Effect of Functional Mitral Regurgitation on Outcome in Patients Receiving Cardiac Resynchronization Therapy for Heart Failure

Pieter van der Bijl, MB, ChB, MMed, DA, Cert. Cardiology (SA)[a], Mand Khidir, MD[a], Nina Ajmone Marsan, MD, PhD[a], Victoria Delgado, MD, PhD[a], Martin B. Leon, MD[b], Gregg W. Stone, MD[b], and Jeroen J. Bax, MD, PhD[a,*]

Functional mitral regurgitation (FMR) is common in heart failure (HF), and negatively impacts prognosis. Cardiac resynchronization therapy (CRT) can improve FMR, but the long-term changes in and impact of FMR after CRT are still unclear. The present study investigated the prevalence, evolution and impact on mortality of FMR before and after CRT in patients with HF. A total of 1,313 patients (66 ± 11 years, 77% male, 59% ischemic heart disease) treated with CRT were evaluated. Patients were divided into 4 groups of FMR according to the evolution at 6 months after CRT: no or mild FMR at baseline which remained unchanged at 6 months (grade 0−1 FMR unchanged, n = 609 [51%]), no or mild FMR which worsened to moderate to severe (grade 0−1 FMR worsened, n = 66 [6%]), moderate to severe FMR which improved to no or mild (grade 2−4 improved, n = 209 [18%]), and moderate to severe FMR which remained unchanged (grade 2−4 unchanged, n = 309 [26%]). Over a mean follow-up of 51 ± 38 months, 297 (25%) patients died. Those with baseline FMR grade 0−1 which remained unchanged at 6-month follow-up, as well as baseline FMR grade 2−4 which improved, had lower mortality rates than patients with 6-month FMR grade 2−4 regardless of baseline FMR grade (p < 0.001). Baseline FMR grade 2−4 that remained unchanged at 6-month follow-up was associated with increased mortality, independent of the clinical and left ventricular volumetric responses to CRT (hazard ratio, 1.77; 95% confidence interval, 1.41−2.22, p < 0.001). In conclusion, moderate to severe FMR at baseline which remains unchanged at 6 months after CRT implantation is strongly associated with long-term mortality in patients with HF. **(Am J Cardiol 2019;123:75−83)**

Functional mitral regurgitation (FMR) is common in heart failure (HF), with a prevalence of approximately 50% in ischemic cardiomyopathy and 56%−65% in nonischemic cardiomyopathy.[1−3] Moderate to severe FMR portends a poor prognosis, increasing HF hospitalizations and death.[2,4] Cardiac resynchronization therapy (CRT) is a well-established HF therapy.[5] The prevalence of FMR after CRT treatment varies in studies.[6−8] FMR may diminish, remain stable, or worsen after CRT, which may impact prognosis after CRT. No randomized study has investigated the prevalence, evolution, and impact on mortality of FMR before and after CRT in patients with HF. We analyzed the prevalence of FMR in a large cohort of HF patients who underwent CRT. Moreover, the relation between the change in FMR after 6 months of CRT, and the clinical and echocardiographic response to CRT was evaluated. Finally, the changes in FMR after CRT were related to long-term outcome during extended follow-up.

Methods

HF patients who underwent quantitative assessment of MR severity at the echocardiographic core laboratory of the Leiden University Medical Center and subsequent CRT implantation according to contemporary guidelines were included in this retrospective evaluation.[5] Patients who underwent mitral valve surgery (replacement or repair) before or after CRT implantation (n = 110) and those with primary MR were excluded. Demographic, clinical, laboratory, electrocardiographic, and echocardiographic parameters were analyzed. Patients with previous infarction or revascularization, as well as significant coronary artery disease on invasive angiography were considered to have ischemic cardiomyopathy, whereas the remainder were considered nonischemic.

Clinical evaluation included assessment of New York Heart Association (NYHA) class, quality of life (QoL, using the Minnesota Living with Heart Failure Questionnaire)[9] and a 6-minute walk test (6MWT) if able.[10] Clinical and echocardiographic assessments were routinely repeated at 6 months after CRT implantation. Thereafter, patients were scheduled for regular outpatient visits.

[a]Department of Cardiology, Heart Lung Center, Leiden University Medical Center, Leiden, The Netherlands; and [b]Center for Interventional Vascular Therapy, Division of Cardiology, New York Presbyterian Hospital and Columbia University, New York, New York. Manuscript received July 19, 2018; revised manuscript received and accepted September 7, 2018.

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*Corresponding author: Tel: +31 71 526 2020; fax: + 31 71 526 6809.
E-mail address: j.j.bax@lumc.nl (J.J. Bax).

