

Prognostic Role of Left Ventricular Dysfunction in Patients With Coronary Artery Disease After an Ambulatory Cardiac Rehabilitation Program



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The relationship between left ventricular ejection fraction (LVEF) and outcomes after cardiac rehabilitation (CR) is not well established; therefore we assessed the prognostic role of LVEF at the end of ambulatory CR program in patients (pts) who received coronary revascularization. LVEF was evaluated at hospital discharge and re-assessed at the end of CR in all ST-elevation myocardial infarction and coronary artery bypass graft pts, while in pts with non-ST-elevation MI or elective percutaneous coronary intervention the echocardiography was repeated if they had an impaired LVEF at discharge. New hospitalizations for cardiovascular causes at 1-year, and cardiovascular mortality during long-term follow-up were analyzed. We enrolled in CR 3078 pts, 86% showed LVEF \geq 40% and 9% LVEF $<$ 40%. Of those with a discharge LVEF $<$ 40%, 56% improved LVEF (LVEF \geq 40%) after CR. At 1-year, heart failure was the main cause of new hospitalizations in LVEF $<$ 40% group compared with LVEF \geq 40% group (5% vs 0.4%, $p < 0.01$). During a mean follow up of 48 ± 25 months, cardiovascular death occurred in 9% of pts with LVEF $<$ 40% and in 2% with LVEF \geq 40% ($p = 0.014$). At Cox multivariate analysis, LVEF $<$ 40% at the end of CR and age were independent predictors of hospitalization and mortality for cardiovascular causes, while coronary artery bypass graft was a protective factor. In conclusion, during CR the improvement of LVEF occurs in a relevant proportion of patients, the re-assessment of LVEF at the end of the CR is helpful for risk stratification because left ventricle dysfunction at the end of CR is associated with worse cardiovascular outcomes. © 2019 Elsevier Inc. All rights reserved. (Am J Cardiol 2019;124:355–361)

The prevalence of heart failure is approximately 1% to 2% of the adult population in developed countries and ischemic heart disease is the predominant cause.¹ Exercise-based cardiac rehabilitation (CR) after an acute coronary syndrome or coronary revascularization evolving in heart failure is a treatment that should be included in the management of these patients.² The safety and efficacy of CR in a modern health care system were demonstrated in several trials and its benefits on ventricular remodeling, exercise capacity and cardiovascular outcome are established.^{3,4,5} However, the relationship between left ventricular ejection fraction (LVEF) and outcome after CR program is not defined. The aim of this study is to assess the prognostic role of LVEF at the end of CR program after ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), elective

percutaneous coronary intervention (PCI), and coronary artery bypass graft with or without valvular surgery (CABG).

Methods

In this study, we analysed the clinical and instrumental characteristics of 3,078 consecutive patients attended an ambulatory CR program from January 1, 2009 to December 31, 2015.

All patients discharged from our Cardiovascular Department were referred to CR with a scheduled visit reported on discharge letter. These patients were unselected, only who were not residents in the region or with severe noncardiac co-morbidities were excluded. The referral rate in our center was 80% of the discharged patients. According to the guidelines, STEMI and CABG patients were convened to the first evaluation within 2 weeks, while NSTEMI and PCI in 4 weeks.

At the first visit, the clinical and risk profile was evaluated and the CR planned. All data were included in the “Observational Cardiac Rehabilitation Division Registry”.^{6,7} Only 4% of patients did not complete the CR program.

Per protocol, LVEF was assessed at discharge from Cardiovascular Department in all patients. In all STEMI and CABG patients LVEF was re-assessed at the end of CR,

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regardless of LVEF value at enrolment in CR; in NSTEMI and PCI patients, LVEF was re-assessed at the end of CR if they had an impaired systolic function at hospital discharge.

At the baseline, the population was divided into 2 groups considering values of LVEF <40% and LVEF ≥40%.

During 1-year follow-up from the end of CR, we evaluated the incidence of new hospitalizations for heart failure, acute coronary syndromes, coronary revascularization (CABG or PCI), and the incidence of cerebrovascular events (stroke or transient ischemic attack).

All-causes mortality and cardiovascular mortality were also evaluated during long-term follow-up.

