Left ventricular ejection fraction and adjudicated, cause-specific hospitalizations after myocardial infarction complicated by heart failure or left ventricular dysfunction

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Abstract

Background Reduced left ventricular ejection fraction (LVEF) after acute myocardial infarction (MI) increases risk of cardiovascular (CV) hospitalizations but evidence regarding its association with non CV outcome is scarce. We investigated the association between LVEF and adjudicated cause-specific hospitalizations following MI complicated with low LVEF or overt heart failure (HF).

Methods In an individual patient data meta-analysis of 19,740 patients from three large randomized trials, Fine and Grey competing risk modelling was performed to study the association between LVEF and hospitalization types.

Results The most common cause of hospitalization was non CV (n = 2,368 for HF, n = 1,554 for MI, and n = 3,703 for non CV). All types of hospitalizations significantly increased with decreasing LVEF. The absolute risk increase associated with LVEF <25% (vs LVEF >35%) was 15.5% (95% confidence interval [CI] 13.4-17.5) for HF, 4.7% (95% CI 3.0-6.4) for MI, and 10.4% (95% CI 8.0-12.8) for non CV hospitalization. On a relative scale, after adjusting for confounders, each 5-point decrease in LVEF was associated with an increased risk of HF (hazard ratio [HR] 1.15, 95% CI 1.12-1.18), MI (HR 1.06, 95% CI 1.03-1.10), and non CV hospitalization (HR 1.03, 95% CI 1.01-1.05).

Conclusions In a high-risk population with complicated acute MI, the absolute risk increase in non CV hospitalizations associated with LVEF <25% was 2/3 of the absolute risk increase in HF hospitalizations and twice the absolute risk increase in MI hospitalizations. LVEF was an independent predictor of all types of hospitalization and appears as an integrative marker of sicker patient status.

Keywords: Heart failure; Hospitalization; Left ventricular dysfunction; Left ventricular ejection fraction; Myocardial infarction.

Abbreviations

ACE	Angiotensin-converting enzyme
ARB	Angiotensin receptor blockers
CI	Confidence interval
CV	Cardiovascular
HR	Hazard ratio
HF	Heart failure
IPD	Individual patient data
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
SD	Standard deviation

Introduction

Despite considerable advance in prevention and treatment of cardiovascular (CV) disease over the past decades, acute myocardial infarction (MI) continues to be a major cause of morbidity and mortality worldwide.[1] An area with potential improvement of care lies in mitigating the number of MI patients readmitted to hospital in the period following their event.[2] Furthermore, the challenge is compounded by the fact that a significant proportion of such hospitalizations may be caused by other conditions conceivably not directly linked to the prior MI event.[3] Patients with heart failure (HF) or left ventricular (LV) dysfunction after acute MI are at high risk of subsequent hospitalization.[4,5] Thus, identifying prognostic factors for these events may reduce morbidity and healthcare expenditure. Low LV ejection fraction (LVEF) is an established predictor of adverse outcome after MI, but its ability to forecast cause-specific hospitalization in a high-risk population is less well defined.[6-8] As well, while the risk of non CV related outcomes has been investigated quite extensively in the field of HF and particularly in HF with preserved LVEF, data for such endpoints following complicated MI are scarce.[9,10] On this background, the present study aimed to investigate the association between LVEF and adjudicated cause-specific hospitalizations for HF, MI, and non CV causes in patients at high risk for hospitalizations following complicated acute MI.

Methods

The High-Risk Myocardial Infarction Database Initiative

The High-Risk MI Database Initiative has been described in detail previously.[11] In brief, it conformed a large-scale database by merging individual patient data (IPD) from several double-blind, randomized, placebo-controlled trials that evaluated pharmacological intervention after acute MI. All subjects had signs of HF, evidence of LV dysfunction, or both of these characteristics (n = 28,771). These were enrolled between 12 hours and 21 days after the index acute MI and followed for a mean of 2,7 years. The main aims of the initiative were to define the prognostic profile of a high-risk population with acute MI, explore important subgroups, and estimate event rates based on baseline demographics.[11] The data used in the present study stem from three of the trials; the Carvedilol Post-Infarct Survival Control in LV dysfunction (CAPRICORN) trial (n = 1959), the Eplerenone Post Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial (n = 6632), and the Valsartan in Acute Myocardial Infarction (VALIANT) trial (n = 14,703). Their rationale, design, inclusion and exclusion criteria, definition of endpoints, and results have been published previously.[12-17] The trials were conducted in accordance with the Declaration of Helsinki and were approved by ethics committees. All patients signed informed consents.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. No extramural funding was used to support this work.