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Two-dimensional transthoracic echocardiography was performed in all patients using a commercially available echocardiographic system (VIVID 7 or E9, General Electric Vingmed Ultrasound, Milwaukee, USA) before CRT implantation and after 6 months. Images were acquired with 3.5 MHz or M5S transducers, adjusting depth and gain settings as appropriate. M-mode, 2-dimensional and Doppler data, triggered to the ECG, were obtained and stored digitally for off-line analysis (EchoPac 113, General Electric Vingmed Ultrasound, Milwaukee). Left ventricular (LV) end-systolic (LVESV) and end-diastolic (LVEDV) volumes and left ventricular ejection fraction (LVEF) were measured from the apical 2- and 4-chamber views, using the modified Simpson's biplane method.[11] The severity of FMR was evaluated according to current recommendations, using a multiparametric approach, including qualitative and semi-quantitative indices and was graded on a 4-point scale: no or mild = 1, moderate = 2, moderate to severe = 3, and severe = 4.[12]

Right atrial and ventricular leads were positioned in a conventional manner, as previously described, and CRT optimization performed during follow-up at the discretion of the treating physician.[13]

Changes in FMR were evaluated at 6-month follow-up. Patients were divided in 4 groups: patients with no or mild FMR (grade 0−1) at baseline which remained unchanged at 6 months; patients with no or mild FMR (grade 0−1) at baseline which worsened to moderate to severe MR at 6 months (grade 2−4); patients with moderate to severe FMR (grade 2−4) at baseline which improved to no or mild (grade 0−1) at 6 months; and patients with moderate to severe FMR (grade 2−4) at baseline which remained unchanged at 6 months.

These FMR changes were related to 6-month response to CRT. A positive clinical response to CRT was defined as ≥ 1 class improvement in NYHA at 6-month follow-up, whereas a positive echocardiographic response was defined as $\geq 15\%$ reduction in LVESV at 6-month follow-up.[13]

Patient data were prospectively collected in the departmental Cardiology Information System (EPD-Vision, Leiden University Medical Center, Leiden, The Netherlands) and subsequently analyzed. The institutional review board approved the research and waived the need for written patient informed consent provided that the data were acquired for routine patient care. In the present evaluation, all data were acquired for clinical purposes and handled anonymously. Data on survival were retrieved from medical records and the municipal civil registries.

Continuous variables are presented as means and standard deviations, and categorical data as numbers and percentages. Continuous variables were compared with 1-way, between-group analysis of variance, using Bonferroni correction for multiple comparisons, and general linear mixed models. Categorical data were compared with the χ^2 and Fisher's exact tests, as appropriate. The event-free survival rates for each FMR group were evaluated with the Kaplan−Meier method and compared with the log-rank test. The follow-up period started at 6 months after CRT implantation, when change in FMR grade was assessed and FMR groups defined. Independent associates of all-cause mortality were evaluated with the Cox proportional hazards model, with the following variables entered into the model: baseline grade 0−1 FMR unchanged, baseline grade 2−4 FMR improved, baseline grade 0−1 FMR worsened, baseline grade 2−4 FMR unchanged, age, male gender, body mass index, diabetes mellitus, ischemic etiology of HF, diuretic use, hemoglobin, renal dysfunction, LVEF at 6 months, positive echo response, positive clinical response, and atrial fibrillation. All analyses were performed with SPSS for Windows, version 23.0 (SPSS, Armonk, New York). All statistical tests were two-sided and a p value < 0.05 was considered statistically significant.

Results

A total of 1,313 patients (mean age 66 ± 11 years, 77% male) with HF and baseline echocardiography who were treated with CRT were included in the analysis. The etiology of HF was ischemic in 59% of patients, the mean LVEF was 27 ± 8% and the mean QRS duration 156 ± 33 ms. No or mild FMR was noted in 735 (56%) patients, whereas 578 (44%) had moderate to severe MR. During 6-month follow-up 120 patients did not return for echocardiography. Thus, the study population consists of 1,193 patients.

The severity of FMR before and after CRT implantation is displayed in Figure 1. Overall, 675 patients (57%) had no or mild FMR at baseline, while 518 patients (43%) had moderate or severe FMR. Of the 675 patients with grade 0−1 FMR at baseline, the MR grade remained unchanged at 6-month follow-up in 609 (90%), whereas the MR grade progressed to grade 2−4 FMR in 66 (10%). Of the 518 patients with grade 2−4 FMR at baseline, the MR grade improved to grade 0−1 in 209 (40%) and remained unchanged in 309 (60%) at 6-month follow-up.