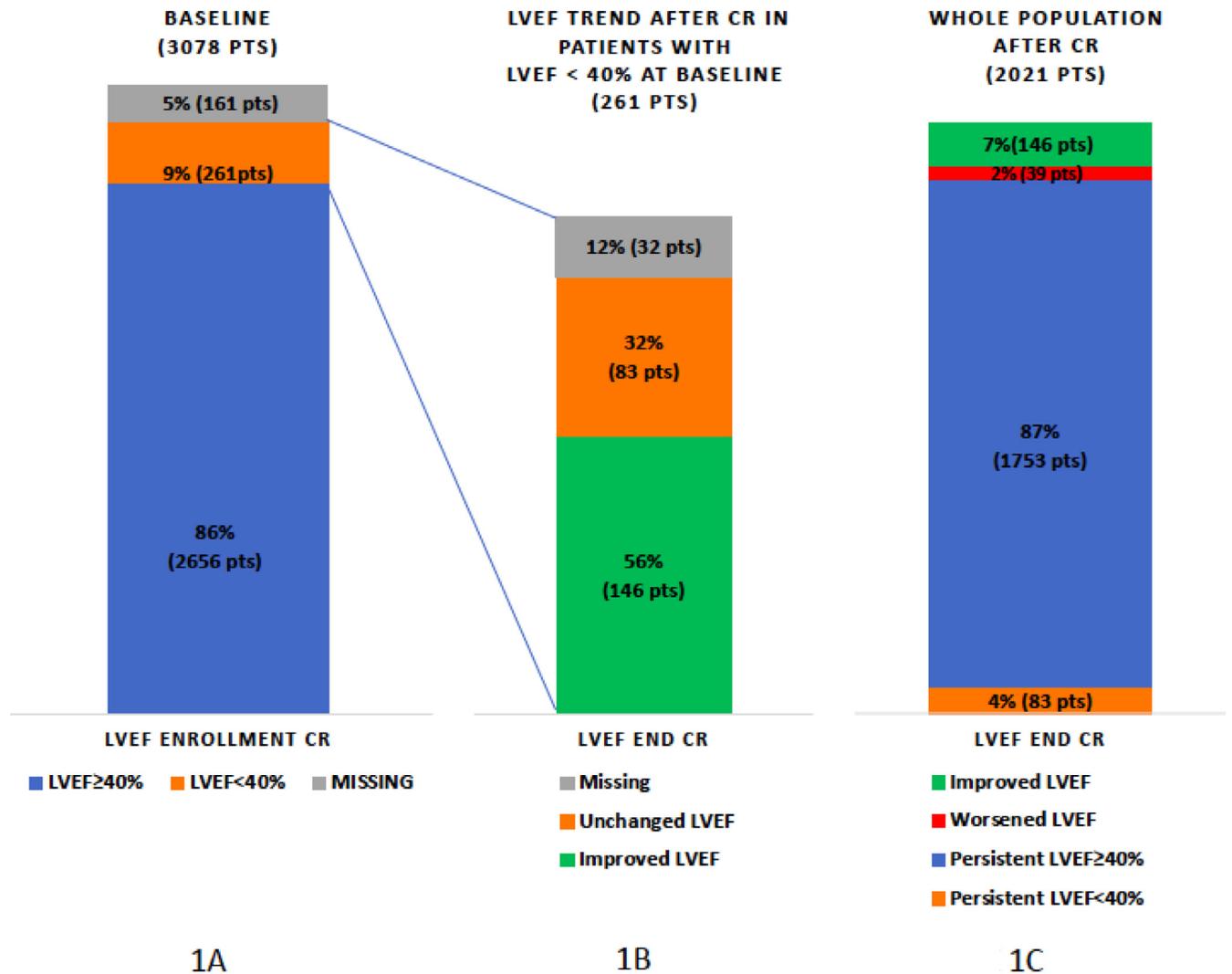
The CR program was performed in a dedicated ambulatory Cardiac Rehabilitation Division.

The NSTEMI or PCI patients received clinical-instrumental evaluations until achievement of therapeutic and

clinical targets, with scheduled visits, cycle-ergometer tests and echocardiogram. STEMI and CABG were also sent to a physical activity, consisting in a first part of 10 sessions of 45 minutes of cyclette training 2 times a week for 5 weeks, and a second part of 12 sessions of 45 minutes of gym training 3 times a week for 6 weeks. The average duration of the CR program for the whole population was 5 months.

The program was considered concluded when the patients demonstrated ischemic stability, absence of heart failure and the achievement of the secondary prevention targets.