Baseline data and evaluation of left ventricular function

Baseline characteristics at the time of acute MI were registered, including demographics, past history, clinical observations, use of medications, and results of relevant blood tests. Patients were at each site per protocol assessed for symptoms and signs of HF and LVEF was determined by echocardiography, contrast ventriculography, or radionucleotide ventriculography.

Clinical events

Clinical events that occurred during follow-up were classified, including subtypes of CV hospitalization. Thus, HF and MI hospitalizations could be extracted as individual endpoints from the database. Non CV hospitalizations were defined as

hospitalizations due to other than predefined CV causes. All cause-specific events were by design adjudicated by independent endpoint committees.

Statistical analysis

Continuous variables are described as mean ± standard deviation (SD) or median (quartiles 1-3), and categorical variables are reported as frequencies (percentages).

We compared baseline characteristics stratified by LVEF categories by using univariable analysis of variance for continuous variables and chi-square tests for categorical variables. We also compared LVEF groups by calculating absolute standardized mean difference. While there is no clear consensus as to what threshold can be taken to indicate the presence of imbalance, some authors have suggested that a standardized difference in excess of 0.10 may be indicative of meaningful imbalance in a covariate between two groups.[18]

The Kaplan Meier method was used to assess risk for each outcome according to LVEF categories and event curves were generated. The risk differences at one year and two years with confidence intervals (CI) at 95%, between each of the two first groups (LVEF <25%, LVEF 25-35%) and the last group (LVEF >35%), are also provided. The relationship between LVEF (continuous per 5-point decrease or categorized (<25%, 25-35%, and >35%)) and events (HF hospitalization, MI hospitalization, and non CV hospitalization) were subsequently tested in Fine and Gray competing risk models with death as competing event. Model 1 included demographic characteristics (age and gender), model 2 included variables in model 1 and clinical characteristics (Killip class, systolic blood pressure), comorbidities (diabetes, hypertension, renal insufficiency, chronic obstructive pulmonary disease, and peripheral artery disease), and medication (beta-blockers, angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARB), diuretics), and model 3 included variables in model 2 and estimated glomerular filtration rate. Hazard ratios (HR) and 95% CIs for time to event are reported. We also performed an exploratory assessment of the discriminative value of LVEF by testing the increase Harrell's c-index and continuous net reclassification improvement at one year. The continuous net reclassification improvement method developed by Uno and implemented in the survIDINRI package of the R software was used.[19]

Statistical analyses were performed in SAS version 9.3 (SAS Institute Inc., Cary, North Carolina, USA) and R software (the R foundation for Statistical

Computing). Relevant methodological assumptions were verified, including pairwise interaction and collinearity, log-linearity, and proportionality of hazards. A p-value <0.05 was regarded statistically significant, and all hypothesis testing was two-tailed.

Results

19,740 patients were included with a mean follow-up of 702 ± 337 days, during which 13,023 hospitalizations occurred. The most frequent cause of hospitalization was non CV (n = 3,703) followed by HF (n = 2,368) and MI (n = 1,554).

Baseline characteristics

Relevant baseline characteristics according to LVEF categories have been published previously and are presented in Table 1.[20] The subjects in the lower LVEF categories were older, had lower body mass index and were more likely to be males. As well, a history of other comorbidities, a more severe presentation with lower systolic blood pressure and higher Killip class, and use of diuretics were more frequent. Typical parameters associated with HF and low LVEF, such as decreased glomerular filtration rate and lower concentrations of hemoglobin and sodium, were also found to be more common in patients with LVEF <25%. Use of pharmacotherapy according to contemporary standards was observed in the majority of patients.

Rates of hospitalizations according to left ventricular ejection fraction categories

As illustrated in Figure 1, the event rates for HF, MI, and non CV hospitalizations increased with decreasing LVEF and were particularly high in subjects with LVEF <25%. At two years, the absolute risk increase associated with LVEF <25% (vs LVEF >35%) was 15.5% (95% CI 13.4-17.5) for HF hospitalization, 4.7% (95% CI 3.0-6.4) for MI hospitalization, and 10.4% (95% CI 8.0-12.8) for non CV hospitalization (Figure 1). The proportions of different types of hospitalizations that occurred during follow-up stratified according to LVEF categories are also provided in Supplementary Table 1.