Baseline characteristics of the 1,193 patients according to the change in FMR are summarized in Table 1, while changes in clinical and echocardiographic parameters are shown in Table 2. Patients with grade 2−4 FMR at baseline which improved or remained unchanged at 6 months after CRT, had larger LV volumes and lower LVEF at baseline. Patients with grade 2−4 FMR at baseline which remained unchanged had more severe symptoms and more frequently had renal failure at baseline.

Changes in NYHA functional class HF symptoms at 6 month follow-up for each FMR group are presented in Figure 2. Overall, there was an improvement in NYHA functional class HF symptoms across all the FMR groups. However, the clinical response rate (≥ 1 class improvement in NYHA class from baseline to 6 months) was significantly lower in patients with grade 0−1 FMR at baseline which worsened at follow-up (45%) compared with the other groups (63% for those with grade 0−1 FMR at baseline which remained unchanged, 70% in patients with grade 2−4 FMR which improved and 66% in patients with grade 2−4 FMR which remained unchanged [p = 0.013]). Changes in LVESV at 6 month follow-up for each FMR group are presented in Figure 3. LVESV decrease was significantly greater in patients with grade 2−4 FMR at baseline which improved and in those with grade 0−1 FMR at baseline which remained unchanged at 6-month follow-up compared with patients with grade 2−4 FMR at baseline which

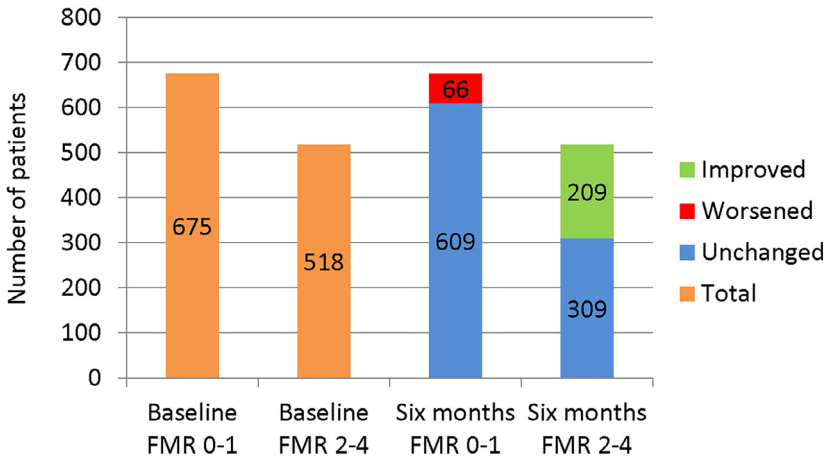


Figure 1. Distribution of no and mild functional mitral regurgitation (FMR), as well as moderate to severe FMR. Data are shown at baseline (before cardiac resynchronization therapy [CRT]) and after 6 months of CRT.

remained unchanged and patients with grade 0−1 FMR at baseline which worsened ($p < 0.001$). LV reverse remodeling was significantly more frequent in patients with grade 0−1 FMR at baseline which remained unchanged and grade 2−4 FMR at baseline which improved at 6-month follow-up (62% and 77%, respectively) compared with those with grade 0−1 FMR at baseline which worsened and grade 2-4 FMR at baseline which remained unchanged (29% and 58%, respectively; $p < 0.001$).

During a mean follow-up of 51 ± 38 months, 297 (25%) patients died. When stratified according to FMR responses over 6 months, a cumulative 44 (7%), 109 (18%), 162 (27%), and 187 (31%) of the 609 patients with grade 0−1 FMR at baseline which remained unchanged at 6 months after CRT, died at 24, 48, 72, and 96 months of follow-up, respectively. Similar survival rates were observed in the group of 209 patients with grade 2−4 FMR which improved at 6 months of follow-up. In contrast, the group of 66 patients with grade 0−1 FMR at baseline which worsened, showed significantly higher cumulative all-cause mortality events. Finally, the group of 309 patients with baseline grade 2−4 FMR which did not improve after CRT showed the highest mortality rates (log-rank test, $p < 0.001$; Figure 4). By multivariable analysis (Table 3), baseline grade 2−4 FMR which remained unchanged at 6 months after CRT was independently associated with increased risk of mortality (hazard ratio, 1.77; 95% confidence interval, 1.41−2.22, $p < 0.001$) whereas the other groups were not associated.

