followed-up in the HF clinic at the Antwerp University Hospital between January 2007 and December 2013 were enrolled in this observational study. From the 220 recruited patients, a total of 56 patients were excluded because of the following: a history of surgical mitral valve treatment or presence of severe degenerative mitral valve disease (n = 11), incomplete echocardiogram data (n = 8), and a follow-up period of <1 year (n = 38). The final study population consisted of 163 patients with a median follow-up period of 56 months (range 13 years to 94 years).

The clinical management of the study patients, as well as the indications for resynchronization therapy and implantation of an internal defibrillator, were standardized according to the HF guidelines and within the Belgium reimbursement criteria (reimbursement for resynchronization therapy only for patients with New York Heart Association [NYHA] functional class ≥2 and left bundle branch block [LBBB] with QRS duration ≥150 ms) (7,11). Doses of standard treatment medications were titrated to the maximally tolerated dose, and each patient's filling status was assessed during each consultation by clinical and/or echocardiographic evaluation. The diuretic doses were adapted according to the patients' filling status. For each patient, the percent of the optimal dosage of angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB), beta blockers, and aldosterone antagonists were calculated at baseline and at follow-up based on the target recommended dose in the 2016 European Society of Cardiology (ESC) HF guidelines.

Information about the patients' medical history, baseline risk profile, electrocardiographic parameters, laboratory results, functional status, cardiac function, cardiac valve function, treatment modalities, and clinical follow-up were retrieved from the HF database and the patients' hospital files.

The study was approved by the ethics committee of the Antwerp University Hospital.

ECHOCARDIOGRAPHY. All of the echocardiographic examinations were performed by trained sonographers using high-quality cardiovascular ultrasound systems (Vivid 7 GE Healthcare or iE33 [Chicago, Illinois] and Philips Healthcare [Amsterdam, the Netherlands]) and were reviewed at the time of the examination by expert supervisors.

MR severity was graded according to the American Society of Echocardiography guidelines, based on a validated multi-integrative method (12). Both qualitative (color flow mapping) as well as quantitative measurements (proximal isovelocity surface area whenever feasible) were used to grade the MR severity from grade 0 to grade 4. In the present study, severe MR was defined as MR grade 3 or 4 and was graded by an effective regurgitant orifice area >20 mm^2 and/or a vena contracta width >4 mm and/or a jet area of at least 4 cm^2 (13).

For this study, all of the echocardiogram images were reviewed a second time off-line by 1 expert, and in cases of discordance with the initial evaluation, a third expert was invited to review the images and make the final decision. All of the expert reviewers were blinded to the clinical status of the patient.

LV function (LVEF) was quantified by measurements of LV dimensions or by visual estimation in the cases when ventricular volume measurements were

ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

AHT = arterial hypertension

ARB = angiotensin receptor blocker

CRT = cardiac resynchronization therapy

FMR = functional mitral regurgitation

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

ICD = implantable cardioverter defibrillator

LAVI = left atrium volume index

LBBB = left bundle branch block

LVEF = left ventricular ejection fraction

LVEDVI = left ventricular end-diastolic volume index

LVESVI = left ventricular end-systolic volume index

MACE = major adverse cardiac event(s)