Left ventricular ejection fraction and clinical events

Table 2 and 3 summarize the findings from the Fine and Grey statistical assessment of LVEF as a predictor of the various endpoints. The overall pattern from the analyses indicated that the strongest association existed between LVEF and HF hospitalization, with a more modest association to MI hospitalizations and non CV hospitalizations. In the most adjusted models that included an extensive selection of covariates (model 3), each 5-point decrease in LVEF was associated with a 15% increased risk of HF hospitalization (HR 1.15, 95% CI 1.12-1.18), a 6% increased risk of MI

194 hospitalization (HR 1.06, 95% CI 1.03-1.10), and a 3% increased risk of non CV
195 hospitalization (HR 1.03, 95% CI 1.01-1.05) (Table 2). When evaluating LVEF by
196 categories and using LVEF >35% as reference, LVEF <25 was associated with a 92%
197 increased risk of HF hospitalization (HR 1.92, 95% CI 1.68-2.21), a 34% increased
198 risk of MI hospitalization (HR 1.34, 95% CI 1.13-1.59), and a 18% increased risk of
199 non CV hospitalization (HR 1.18, 95% CI 1.05-1.32) (Table 3). As depicted in the
200 table, the increased risk for events in the LVEF 25-35% category was less distinct, but
201 still significant for the majority of hospitalization types. The trend of LVEF being
202 most strongly associated with HF hospitalization was also present in the less adjusted
203 models (Table 2 and 3). Moreover, a similar pattern was observed in the exploratory
204 assessment of the discriminative properties of LVEF, where the increase Harrell's c-
205 index and continuous net reclassification improvement at one year were found to be
206 statistically significantly improved after addition of continuous LVEF to all models
207 that were tested for prediction of HF and MI events (continuous net reclassification
208 improvement on top of the most complete model 9.4, 6.3 to 12.0, $p<0.0001$ for HF
209 hospitalization and 4.5, 1.5 to 6.9, $p=0.013$ for MI hospitalization, Supplementary
210 Table 2 and 3).

Discussion

This IPD meta-analysis of 19,740 high-risk acute MI individuals assessed the association between LVEF and independently adjudicated cause-specific hospitalizations. We have shown that lower LVEF was associated with various types of hospitalizations in the period following the index acute MI, including non CV hospitalizations. The absolute risk increase in non CV hospitalizations associated with LVEF<25% was 2/3 of the absolute risk increase in HF hospitalizations and twice the absolute risk increase in MI hospitalizations. On a relative scale, the association of lower LVEF with MI and non CV hospitalizations were milder than with HF hospitalizations; However, this milder association should be interpreted in light of the absolute risk of these causes of hospitalization. Lower LVEF consequently appears as an integrative marker of sicker patient status.

HF is a clinical syndrome that is defined by the presence of classical symptoms and abnormal cardiac function leading to reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.[21] Our finding of a strong relationship between LVEF (as surrogate of stroke volume) and HF hospitalizations during follow-up after high-risk MI is not surprising. It is also supported by the results from other investigations which have documented an increased risk of HF death and/or HF hospitalizations associated with lower LVEF in study samples of post MI or chronic HF patients.[5,8,20,22] In an earlier study of long-term myocardial infarction survivors, each 1-point decrease in LVEF was associated with a 4% increased risk of a HF hospitalization.[22] The strength of LVEF as an independent predictor of HF events has also been demonstrated in chronic HF patients, such as in "PARADIGM-HF", where each 5-point decrease in LVEF was associated with a 9% increased risk of HF hospitalization in multivariable models.[23] Thus, as individuals in our study were high-risk acute MI patients, our finding of a 15% increased risk concord well with these prior investigations. Furthermore, the importance of identifying independent predictors of these events are additionally reinforced by an analysis of stable MI survivors demonstrating that a HF hospitalization is associated with a highly significant increased risk of death.[5,22]