Discussion

In this study, a fairly high prevalence of moderate or severe FMR (43%) was present at baseline in HF recipients of CRT. The FMR grade improved to no or mild FMR after 6 months of CRT in a substantial proportion (40%) of patients. In addition, in those with no or mild FMR at baseline, a minority (10%) developed moderate to severe FMR after CRT. Patients in whom baseline no/mild FMR progressed to moderate to severe FMR and those with

Table 1
Baseline characteristics according to FMR evolution groups

	Baseline grade 0-1 FMR unchanged (n = 609)	Baseline grade 0-1 FMR worsened (n = 66)	Baseline grade 2-4 FMR improved (n = 209)	Baseline grade 2-4 FMR unchanged (n = 309)
Age (years)	64.4 ± 10.5	65.7 ± 9.7	67.1 ± 9.0*	66.5 ± 10.8*
Men	494 (81.1%)	56 (85%)	150 (71.8%)	225 (72.8%)
Ischemic aetiology	371 (60.9%)	36 (55%)	113 (54.1%)	174 (56.3%)
Sinus rhythm	472 (77.5%)	50 (76%)	156 (74.6%)	200 (64.7%)
Paced	59 (9.7%)	6 (9%)	19 (9.1%)	33 (10.7%)
Atrial fibrillation	78 (12.8%)	10 (15%)	34 (16.3%)	76 (24.6%)
Diabetes mellitus	142 (23.3%)	15 (23%)	36 (17.2%)	57 (18.4%)
eGFR < 60 ml/min/1.73 m^2	209 (34.3%)	21 (32%)	71 (34.0%)	173 (56.0%)
Medication				
Diuretic	466 (76.5%)	47 (71%)	172 (82.3%)	267 (86.4%)
Digoxin	74 (12.2%)	6 (9%)	35 (16.7%)	61 (19.7%)
β-blocker	472 (77.5%)	50 (76%)	159 (76.1%)	203 (65.7%)
Mineralocorticoid antagonist	253 (41.5%)	24 (36%)	88 (42.1%)	159 (51.5%)
ACE-inhibitor	553 (90.8%)	51 (77%)	190 (90.9%)	262 (84.8%)

Continuous variables are mean ± standard deviation. ACE = angiotensin-converting enzyme; eGFR = estimated glomerular filtration rate; FMR = functional mitral regurgitation.

* $p < 0.05$ vs baseline none or mild FMR unchanged at 6 months.

Table 2
Changes in clinical and echocardiographic characteristics according to FMR evolution groups

	Baseline grade 0-1 FMR unchanged (n = 609)			Baseline grade 0-1 FMR worsened (n = 66)			Baseline grade 2-4 FMR improved (n = 209)			Baseline grade 2-4 FMR unchanged (n=309)		
	Baseline	6 months	p	Baseline	6 months	p	Baseline	6 months	p	Baseline	6 Months	p
NYHA class												
I	36 (5.9%)	151 (24.8%)	< 0.001	8 (12%)	21 (32%)	< 0.001	6 (2.9%)	66 (31.6%)	0.007	3 (1.0%)	63 (20.4%)*,†,‡	0.003
II	178 (29.2%)	296 (48.6%)	0.008	16 (24%)	27 (41%)	0.643	66 (31.6%)	111 (53.1%)	0.032	57 (18.4%)	157 (50.8%)	0.301
III	359 (58.9%)	155 (25.5%)	< 0.001	37 (56%)	16 (24%)	0.001	120 (57.4%)	26 (12.4%)	0.028	219 (70.9%)	81 (26.2%)‡	0.253
IV	36 (5.9%)	7 (1.0%)	< 0.001	5 (8%)	2 (3%)	0.036	17 (8.1%)	6 (2.8%)	< 0.001	30 (9.7%)	8 (2.6%)	< 0.001
6 MWT (meters)	346.5 ± 117.0	406.6 ± 118.2	< 0.001	336.4 ± 159.1	401.7 ± 140.0	0.005	337.8 ± 105.5	416.2 ± 106.3	< 0.001	295.1 ± 115.4*,†,‡	361.9 ± 130.0*,†,‡	< 0.001
QoL score	30.8 ± 19.1	22.3 ± 18.3	< 0.001	31.8 ± 20.3	22.8 ± 20.4	0.004	28.9 ± 17.7	17.2 ± 16.3*	< 0.001	37.2 ± 19.0*,†,‡	25.5 ± 19.3‡	< 0.001
LVEF (%)	28.2 ± 7.8	35.0 ± 9.8	< 0.001	28.5 ± 7.5	30.4 ± 9.4*	0.148	25.4 ± 7.6*,†	33.8 ± 9.7†	< 0.001	25.3 ± 8.3*,†	30.0 ± 9.2*,†,‡	< 0.001
LVEDV (ml)	194.6 ± 70.9	172.7 ± 70.4	< 0.001	203.3 ± 87.5	202.4 ± 71.4	0.891	217.4 ± 75.7*	179.3 ± 67.5	< 0.001	231.8 ± 86.0*,†	216.2 ± 78.9*,‡	< 0.001
LVESV (ml)	142.0 ± 60.7	115.4 ± 58.8	< 0.001	148.3 ± 72.4	144.0 ± 63.6*	0.420	164.5 ± 67.0*	121.8 ± 56.7	< 0.001	176.2 ± 76.6*,†	154.7 ± 67.6*,‡	< 0.001
LA (ml)	66.0 ± 26.8	62.8 ± 26.1	< 0.001	73.7 ± 26.7	74.2 ± 29.6	0.896	74.4 ± 25.8	66.1 ± 24.6	< 0.001	81.6 ± 29.8	80.7 ± 34.6*,‡	0.588
Coaptation depth (millimeters)	10.9 ± 2.6	10.1 ± 2.8	< 0.001	11.5 ± 2.8	11.4 ± 3.2	0.657	12.1 ± 2.8	11.1 ± 3.0*	< 0.001	12.3 ± 3.1	11.8 ± 3.2*	0.010