MR = mitral regurgitation

NYHA = New York Heart Association

OR = odds ratio

TABLE 1 Baseline Characteristics

	All Patients (N = 163)	Nonsevere MR (n = 113, 69%)	Severe MR (n = 50, 31%)	p Value
Female	39 (24)	22 (20)	17 (34)	0.045
Age, yrs	62 ± 14	64 ± 12	59 ± 17	0.039
Weight, kg	80 ± 16	83 ± 16	75 ± 15	0.01
Length, cm	173 ± 9	173 ± 9	172 ± 10	0.25
Risk factors				
AHT	72 (44)	52 (46)	20 (40)	0.45
Diabetes	34 (21)	26 (23)	8 (16)	0.31
Renal failure	24 (15)	17 (15)	7 (14)	0.84
Active smoking	30 (18)	21 (19)	9 (18)	0.92
Heart failure				
Ischemic etiology	83 (51)	55 (49)	28 (56)	0.38
Prior hospitalization	78 (48)	52 (46)	26 (52)	0.51
LVEF, %	29 ± 8	30 ± 7	27 ± 8	0.012
NYHA functional class >2	30 (18)	18 (16)	12 (24)	0.22
Diastolic dysfunction >2	43 (30)	25 (25)	18 (42)	0.037
Electrophysiology				
Atrial fibrillation	20 (12)	15 (13)	5 (10)	0.55
QRS duration, ms	130 ± 31	130 ± 31	131 ± 31	0.59
LBBB	56 (34)	39 (35)	17 (34)	0.95
Prior CRT	24 (15)	17 (15)	7 (14)	0.90
Prior ICD	79 (48)	55 (49)	24 (48)	0.93
MR grade 1/2/3/4, (%)	39/31/27/3	56/44/./.	././90 /10	<0.0001
Medication				
ACEI/ARB	153 (94)	106 (94)	47 (94)	0.96
optimal dose, %	58	64	45	0.004
Beta blocker	148 (91)	101 (89)	47 (94)	0.34
optimal dose, %	55	58	49	0.12
Loop diuretic agent	129 (79)	86 (76)	43 (86)	0.15
Aldosterone antagonist	71 (43)	45 (40)	26 (52)	0.15
optimal dose, %	47	47	46	0.7
Left cardiac dimensions (echocardiogram, n = 128)				
LVEDVI, ml/m^2	95 ± 35	90 ± 32	107 ± 42	0.01
LVESVI, ml/m^2	68 ± 33	63 ± 29	79 ± 39	0.01
LAVI, ml/m^2	48 ± 26	45 ± 23	59 ± 30	0.007

Values are n (%) or mean ± SD.

ACEI = angiotensin-converting enzyme inhibitor; AHT = arterial hypertension; ARB = angiotensin receptor blocker; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter defibrillator; LAVI = left atrium volume index; LBBB = left bundle branch block; LVEDVI = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESVI = left ventricular end-systolic volume index; MR = mitral regurgitation; NYHA = New York Heart Association.

not feasible. Diastolic function was evaluated using diastolic mitral inflow signals and diastolic tissue Doppler signals and graded from 1 until 4. A diastolic grade >2 was defined as a restrictive filling status.

The assessment of the evolution of the MR was based on the comparison of the baseline echocardiography and the last available echocardiography at follow-up with a median time delay of 50 months (range 6 to 90 months) between both examinations. If the study patient underwent cardiac transplantation, the follow-up echocardiogram was defined as the last echocardiogram before cardiac transplantation or LV assist device implantation. An improvement in the MR was defined as a reduction from severe MR to nonsevere MR. Worsening of MR was defined as an increase from nonsevere MR to severe MR.

In a subgroup of 128 patients, the serial LV volume indices were calculated off-line by 1 expert using Simpson's biplane method. LV remodeling and left arterial (LA) remodeling were assessed by calculating the percent of volume changes over time.

CLINICAL FOLLOW-UP. The primary study endpoint was freedom from major adverse cardiac events (MACE) defined as a composite of all-cause death, the need for cardiac transplantation, and hospitalization for HF or malignant arrhythmias. All of the endpoints were obtained from the patient records or from telephone calls with the patient or the patient's family if the patient was deceased.

STATISTICAL ANALYSIS. Continuous variables are presented as the mean ± SD or the median (with range), where appropriate. Categorical variables are presented as counts and percentages. Characteristics were compared across groups with chi-square tests for categorical variables and analysis of variance for continuous variables. Comparisons of LV volume changes and changes in the filling status for the different study subgroups were performed using analysis of variance for repeated measurements.