Our documentation of reduced LVEF being an independent risk factor for future MI hospitalization and non CV hospitalization in models that consider death as competing risk is novel and has, to the best of our knowledge, not been described before in this particular population. Previously published analyses of the same study

sample have demonstrated a congruent pattern of results with both continuous and categorical LVEF variables being statistically significant predictors of non-HF CV and non CV mortality endpoints, which may be seen as further strengthening the confidence in the aforementioned observation.[20] The mechanisms underpinning these observed relationships are likely multifactorial and there are several potential pathophysiological explanations that support an increased occurrence of new events. Patients with lower LVEF might have more complex coronary disease, and subsequent higher risk of recurrent MI. One explanation of the increased frequency of non CV hospitalizations in the lower categories may be that a poorer LV contractile function makes patients more vulnerable to transient and/or undetected pulmonary oedema. One may speculate that this could lessen the respiratory reserves needed to tackle bouts of chronic obstructive pulmonary disease or pneumonia and subsequently result in admission to hospital for these conditions. Alternatively, LVEF may just be a marker for frailty or other unknown risk factors for non CV causes that were not evaluated in the models. It is also possible that some individuals presenting with typical HF symptoms such as dyspnoea and cough, which conceivably would be more frequent in patients with reduced LVEF, were misdiagnosed with symptomatically similar conditions such as pneumonia. If so, this could contribute to the independent association that were observed between decreasing LV function and non CV hospitalizations. Nonetheless, even though the underlying pathophysiological mechanisms and the discriminative properties of LVEF for these endpoints appear less robust than for HF hospitalizations, we value the fact that particularly non CV hospitalizations occurred more frequent than previously assumed in post acute MI patients as an important finding.

The strength of association on a relative scale was weaker for MI hospitalization and non CV hospitalization. However, we should keep in mind, as our group already emphasized, that the absolute scale is more relevant than the relative scale in a number of clinical settings.[24,25] In the analysis reported herein, the increase in the risk of non CV hospitalizations associated with LVEF <25% was fairly similar (2/3) to the absolute risk increase in HF hospitalizations, and may consequently be considered to have significant implications. In other words, in routine practice, we should keep in mind that patients with the lowest LVEF are almost at similarly increased risk of non CV hospitalization than HF hospitalization. Whether novel interventions targeting LVEF are able to reduce the number of these types of

hospitalizations following MI remains unknown and should be tested in future trials. However, as is, our results suggest that LVEF is an integrated marker of sicker patients rather than a specific HF marker.

Strengths and limitations

We see the independent adjudication of prospectively defined endpoints as an important strength of the present study, as it reduces the impact from differences in local practice and investigator bias thus enhancing accuracy, precision, interpretability and potential for generalizability of the results.[26] The IPD meta-analysis design allowed for adequate power in assessing subgroups and facilitated adjustment of a vast number of covariates in the models.[27] However, the inherent selection of patients during the inclusion process of clinical trials must be considered when considering transferability to local practice. Use of mineralocorticoid receptor antagonists, an important component of guidelines-conform HF treatment, was not part of standard care when the trials were conducted.[28] Another limitation is that non-HF CV hospitalization, non CV hospitalization, and use of beta-blockers were not available from the CAPRICORN trial data, and that hemoglobin and sodium were not reported for VALIANT subjects.

Conclusions

In a high-risk population with complicated acute MI, LVEF was an independent predictor of all types of hospitalization. The absolute risk increase in non CV hospitalizations associated with LVEF <25% appears important as it represent 2/3 of the absolute risk increase in HF hospitalizations and twice the absolute risk increase in MI hospitalizations. Lower LVEF appears as an integrative marker of sicker patient status, associated with HF and non HF related hospitalizations.

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Figure legends

Figure 1 *Kaplan-Meyer estimates for types of hospitalization.* Curves according to different left ventricular ejection fraction categories.

Table 1

Table 1. Baseline characteristics according to left ventricular ejection fraction categories