Continuous variables are mean ± standard deviation. FMR = functional mitral regurgitation; LA = left atrial volume; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; 6 MWT = six-minute walk test; NYHA = New York Heart Association class; QoL = quality of life.

* $p < 0.05$ vs baseline no/mild FMR unchanged at 6 months.

† $p < 0.05$ vs baseline no/mild FMR worsened at 6 months.

‡ $p < 0.05$ vs baseline moderate to severe FMR improved at 6 months.

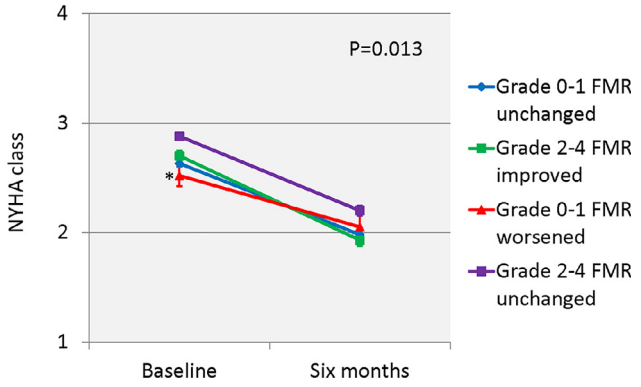


Figure 2. Changes in New York Heart Association (NYHA) class, according to different patterns of evolution of functional mitral regurgitation (FMR). Changes in NYHA class are shown from baseline to six months after cardiac resynchronization therapy (CRT), according to the different patterns of evolution of FMR. *p <0.05 vs other groups. Vertical bars represent standard error of the mean.

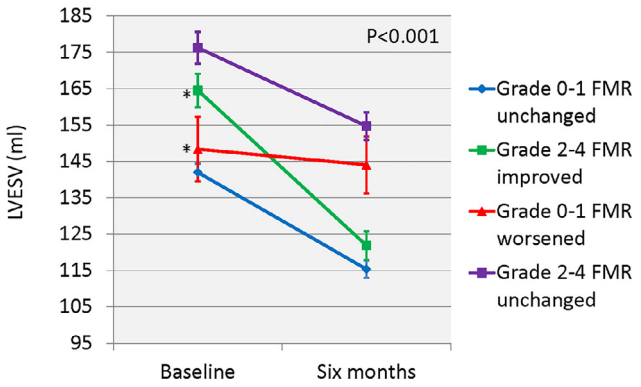
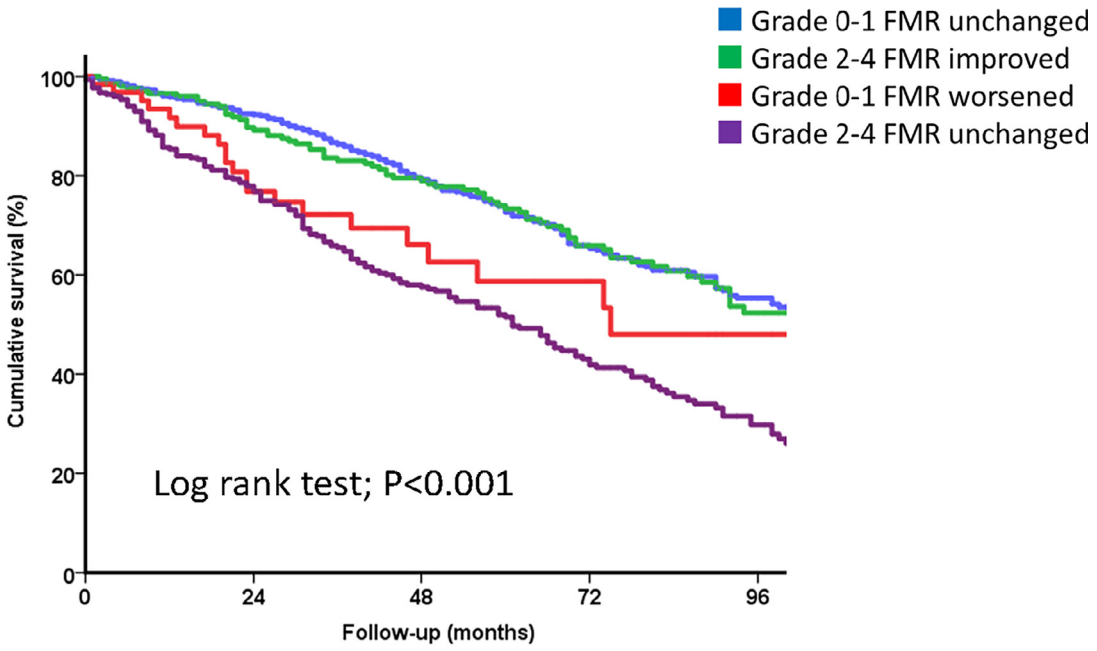