Cumulative event-free survival estimates were plotted using the Kaplan-Meier technique. Differences between the survival curves were tested with the log-rank test. The Cox proportional hazards model was applied to identify independent predictors of MACE. The following baseline factors were included in the model: age, sex, weight, baseline LVEF, baseline NYHA functional classification, renal failure (defined as glomerular filtration rate <30 ml/min/1.73 m^2), diabetes, etiology of cardiac dysfunction, presence of LBBB and the degree of baseline and follow-up MR. For the identification of predictors of improvement/deterioration of FMR, forward stepwise logistic regression analysis was performed with stepwise inclusion of previously mentioned baseline factors. A 2-tailed p value <0.05 was considered statistically significant. Statistical analyses were performed using MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium).

RESULTS

PATIENT CHARACTERISTICS. Table 1 depicts the baseline characteristics of the total study population and compares the baseline risk profiles between the patients with versus patients without severe FMR. A total of 31% of our study population had severe FMR

at baseline. Patients with severe FMR were more likely to be female, were older, had a lower LVEF and had a lower body weight. In addition, the left cardiac dimensions were larger in the patients with severe MR. Although both study groups received recommended HF medications, severe FMR patients were treated with lower dose of ACEI/ARBs than nonsevere FMR patients. For all of the other parameters, the 2 groups were not significantly different.

EVOLUTION OF FMR, DIASTOLIC FUNCTION, AND LV CARDIAC DIMENSIONS. Based on the evolution of the FMR under optimal medical management, the study population was divided into the following 4 groups:

1. Patients who had nonsevere FMR at the time of inclusion, which remained nonsevere (nonsevere/nonsevere, n = 92) (period between both echocardiograms, 1,441 days)
2. Patients who had nonsevere FMR at baseline but deteriorated to severe FMR (nonsevere/severe, n = 21) (period between both echocardiograms, 1,400 days)
3. Patients who had severe FMR at baseline and improved to nonsevere FMR (severe/nonsevere, n = 19) (period between both echocardiograms, 1,501 days)
4. Patients who had severe FMR at the time of inclusion and maintained a severe FMR (severe/severe, n = 31) (period between both echocardiograms, 1,060 days)

There was a tendency to a shorter period between the 2 echocardiograms in the subgroup with persistent severe MR (p = 0.09). This was probably related to shorter survival of this subgroup.

The medical treatment of those 4 groups at the time of the echocardiogram follow-up is shown in Table 2. There were no significant changes over time in posology for ACEI/ARB, beta-blockers, and aldosterone antagonists. During the follow-up period there were 8 additional cardiac resynchronization therapy implantations.

Our analysis revealed that 38% (19 of 50) of the patients with severe FMR evolved to nonsevere FMR and that 18% (21 of 113) of the patients with a nonsevere FMR evolved to severe FMR despite optimal medical management. Stepwise logistic regression analysis revealed that the absence of LBBB was the only independent predictor of the improvement of severe FMR. The independent predictors for the deterioration of FMR were the presence of LBBB and diabetes (Table 3). One patient who experienced deterioration in their FMR had a new MI, which could have contributed to the development of severe FMR.

TABLE 2 Treatment at Follow up

	Nonsevere/ Nonsevere (n = 92)	Nonsevere/ Severe (n = 21)	Severe/ Nonsevere (n = 19)	Severe/ Severe (n = 31)	All (N = 163)
CRT	20	25	16	19	20
ACEI/ARB	92	75	74	78	85
Optimal dose	60	54	44	45	55
Beta blocker	95	90	100	91	94
Optimal dose	62	65	55	47	59
Loop diuretic agent	69	85	79	91	76
Aldosterone antagonist	35	45	47	62	43
Optimal dose	50	44	55	67	55

Values are %.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CRT = cardiac resynchronization therapy.

In Figure 1, the changes in the proportion of patients with a restrictive filling pattern are depicted for the 4 different subgroups. The patients with improved FMR showed improvement in their filling status (e.g., proportion of patients with restrictive filling decreased from 47% to 28%). The patients who experienced deterioration in their FMR experienced an increase in restrictive filling patterns (from 38% to 62%).