There were 3 different levels of physical activity: low, medium, and high. Six minutes walking test (MWT) was used to assess exercise capacity of patients, for insert them in appropriate level of work. The physical session was supervised by a nurse and physiotherapist, with continuous



LEGEND. CR: Cardiac Rehabilitation; LVEF: Left ventricular ejection fraction; PTS: patients.

Figure 1. LVEF values at enrollment in CR and the variations of LVEF at the end of CR. CR =cardiac rehabilitation; LVEF =left ventricular ejection fraction.

cardiac monitoring assessment. Moreover, the CR program was tailored for “frail” patients, such as very old patients (>80 years) or affected by several comorbidities and functional limitations, with specific physical exercises, clinical and instrumental evaluations.

All groups benefited of individual counseling about lifestyle (diet, smoke, physical activity) with nutritionist and psychologist. After CR, all patients were referred to cardiology ambulatory service, where were periodically visited.

Continuous variables were expressed as mean \pm standard deviation or as median with interquartile range for continuous variables depending on the distribution shape. For continuous variables, differences between 2 groups were compared using Students' *t* test or Mann–Whitney *U* test. Categorical variables were expressed as counts and percentages and compared by Chi-square test or Fisher exact test, when appropriate.

In order to evaluate the prognostic value of left ventricular dysfunction, we used univariate and multivariate Cox proportional hazards regression analysis to calculate unadjusted and adjusted hazard ratios and 95% confidence intervals.

Survival curves were estimated by the Kaplan-Meier method and compared by log-rank tests. The statistical analysis was performed using the IBM-SPSS version 21 (Armonk, NY: IBM Corp).

Results

From January 1, 2009 to December 31, 2015, we enrolled in ambulatory CR program 3,078 patients, in which 86% showed LVEF \geq 40%, 9% LVEF <40%, while

in 5% of cases the data were missing (Figure 1A). The clinical characteristics of the 2 groups at baseline are reported in Table 1. CR program lasted 5 ± 4 months, 2% were referred to in-hospital CR before to start the ambulatory CR and only 4% of patients did not complete the program.

In comparison with group with LVEF \geq 40%, patients with LVEF <40% were older, more frequently male and were enrolled in CR mainly after CABG, only 11% after PCI. There were not significant differences on risk profile and co-morbidities between the 2 groups; however, in patients with reduced LVEF, CR lasted longer than patients with LVEF \geq 40%.

At the end of CR, per protocol, 2,021 pts had a re-evaluation of LVEF. Of those with a discharge LVEF <40% (261 pts), 56% (146 pts) improved LVEF (LVEF \geq 40%) after CR (Figure 1B), conversely of those with discharge LVEF \geq 40% and per protocol re-evaluation of LVEF, 2% (39 pts) worsened LVEF (<40%) after CR. Overall after CR, 87% of patients had persistent LVEF \geq 40%, 4% persistent LVEF <40%, 7% improved LVEF \geq 40% and 2% worsened LVEF <40% (Figure 1C).

The individuals with stable LVEF <40% and worsened LVEF were mainly represented by STEMI and CABG patients, 23% of those with stable LVEF <40%, were enrolled in CR with ICD while 13% were implanted during CR (supplementary Table 1). The achievement of secondary prevention targets in this population is reported in supplementary Table 2.

At 1-year follow-up from the end of CR program, heart failure was the leading cause of new hospitalizations in LVEF <40% group compared with LVEF \geq 40% group (Table 2). At subgroup analysis, heart failure at 1-year follow-up occurred more frequently in patients with worsened

Table 1
Baseline characteristics

	Left ventricular ejection fraction		p Value
	\geq 40% (n = 2656)	< 40% (n = 261)	
Age (mean \pm standard deviation; years)	69\pm11	73\pm10	<0.001
Male	1891 (71%)	205 (79%)	0.012
Dyslipidaemia	1629 (61%)	163 (62%)	0.723
Diabetes mellitus	522 (20%)	53 (20%)	0.800
Smoke	716 (58%)	78 (56%)	0.585
Chronic renal failure	404 (40%)	60 (48%)	0.085
Chronic obstructive pulmonary disease	279 (31%)	21 (22%)	0.062
Hypertension	2024 (76%)	186 (71%)	0.064
In-hospital rehabilitation	53 (2%)	5 (2%)	0.569
ST-elevation myocardial infarction	816 (31%)	83 (32%)	0.719
Non-ST-elevation myocardial infarction	586 (22%)	57 (22%)	0.934
Percutaneous coronary intervention	434 (16%)	29 (11%)	0.027
Coronary artery by-pass	791 (30%)	88 (34%)	0.186
Implantable cardioverter defibrillator	0 (0%)	31 (13%)	0.009
Low-density lipoprotein (mg/dL) (mean \pm standard deviation)	85 \pm 30	88 \pm 35	0.178
Heart rate (bpm) (mean \pm standard deviation)	67 \pm 13	68 \pm 12	0.655
Systolic blood pressure (mm Hg) (mean \pm standard deviation)	137 \pm 20	136 \pm 19	0.370
Diastolic blood pressure (mm Hg) (mean \pm standard deviation)	79 \pm 10	81 \pm 43	0.089
Glycated hemoglobin (%) (mean \pm standard deviation)	7 \pm 1	7 \pm 1	0.803
Cardiac rehabilitation duration (days) (mean \pm standard deviation)	156 \pm 88	174 \pm 104	0.005