Figure 3. Changes in left ventricular, end-systolic volume (LVESV), according to different patterns of evolution of functional mitral regurgitation (FMR). Changes in LVESV from baseline to six months after cardiac resynchronization therapy (CRT) are shown, according to different patterns of evolution of FMR. *p $<$ 0.01 vs other groups. Vertical bars represent standard error of the mean.

moderate to severe baseline FMR in whom CRT did not improve FMR, had a worse long-term prognosis compared with patients who exhibited no or mild FMR after 6 months of CRT (Figure 5). This association with mortality was independent of LV volume changes and clinical CRT response.

The reported prevalence of FMR in patients with HF has varied in previous studies.[4,8,14] In the present study of a large, unselected group of patients, the 43% prevalence of moderate or severe FMR at baseline was similar to the series of Rossi et al[4] (moderate 49%, severe 24%) and Cipriani et al[8] (55% moderate/severe). Numerous studies have documented CRT's ability to reduce FMR both acutely, long-term, during rest and exercise.[15–20] CRT addresses various aspects of FMR pathophysiology; by resynchronizing the atrioventricular and inter- and intraventricular contraction, LV preload is optimized and mitral valve closing forces increased, leading to FMR reduction. By inducing LV reverse remodeling, papillary muscle tethering on mitral leaflets is reduced and mitral annulus dimensions shrink, resulting in improved leaflet coaptation.[19,21–23] In the present study, patients with no or mild FMR at baseline which remained unchanged at 6-month follow-up and patients with moderate to severe FMR at baseline which improved at 6 months after CRT showed the most pronounced LV reverse remodeling, suggesting that CRT ameliorates the underlying pathophysiology of FMR. Interestingly, we found less NYHA functional class improvement and less LVESV reduction in CRT recipients with no or mild FMR at baseline which worsened at 6 months compared with other groups, whereas the worst survival was seen in those with moderate to severe FMR at baseline which remained unchanged. These data demonstrate that mechanisms underlying symptomatic improvement and LVESV changes after CRT are multifactorial in origin, reflecting more than just changes in FMR.

Most important is whether the changes in FMR grade after CRT impact the long-term prognosis of HF patients. In the Cardiac Resynchronization Therapy in Heart Failure (CARE-HF) trial, FMR grade at 3 months follow-up was an independent predictor of survival.[24] In a study by Verhaert et al,[25] at 6 months post-CRT both the extent of decrease and the degree of residual FMR were independently associated with survival.[25] More recently, data from the Italian ClinicalService Project (Clinical-Trials.gov Identifier: NCT01007474) reported that at 1 year after CRT implantation, FMR worsened by 1 grade in 42% of patients and remained significant but unchanged from baseline in 58%.[8] The absence of improvement in FMR at 1-year follow-up after CRT was independently associated with increased all-cause mortality. Findings from our large-scale study support the fact that FMR response to CRT during the first 6 months is an important predictor of long-term survival, and provide new insights to this relation. Moderate to severe FMR at baseline, which remained unchanged at 6 months after CRT implantation, was independently associated with all-cause mortality in HF patients. This association remained significant after adjusting for multiple variables known to impact on HF mortality, including the LV remodeling response to CRT. Although FMR and LV volumetric response to CRT are intertwined, the fact that a reduction in FMR was an independent predictor of survival after accounting for LV reverse remodeling demonstrates that the FMR reduction is not merely a reflection of the volumetric response of the LV, but contributes uniquely to long-term survival. The results of the present study are clinically relevant as they emphasize the unmet need for HF patients in whom FMR persists or worsens after CRT. Therapeutic options for patients with residual moderate to severe FMR after CRT are limited, and they may be considered for percutaneous mitral valve repair. The use of the MitraClip device (Abbott Vascular, Menlo Park, California) impacted favorably on symptoms, LV remodeling and LV function in the Percutaneous Mitral Valve Repair in Cardiac Resynchronization Therapy (PERMIT-CARE) study of 51 patients with residual moderate to severe FMR after CRT.[26] More recently, the results of the MITRA-FR study, randomizing 152 HF patients to optimal medical therapy (including CRT) and 152 patients to optimal medical therapy and MitraClip implantation, showed similar