In Figure 2, the change in LV end-diastolic volume (LVEDV) is depicted for the 4 different subgroups. There was a significantly different pattern with more LV deterioration in the patients with severe FMR during the follow-up; on average there was a 13% increase of LVEDV in the severe/severe subgroup and an 18% increase in the nonsevere/severe subgroup. In patients with sustained nonsevere FMR, a mild increase was observed (+3%), whereas for patients who experienced an improvement in their severe FMR, an average LVEDV reduction of 2% was observed.

A similar pattern was observed with LVEF changes and left atrium size changes (data not shown).

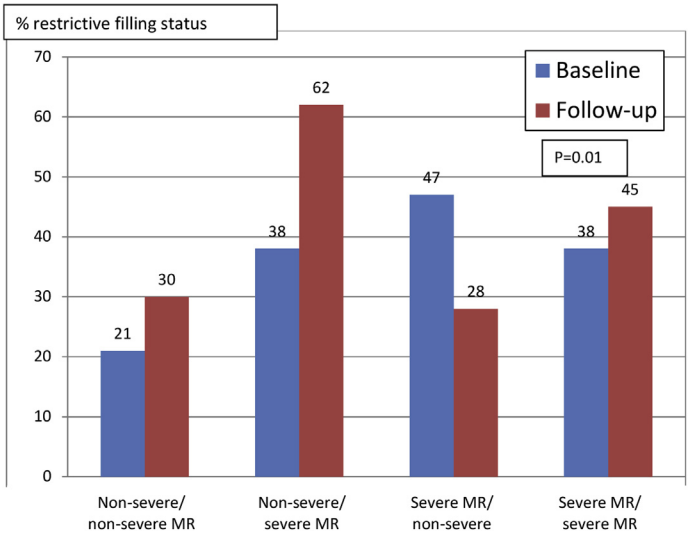
CLINICAL ENDPOINTS. At least 1 MACE occurred in 56% (n = 91) of the patients during the median follow-up period of 56 months (range 13 months to 94 months). All-cause death occurred in 31% (n = 51) of the patients. Another 29% (n = 47) of the patients had

TABLE 3 Independent Predictors of Improvement and Deterioration of FMR

	Improvement FMR		Deterioration FMR	
	Adjusted OR	95% CI	Adjusted OR	95% CI
LBBB	0.12	0.02–0.64	3.0	1.1–8.4
Diabetes			4.1	1.4–11.6

FMR = functional mitral regurgitation; CI = confidence interval; LBBB = left bundle branch block; OR = odds ratio.

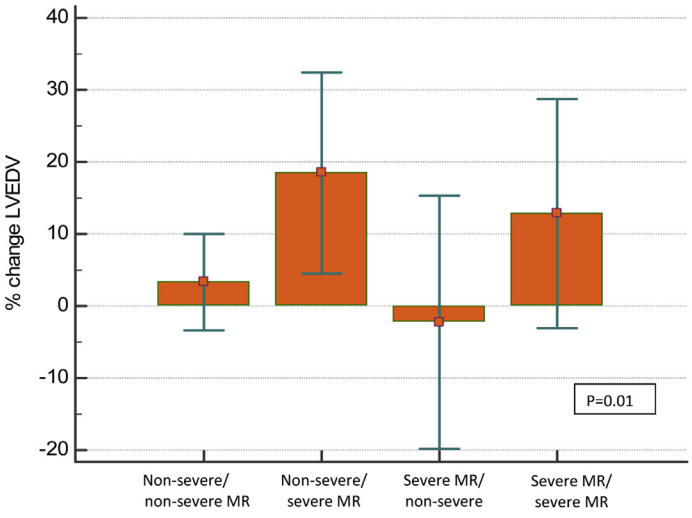
FIGURE 1 Proportion of Patients With Restrictive Filling Status



MR = mitral regurgitation.

to be hospitalized for an exacerbation of HF, whereas 14% (n = 23) had to be hospitalized for malignant arrhythmias (ventricular tachycardia/ventricular fibrillation). Cardiac transplantation needed to be performed in 12% (n = 19) of the patients.