Table 2
Events (hospitalizations and mortality)

	Left ventricular ejection fraction		p Value
	≥40% (n = 1899)	< 40% (n = 122)	
	Hospitalizations (1-year follow-up)		
Heart failure	7 (0.4%)	6 (5%)	<0.001
Acute coronary syndrome	18 (1%)	0 (0%)	0.621
Percutaneous coronary intervention	12 (0.6%)	1 (1%)	0.548
Coronary artery by-pass	2 (0.1%)	0 (0%)	1.000
ICTUS/Transient ischemic attack	3 (0.1%)	1 (1%)	0.202
	Long-term mortality*		
Total death	162 (9%)	23 (19%)	0.001
Cardiovascular death	45 (2%)	13 (9%)	0.014

* 48 ± 25 months of follow up.

LVEF, and patients with persistent LVEF <40%. On the other hand, patients who improved their LVEF, registered few adverse cardiovascular events at 1-year follow-up (supplementary Table 2).

During the entire follow-up (48 ± 25 months), long-term death for cardiovascular causes occurred in 9% of patients with LVEF <40% and in 2% with LVEF ≥40% (p = 0.014), and all cause death occurred in 19% versus 9% (0.001) in LVEF <40% group compared with LVEF ≥40% group, respectively (Table 2). At subgroup analysis, long-term cardiovascular mortality occurred more frequently in patients with persistent LVEF <40% and worsened LVEF (supplementary Table 3). Kaplan Meier survival curves for the composite end point, cardiovascular hospitalizations and cardiovascular mortality in patients with persistent LVEF ≥40%, improved LVEF and persistent LVEF <40% are showed in Figure 2.

Univariate analysis is showed in Table 3. The multivariate Cox proportional hazard analysis showed that LVEF <40% at the end of CR and age were independent predictors of hospitalizations and mortality for cardiovascular causes while CABG was a protective factor (Table 3).

Discussion

In this study, performed in a large cohort of patients and with a long-term follow-up, we showed the prognostic role of LVEF assessed at the end of CR demonstrating that was associated with worse outcomes. Interestingly, in patients with baseline LVEF <40% an improvement of left ventricular function was obtained in a relevant proportion of patients (56%) during participation in a CR program.