Number of patients at risk					
Grade 0-1 FMR unchanged	609	495	362	207	96
Grade 2-4 FMR improved	209	167	134	83	38
Grade 0-1 FMR worsened	66	38	19	11	6
Grade 2-4 FMR unchanged	309	210	139	72	34

Figure 4. Kaplan−Meier survival curves for time to cumulative survival in different patterns of functional mitral regurgitation (FMR) evolution. Data are shown for patients with baseline grade 0-1 FMR which remained unchanged at 6 months, baseline grade 2−4 FMR which improved at 6 months, baseline grade 0−1 FMR which worsened at 6 months and baseline grade 2−4 FMR which remained unchanged at 6 months.

Table 3
Predictors of all-cause mortality risk, univariable, and multivariable Cox proportional hazards models

	Univariable analysis			Multivariable analysis		
Variable	HR	95% CI	p value	HR	95% CI	p value
Baseline grade 0-1 FMR unchanged	-	-	-	-	-	-
Baseline grade 2-4 FMR improved	1.03	0.79-1.34	0.821	1.19	0.89-1.59	0.239
Baseline grade 0-1 FMR worsened	1.58	1.01-2.48	0.046	1.30	0.76-2.23	0.337
Baseline grade 2-4 FMR unchanged	2.16	1.77-2.65	< 0.001	1.77	1.41-2.22	< 0.001
Age (years)	1.04	1.03-1.05	< 0.001	1.03	1.02-1.04	< 0.001
Men	1.37	1.10-1.71	0.005	1.42	1.09-1.85	0.009
Body mass index (kg/m^2)	0.97	0.95-0.99	0.009	0.98	0.96-1.01	0.131
Diabetes mellitus	1.72	1.42-2.09	< 0.001	1.56	1.23-1.99	< 0.001
Ischemic etiology of heart failure	1.58	1.32-1.90	< 0.001	1.18	0.95-1.47	0.138
Diuretic use	1.77	1.38-2.28	< 0.001	1.23	0.91-1.66	0.176
Hemoglobin (g/dL)	0.80	0.73-0.87	< 0.001	0.92	0.83-1.03	0.147
Renal dysfunction (eGFR < 60 ml/min/1.73 m^2)	2.71	2.28-3.23	< 0.001	1.94	1.57-2.40	< 0.001
LVEF at 6 months (%)	0.96	0.95-0.97	< 0.001	0.98	0.96-0.99	< 0.001
Positive echo response*	0.61	0.52-0.73	< 0.001	0.82	0.66-1.02	0.080
Positive clinical response	0.82	0.68-0.99	0.040	0.82	0.67-1.01	0.059
Atrial fibrillation	1.76	1.43-2.18	< 0.001	1.39	1.08-1.79	0.010

CI = confidence interval; eGFR = estimated glomerular filtration rate; FMR = functional mitral regurgitation; HR = hazard ratio; LVEF = left ventricular ejection fraction.

* LVESV reduction of ≥ 15% at 6 months after cardiac resynchronization therapy.