Characteristics	LVEF < 25% (n=1919)	LVEF 25-35% (n=10999)	LVEF > 35% (n=6822)	p-value	ASMD <25% vs. 25-35%	ASMD <25% vs. >35%	ASMD 25-35% vs. >35%	Mean ASMD
Demography								
Age (years)	65.6 ± 11.7	64 ± 11.8	63.6 ± 11.6	< 0.0001	0.132	0.169	0.036	0.112
Female	26.8	28.8	31.2	0.0001	0.043	0.095	0.052	0.064
Weight (kg)	78.1 ± 15.7	79.6 ± 15.9	79.6 ± 15.8	0.0003	0.099	0.095	0.004	0.066
BMI (kg/m²)	27.1 ± 4.7	27.6 ± 4.7	27.8 ± 4.7	< 0.0001	0.115	0.153	0.038	0.102
Medical history								
Renal insufficiency	7.2	3.6	3.1	< 0.0001	0.161	0.186	0.025	0.124
COPD	11.0	8.5	8.3	0.0005	0.086	0.093	0.007	0.062
Peripheral artery disease	12.2	9.4	9.7	0.0008	0.089	0.081	0.008	0.059
Diabetes	32.2	28.1	26.9	< 0.0001	0.088	0.115	0.027	0.076
Hypertension	56.3	58.2	59.9	0.010	0.038	0.072	0.034	0.048
Obesity (BMI > 30)	22.7	26.1	26.3	0.004	0.079	0.084	0.006	0.056
Clinical								
Killip class (III-IV vs. I-II)	25.7	18.0	18.9	< 0.0001	0.188	0.166	0.022	0.125
Systolic BP (mmHg)	118 ± 16	121 ± 16	122 ± 17	< 0.0001	0.185	0.295	0.111	0.197
Medication use								
ACE inhibitors and/or ARB	67.2	58.1	61.2	< 0.0001	0.190	0.125	0.065	0.127
Beta-blockers	64.2	72.5	71.5	< 0.0001	0.178	0.156	0.022	0.119
Diuretics	65.8	48.9	49.6	< 0.0001	0.347	0.332	0.015	0.231
Biochemistry								
eGFR (ml/min/1.73m²)	67.4 ± 21.8	70.6 ± 21.9	71.1 ± 21.3	< 0.0001	0.148	0.174	0.024	0.115
Hemoglobin (g/dL)	13.1 ± 1.9	13.3 ± 1.7	13.4 ± 1.6	0.0003	0.098	0.152	0.054	0.102
Sodium (mmol/L)	138.5 ± 4.2	139.1 ± 4.1	139.7 ± 3.9	< 0.0001	0.146	0.293	0.147	0.195
LVEF								
Mean ± SD	19.8 ± 3.1	31.5 ± 3.3	42.3 ± 6.6					
Range	10 - 24.9	25 - 35	35.2 - 65					

ASMD: absolute standardized mean difference; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blockers; BMI: body mass index; BP: blood pressure; COPD: chronic obstructive pulmonary disease; eGFR: estimated glomerular filtration rate; LVEF: left ventricular ejection fraction; SD: standard deviation

Table 2

Table 2. Univariable and multivariable competing risk models for continuous (per 5-point decrease) left ventricular ejection fraction with hospitalization outcomes, with death as competing risk event

Cox models	HF hospitalization		MI hospitalization		Non CV hospitalization	
	HR (CI 95 %)	p-value	HR (CI 95 %)	p-value	HR (CI 95 %)	p-value
Univariable Analysis	1.22 (1.19 - 1.26)	<0.0001	1.08 (1.05 - 1.12)	<0.0001	1.06 (1.04 - 1.08)	<0.0001
Model 1	1.21 (1.18 - 1.24)	<0.0001	1.08 (1.04 - 1.11)	<0.0001	1.05 (1.03 - 1.07)	<0.0001
Model 2	1.15 (1.12 - 1.19)	<0.0001	1.06 (1.03 - 1.10)	<0.0001	1.03 (1.01 - 1.05)	0.002
Model 3	1.15 (1.12 - 1.18)	<0.0001	1.06 (1.03 - 1.10)	<0.0001	1.03 (1.01 - 1.05)	0.002

Model 1 is adjusted on age and gender.

Model 2 is adjusted on age, gender, Killip class (III-IV vs. I-II), SBP, comorbidities (diabetes, hypertension, renal insufficiency, COPD, peripheral artery disease) and medication use (beta-blockers, ACE inhibitors and/or ARB, and diuretics).

Model 3 includes variables of model 2 and estimated glomerular filtration rate <60 mL/min/1.73 m².