FIGURE 2 Percent Change in LVEDV



Bar graph showing percent change in the LVEDV expressed as the mean ± 95% CI for the different subgroups. CI = confidence interval; LVEDV = left ventricular end-diastolic volume; MR = mitral regurgitation.

Figures 3 to 5 describe the Kaplan-Meier survival analysis for the different clinical endpoints stratified according to the previously mentioned 4 subgroups. For the composite clinical endpoint, as well as for mortality and hospitalization for HF or ventricular tachycardia/ventricular fibrillation, a significantly worse prognosis was observed in the patients with sustained severe FMR or with deterioration in FMR compared to the patients without severe FMR or with improvement in FMR.

In the Cox regression analysis, the presence of severe FMR at follow-up was the most important independent predictor of MACE and mortality with an odds ratio (OR) of 2.5. (MACE: 83% vs. 43%) (Table 4).

Deterioration of FMR was associated with a poor outcome comparable with the outcome of patients with sustained severe FMR (MACE: 90% vs. 77%, adjusted OR: 1.6 [95% confidence interval (CI): 0.7 to 3.4]), whereas the outcome of patients with improved FMR was as good as the outcome of patients with sustained nonsevere FMR (MACE: 42% vs. 43%, adjusted OR: 1.2 [95% CI: 0.5 to 2.8]).

DISCUSSION

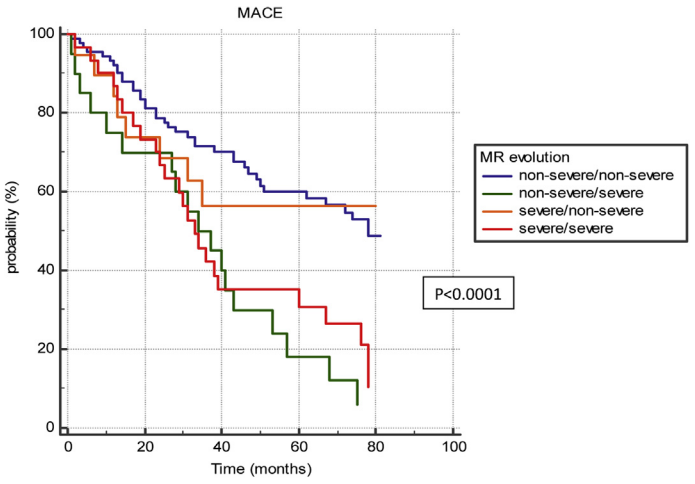
The present study is the first to show that optimal medical HF therapy can result in a sustained reduction in severe FMR in patients with HFrEF, and this reduction in MR was associated with prevention of LV adverse remodeling and with an improved long-term prognosis.

Severe FMR was present in 30% of our study population, which is higher than in previous reports including an unselected group of post-MI patients but is in concordance with more recent papers focusing only on patients with severely depressed LV function (2–5). In most of those studies, severe FMR was an independent predictor of mortality, whereas in our study the correlation between baseline FMR severity and outcome was weak. This could have been related to the smaller sample size in our study, but more likely it is related to the incorporation of MR severity at follow-up in the multivariate regression model. The evolution of FMR allowed a more accurate risk stratification of the patients and de-emphasized the importance of baseline FMR severity. Stolfo et al. (14) also showed the additive prognostic value of re-assessment of MR grade. In their study, an early improvement in FMR was observed in 53% of the patients and emerged as a favorable independent prognostic factor with an incremental short- and long-term power compared with the baseline FMR evaluation. In the study by Stolfo et al. (14), the reassessment was performed after 6 months, whereas in our study, follow-up FMR was assessed after a median of 50 months. One might assume that some of the patients with an initial FMR improvement again develop severe FMR after some years, and this may explain the lower rate of (sustained) improved FMR (38%) in our study population.

In the present study, LVEF was not identified as an independent prognostic determinant, probably because only HFrEF patients were included and/or because LVEF underestimates the severity of myocardial dysfunction in the presence of a severe MR.