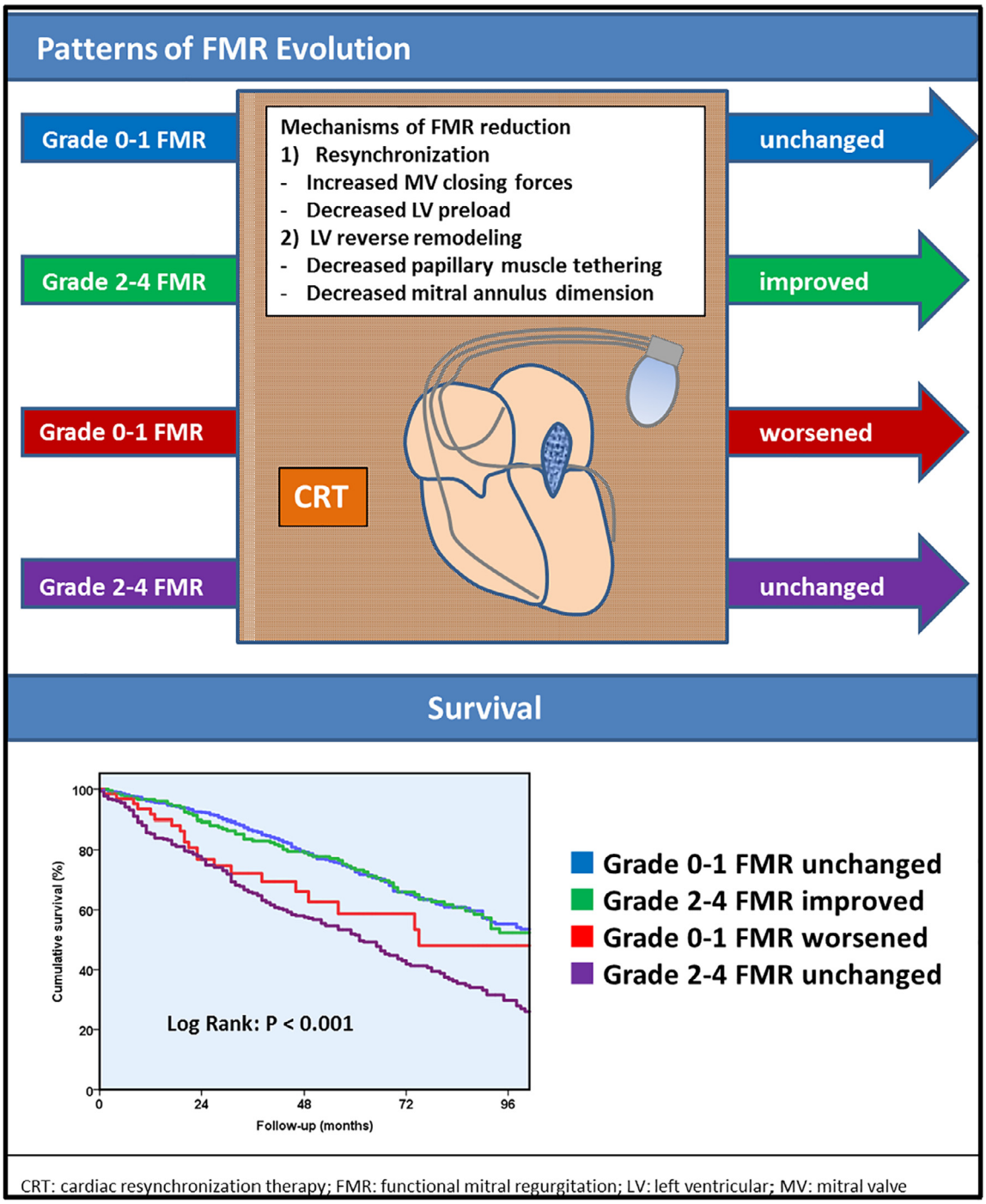


Figure 5. Clinical outcome of different patterns of evolution of functional mitral regurgitation (FMR) after cardiac resynchronization therapy (CRT). Mechanisms of the effect of CRT on FMR are shown for four different patterns of evolution of FMR and their impact on clinical outcomes.

outcomes in terms of all-cause mortality and unplanned hospitalization for HF.[27] The ongoing Cardiovascular Outcomes for Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional MR trial (Clinical-Trials.gov Identifier: NCT01626079) will provide further evidence on the efficacy of transcatheter mitral valve repair in this high-risk group.

Some limitations should be acknowledged. This was a retrospective, single-center study. FMR severity may be influenced by LV loading conditions, that is, preload (e.g., diuretics) or afterload (e.g., general anesthesia), which may vary over time. Patients who died before 6 months, underwent mitral valve repair or replacement and those without follow-up echocardiography at 6 months were excluded, potentially introducing selection bias. Nonetheless, medical therapy (with CRT when appropriate) is the accepted standard of care for most HF patients with FMR,[28] and thus the outcomes of the present study are likely representative of

what may be expected post-CRT. Finally, although the largest study to date examining the outcomes of FMR after CRT in HF patients, it was likely underpowered to determine whether FMR worsening from grade 0−1 at baseline to 2−4 at 6 months is an independent predictor of mortality, as this occurred in only 66 patients.

In conclusion, in the present, large-scale study of HF patients treated with CRT, moderate to severe FMR at baseline, which remained unchanged at 6 months, was strongly associated with increased all-cause mortality independent of LV remodeling and the clinical response to CRT.

Disclosures

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All individuals who contributed to this publication, have been included as investigators.

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