Table 3

Table 3. Univariable and multivariable competing risk models for left ventricular ejection fraction groups with hospitalization outcomes, with death as competing risk event

Cox models	LVEF categories	HF hospitalization		MI hospitalization		Non CV hospitalization	
		HR (CI 95 %)	p-value	HR (CI 95 %)	p-value	HR (CI 95 %)	p-value
Univariable analysis			<0.0001		<0.0001		<0.0001
	> 35	1.00	-	1.00	-	1.00	-
	25-35	1.36 (1.24 - 1.50)	<0.0001	1.17 (1.04 - 1.31)	0.007	1.07 (1.00 - 1.15)	0.062
	< 25	2.53 (2.24 - 2.87)	<0.0001	1.50 (1.27 - 1.77)	<0.0001	1.37 (1.22 - 1.52)	<0.0001
Model 1			<0.0001		0.0002		<0.0001
	> 35	1.00	-	1.00	-	1.00	-
	25-35	1.35 (1.23 - 1.49)	<0.0001	1.16 (1.04 - 1.30)	0.008	1.07 (1.00 - 1.15)	0.062
	< 25	2.41 (2.13 - 2.73)	<0.0001	1.42 (1.20 - 1.68)	<0.0001	1.32 (1.19 - 1.48)	<0.0001
Model 2			<0.0001		0.001		0.011
	> 35	1.00	-	1.00	-	1.00	-
	25-35	1.35 (1.22 - 1.49)	<0.0001	1.18 (1.05 - 1.32)	0.005	1.07 (1.00 - 1.15)	0.060
	< 25	1.95 (1.70 - 2.23)	<0.0001	1.33 (1.12 - 1.58)	0.001	1.18 (1.06 - 1.32)	0.004
Model 3			<0.0001		0.001		0.011
	> 35	1.00	-	1.00	-	1.00	-
	25-35	1.33 (1.20 - 1.47)	<0.0001	1.17 (1.05 - 1.31)	0.006	1.07 (1.00 - 1.16)	0.052
	< 25	1.92 (1.68 - 2.21)	<0.0001	1.34 (1.13 - 1.59)	0.0009	1.18 (1.05 - 1.32)	0.004

Model 1 is adjusted on age and gender.

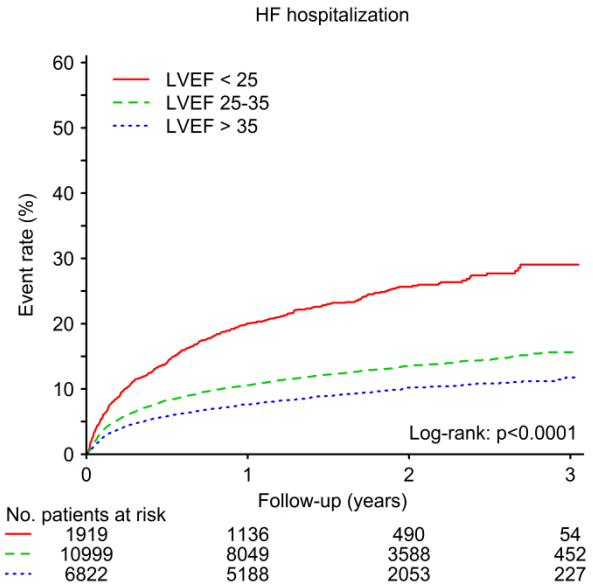
Model 2 is adjusted on age, gender, Killip class (III-IV vs. I-II), SBP, comorbidities (diabetes, hypertension, renal insufficiency, COPD, peripheral artery disease) and medication use (beta-blockers, ACE inhibitors and/or ARB, and diuretics).

Model 3 includes variables of model 2 and estimated glomerular filtration rate <60 mL/min/1.73 m².

Figure 1

Figure 1A. HF hospitalization.

	N total	N event	% event
LVEF < 25	1919	413	21.5
LVEF 25-35	10999	1343	12.2
LVEF > 35	6822	612	9.0