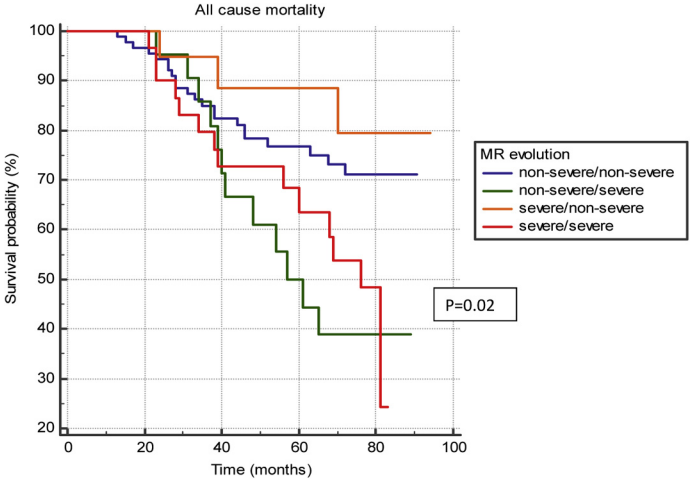
Medication-induced improvement in FMR has been linked to the beneficial effect of inhibitors of the renin-angiotensin-aldosterone axis on LV remodeling (8,11). In our study population, the patients were already receiving standard HF therapy including beta-blocking agents and renin-angiotensin-aldosterone blockers at baseline, although at approximately one-half of the recommended dose target. During the follow-up, no significant increase in the dosage of those anti-HF drugs were observed, which suggests that the prescribed posology reflects the maximal tolerable dose. Our data showed that changes in volume status played a major role in the severity of MR. In the HF clinic, diuretic treatment was uptitrated according to the filling status of the patient to the maximal tolerated dose. In addition, much attention was given to help patients follow strict salt and fluid restriction. With this approach, FMR could be steadily improved in approximately 40% of the patients. The improvement of FMR was also associated with the prevention/attenuation of adverse LV remodeling. In previous studies looking at the short-term effect of HF medication on FMR, more pronounced reductions in LV volumes were observed in patients with improved FMR, but given the ongoing process of primary failing ventricles, those strong effects could partially fade over time (10,14). Our findings support the hypothesis that volume overload induced by FMR is the key factor for the poor prognosis of patients with HFrEF and

FIGURE 3 Cumulative Event-Free Plot for MACE



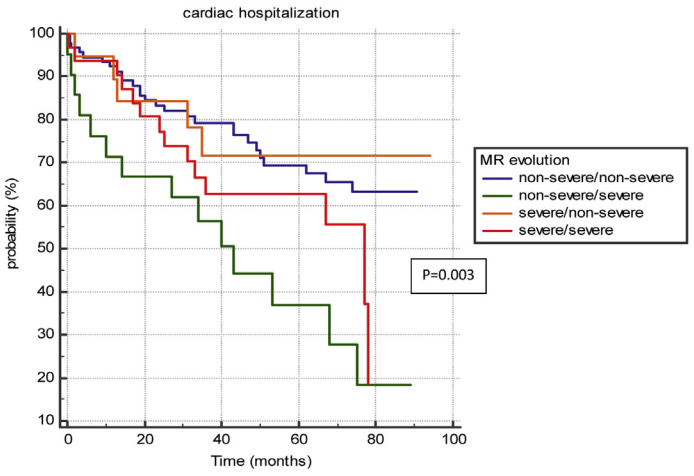
Kaplan-Meier curves representing cumulative event-free plot for MACE for the different subgroups. MACE = major adverse cardiac event(s); other abbreviation as in Figure 1.

FIGURE 4 Cumulative Event-Free Plot for All-Cause Death



Kaplan-Meier curves representing cumulative event-free plot for all-cause death for the different subgroups. MR = mitral regurgitation.

FIGURE 5 Cumulative Event-Free Plot for Cardiac Hospitalization



Kaplan-Meier curves representing cumulative event-free plot for cardiac hospitalization (for heart failure and/or malignant arrhythmias) for the different subgroups. MR = mitral regurgitation.