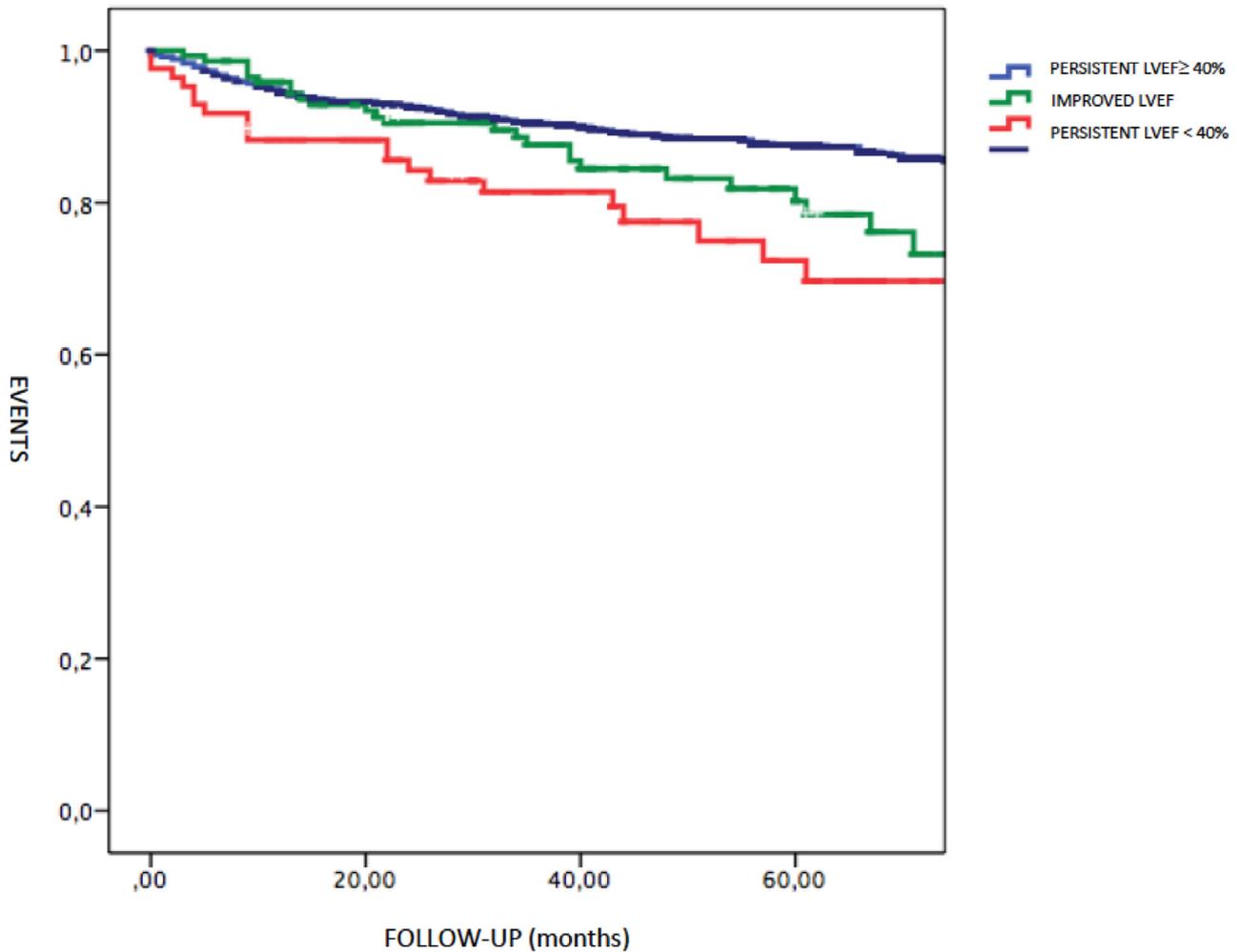
In our population, patients enrolled in CR with LVEF <40% at discharge from Cardiovascular Department and persistent left ventricular dysfunction after CR, showed high rate of hospitalizations for heart failure at 1-year follow-up. A significant difference between the 2 groups emerged also during the long-term follow-up, in which mortality was significantly higher in patients with LVEF <40%. However, patients with LVEF improvement presented a low rate of new hospitalizations and cardiovascular mortality during follow-up.

Our findings are consistent with previous observations demonstrating the prognostic value of LVEF in terms of mortality and hospital readmission rates for cardiovascular events after an acute coronary syndrome or revascularization.^{8,9,10,11,12}

In our population, LVEF dysfunction at the end of CR emerged not only as risk factor for cardiovascular events but also as an independent predictor of worse prognosis at multivariate analyses. These results are in agreement with study of Van der Vleuten et al¹³ in which in smaller population of 925 patients after PCI, age and LVEF were independent predictors of 1- and 3-year mortality. Likewise, Schwammenthal et al reported that in a cohort of 417 patients with AMI, an LVEF <40% was an independent predictor of the combined endpoint of death, congestive HF, and recurrent AMI at 30 days after AMI.¹⁴ However, these studies were performed on LVEF measured at discharge from index hospitalization for acute coronary syndrome or revascularization, while the original point of view of our analyses is that we evaluated also the prognostic role of LVEF after CR program.