TABLE 4 Independent Predictors of MACE and All-Cause Mortality

	MACE		All-Cause Mortality	
	Adjusted OR	95% CI	Adjusted OR	95% CI
Female	0.8	0.5–1.5	1.2	0.6–2.5
Age	1.01	0.99–1.02	1.035	1.01–1.06
Weight	0.99	0.98–1.01	1.01	0.98–1.03
Diabetes	1.04	0.6–1.8	1.2	0.6–2.5
Renal failure	1.2	0.7–2.2	1.2	0.6–2.5
Ischemic etiology	1.4	0.9–2.3	2.6	1.3–5.0
LVEF	0.99	0.96–1.02	1.02	0.98–1.06
NYHA functional class >2	0.96	0.5–1.7	0.7	0.4–1.6
LBBB	0.7	0.5–1.3	0.8	0.4–1.5
Severe MR at baseline	0.9	0.5–1.5	0.8	0.4–1.6
Severe MR at follow-up	2.5	1.5–4.3	2.6	1.3–5.0

MACE = major adverse cardiac event(s); other abbreviations as in Tables 1 and 3.

concomitant severe FMR. The effect of volume overload in a primary failing ventricle is deleterious and stimulates further modifications at the molecular, cellular, tissue, and cardiac chamber levels. MR increases diastolic wall stress, which is associated with an increase in extracellular matrix turnover, and neurohormone and cytokine activation, which lead to further eccentric hypertrophy, ventricular dilatation, and failure (15,16). FMR leads to a vicious circle of continuous volume overload with the subsequent progression of adverse remodeling and HF, ultimately worsening the prognosis. There is clearly a subgroup of patients in whom this vicious circle can be interrupted by decreasing the filling pressure with medications (particularly diuretic agents) and with adequate salt/fluid restriction. According to our data, patients without LBBB had the highest chance of improved FMR under optimal HF therapy. The presence of LBBB seemed to make the FMR less responsive to medical treatment, most likely because the MR was related to electromechanical dyssynchrony. Resynchronization therapy has been shown to reduce FMR, a pattern that supports causality (17).

Almost one-third of our patients showed severe FMR during the follow-up period, and this was associated with adverse LV remodeling and a poor prognosis. Those patients might have benefitted from a more invasive approach. Mitral valvular repair of severe FMR, either surgical or percutaneous, has been shown to prevent and even reverse adverse remodeling, improve cardiac function and functional status, and reduce the risk of HF (18–21). Whether or not those invasive techniques will result in an improved prognosis is currently being studied in some large-scale randomized trials.

STUDY LIMITATIONS. Because of the nonrandomized observational study design, some unreported factors might have influenced the outcomes in the different subgroups. We tried to minimize this effect by including the most important known prognostic risk factors for HF in the multivariate analysis. Furthermore, we have no information on the patients' medication compliance or compliance with fluid restrictions. All of the patients were treated at the specialized HF clinic by HF specialists and nurses who were trained to motivate the patients in their compliance.

CONCLUSIONS

Severe FMR was present in almost one-third of the patients with HFrEF and was successfully treated with medication in almost 40% of the patients. However, severe FMR despite optimal HF treatment was associated with adverse LV remodeling and with a poor prognosis and may benefit from a more invasive approach.

ACKNOWLEDGMENT The authors thank Ella Roelant for her statistical advice.

ADDRESS FOR CORRESPONDENCE: Prof. Dr. Marc J. Claeys, Department of Cardiology, University of Antwerp Hospital (Edegem), Wilrijkstraat 10 2650 Edegem, Belgium. E-mail: marc.claeys@uantwerpen.be.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: FMR is a common finding in patients with underlying myocardial dysfunction and is associated with increased morbidity and mortality. The present study highlights that, in almost 40% of the patients, FMR can be successfully treated with medication that reduces the filling pressure (mainly diuretics) with subsequent prevention of LV adverse remodeling and with an improved long-term prognosis.

TRANSLATIONAL OUTLOOK: More research is needed to better predict the poor responders to medication to identify patients that are more prone for an invasive correction of the FMR.

REFERENCES

1. Pierard LA, Carabello BA. Ischaemic mitral regurgitation: pathophysiology, outcomes and the conundrum of treatment. Eur Heart J 2010;31:2996–3005.

2. Bursi F, Enriquez-Sarano M, Nkomo VT, et al. Heart failure and death after myocardial infarction in the community: the emerging role of mitral regurgitation. Circulation 2005;111:295–301.

3. Rossi A, Dini FL, Faggiano P, et al. Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy. Heart 2011;97:1675–80.

4. Trichon BH, Felker GM, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. Am J Cardiol 2003;91:538–43.

5. Agricola E, Ielasi A, Oppizzi M, et al. Long-term prognosis of medically treated patients with functional mitral regurgitation and left ventricular dysfunction. Eur J Heart Fail 2009;11:581–7.

6. Cioffi G, Tarantini L, De Feo S, et al. Functional mitral regurgitation predicts 1-year mortality in elderly patients with systolic chronic heart failure. Eur J Heart Fail 2005;7:1112–7.

7. Ponikowski P, Voors AA, Anker SD, 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 2016;37:2129–200.

8. Cioffi G, Tarantini L, De Feo S, et al. Pharmacological left ventricular reverse remodeling in elderly patients receiving optimal therapy for chronic heart failure. Eur J Heart Fail 2005;7:1040–8.

9. Xie M, Burchfield JS, Hill JA. Pathological ventricular remodeling: therapies: part 2 of 2. Circulation 2013;128:1021–30.

10. Seneviratne B, Moore GA, West PD. Effect of captopril on functional mitral regurgitation in dilated heart failure: a randomised double blind placebo controlled trial. Br Heart J 1994;72:63–8.

11. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012). Eur Heart J 2012;33:2451–96.

12. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. J Am Soc Echocardiogr 2003;16:777–802.

13. Lancellotti P, Moura L, Pierard LA, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). Eur J Echocardiogr 2010;11:307–32.

14. Stolfo D, Merlo M, Pinamonti B, et al. Early improvement of functional mitral regurgitation in patients with idiopathic dilated cardiomyopathy. Am J Cardiol 2015;115:1137–43.

15. Burchfield JS, Xie M, Hill JA. Pathological ventricular remodeling: mechanisms: part 1 of 2. Circulation 2013;128:388–400.

16. Spinale FG, Ishihra K, Zile M, DeFryte G, Crawford FA, Carabello BA. Structural basis for changes in left ventricular function and geometry because of chronic mitral regurgitation and after correction of volume overload. J Thorac Cardiovasc Surg 1993;106:1147–57.

17. Sutton MS, Keane MG. Reverse remodelling in heart failure with cardiac resynchronisation therapy. Heart 2007;93:167–71.

18. Foster E, Kwan D, Feldman T, et al. Percutaneous mitral valve repair in the initial EVEREST cohort: evidence of reverse left ventricular remodeling. Circ Cardiovasc Imaging 2013;6:522–30.

19. Deja MA, Grayburn PA, Sun B, et al. Influence of mitral regurgitation repair on survival in the surgical treatment for ischemic heart failure trial. Circulation 2012;125:2639–48.

20. Fattouch K, Guccione F, Sampognaro R, et al. POINT: efficacy of adding mitral valve restrictive annuloplasty to coronary artery bypass grafting in patients with moderate ischemic mitral valve regurgitation: a randomized trial. J Thorac Cardiovasc Surg 2009;138:278–85.

21. Nickenig G, Estevez-Loureiro R, Franzen O, et al. Percutaneous mitral valve edge-to-edge repair: in-hospital results and 1-year follow-up of 628 patients of the 2011-2012 Pilot European Sentinel Registry. J Am Coll Cardiol 2014;64:875–84.

KEY WORDS functional mitral regurgitation, heart failure, medical management