Regular physical activity and structured exercise training are a recommendation class I in the European Society of Cardiology heart failure guidelines,² since physical activity does not adversely affect left ventricular remodeling, and may reduce mortality and hospitalization in patients with chronic heart failure.^{15,16,17,4,18,19} HF-ACTION²⁰ was the largest multicenter, randomized controlled trial that demonstrated the safety of physical exercise in a large population of patients with heart failure. In this analysis, exercise training was associated with an 11% reduction in all-cause mortality and hospitalizations, as well as a 15% reduction in cardiovascular mortality and hospitalizations. Similar results were reported in the updated Cochrane systematic review and meta-analysis on 33 trials including 4,740 participants with a reduced ejection fraction (<40%) and New York Heart Association class II and III. In this meta-analysis is reported an improvements in hospitalization and health-related quality of life with exercise-based CR, but it was not able to demonstrated an impact on mortality in the short term.²¹

Recently, we demonstrated the protective role of CR program in reduction of hospitalizations and mortality for



Log Rank Persistent LVEF \geq 40 vs Persistent LVEF < 40: $p = < 0.001$

Legend: LVEF: left ventricular ejection fraction

Figure 2. Kaplan-Meier survival curves for the composite end-point, cardiovascular hospitalization and cardiovascular mortality. CR = cardiac rehabilitation; LVEF = left ventricular ejection fraction.

cardiovascular causes in patients with coronary disease independently from LVEF, during a long-term follow-up.²²

Although the reported evidence and guideline recommendations, CR in patients with reduced LVEF is poorly implemented in daily clinical practice. The last European CR Inventory Survey highlighted that less than 20% of patients with LVEF dysfunction were involved in a CR program.²³ In our CR service, we tried to reduce a possible selection bias registering a high rate of enrollment with almost 80% of eligible patients referred to CR.

Usually, CR for patients with heart failure is provided on appropriate ambulatory centers²⁴ but novel strategies are developing in order to improve the accessibility, effect of CR, and adherence to treatment in patients with heart

failure. In select populations, home-based CR has been demonstrated to be as effective as center-based CR in improving exercise capacity, risk factor control, and health-related quality of life.²⁵ Alternative models for program delivery are represented by tele-health and web-based platforms.²⁶

Our findings should be interpreted in light of the common limitations of observational studies, however the “Observational Cardiac Rehabilitation Division Registry” was built and prospectively filled in order to periodically evaluate and monitor the epidemiology and the efficacy of the ambulatory CR program. The results of this study derived from a single center CR program with its own specific CR protocols, however the CR program in our

Table 3
Univariable and multivariable analysis (hospitalizations and mortality)

	Univariable analysis		Multivariable analysis	
	Hazard ratio (95% CI)	p Value	Hazard ratio (95% CI)	p Value
Male	0.903 (0.692-1.180)	0.455		
Age	1.057 (1.044-1.071)	<0.001	1.055 (1.042-1.069)	<0.001
Heart rate end cardiac rehabilitation	0.985 (0.971-0.999)	0.032		
In-hospital rehabilitation	1.790 (0.186-17.234)	0.614		
ST-elevation myocardial infarction	1.066 (0.832-1.365)	0.615		
Non-ST-elevation myocardial infarction	1.425 (1.020-1.989)	0.038		
Percutaneous coronary intervention	1.609 (1.094-2.367)	0.016		
Coronary artery by-pass	0.649 (0.500-0.843)	0.001	0.636 (0.488-0.829)	0.001
Implantable cardioverter defibrillator end CR	0.046 (0.000-13.782)	0.290		
LVEF <40% end cardiac rehabilitation	2.244 (1.532-3.286)	<0.001	2.087 (1.425-3.058)	<0.001
Improved left ventricular ejection fraction	1.479 (0.979-2.234)	0.063		
Dyslipidaemia	1.246 (0.965-1.609)	0.091		
Diabetes mellitus	0.763 (0.548-1.061)	0.108		
Chronic renal failure	1.038 (0.712-1.513)	0.845		
Chronic obstructive pulmonary disease	0.761 (0.474-1.222)	0.259		
Hypertension	0.885 (0.673-1.164)	0.381		
Glycated hemoglobin	0.935 (0.780-1.122)	0.473		
Low-density lipoprotein	1.003 (0.998-1.008)	0.297		

institution is inspired and follows strictly, the international guidelines recommendations. Finally, we did not collect information about adherence on pharmacological therapy.

We confirmed the predictive role of LVEF after an acute coronary syndrome or coronary revascularization and we highlighted that its assessment should be recommended for risk stratification not only at discharge of the index event, but also at the end of cardiac rehabilitation program. Indeed, the recovery of left ventricular function is present in a significative number of patients after CR. This may support the proven role of CR on better long-term outcomes; however, the accessibility and the quality of program should be increased to favor a better prognosis in patients with coronary disease and left ventricular dysfunction.

Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.amjcard.2019.04.050>.

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