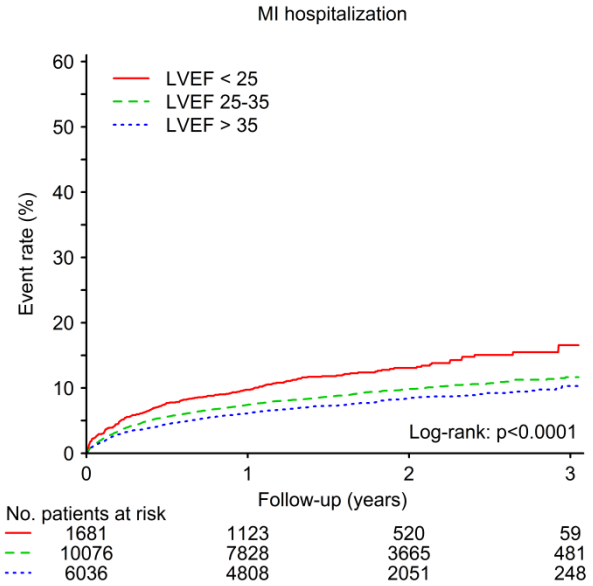


	Risk at 1 year (CI 95%)	Risk at 2 years (CI 95%)
LVEF < 25	20.0 (18.1 - 21.9)	25.7 (23.4 - 27.9)
LVEF 25-35	10.6 (10.0 - 11.2)	13.6 (12.9 - 14.3)
LVEF > 35	7.7 (7.0 - 8.3)	10.2 (9.4 - 11.0)

	Risk difference at 1 year (CI 95 %)	Risk difference at 2 years (CI 95 %)
LVEF < 25	12.4 (10.4 - 14.4)	15.5 (13.4 - 17.5)
LVEF 25-35	2.9 (2.0 - 3.8)	3.4 (2.4 - 4.4)
LVEF > 35	-	-

Figure 1B. MI hospitalization.

	N total	N event	% event
LVEF < 25	1681	191	11.4
LVEF 25-35	10076	905	9.0
LVEF > 35	6036	458	7.6

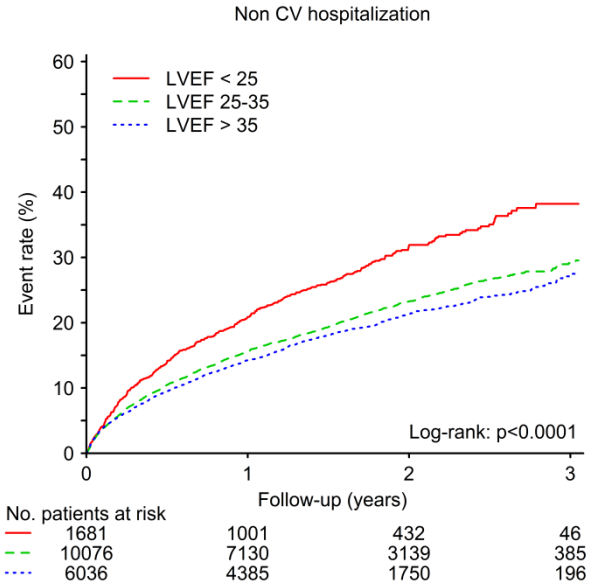


	Risk at 1 year (CI 95%)	Risk at 2 years (CI 95%)
LVEF < 25	9.7 (8.2 - 11.2)	13.1 (11.2 - 14.9)
LVEF 25-35	7.4 (6.9 - 8.0)	9.8 (9.2 - 10.5)
LVEF > 35	6.1 (5.5 - 6.7)	8.4 (7.6 - 9.1)

	Risk difference at 1 year (CI 95 %)	Risk difference at 2 years (CI 95 %)
LVEF < 25	3.6 (2.0 - 5.2)	4.7 (3.0 - 6.4)
LVEF 25-35	1.3 (0.5 - 2.1)	1.5 (0.5 - 2.4)
LVEF > 35	-	-

Figure 1C. Non CV hospitalization.

	N total	N event	% event
LVEF < 25	1681	437	26.0
LVEF 25-35	10076	2112	21.0
LVEF > 35	6036	1154	19.1



	Risk at 1 year (CI 95%)	Risk at 2 years (CI 95%)
LVEF < 25	20.9 (18.8 - 23.0)	31.8 (29.0 - 34.4)
LVEF 25-35	15.6 (14.9 - 16.3)	23.2 (22.3 - 24.2)
LVEF > 35	14.2 (13.3 - 15.1)	21.3 (20.2 - 22.5)

	Risk difference at 1 year (CI 95 %)	Risk difference at 2 years (CI 95 %)
LVEF < 25	6.6 (4.4 - 8.9)	10.4 (8.0 - 12.8)
LVEF 25-35	1.4 (0.2 - 2.5)	1.9 (0.5 - 3.3)
LVEF > 35	-	-

Figure 1A high res panel
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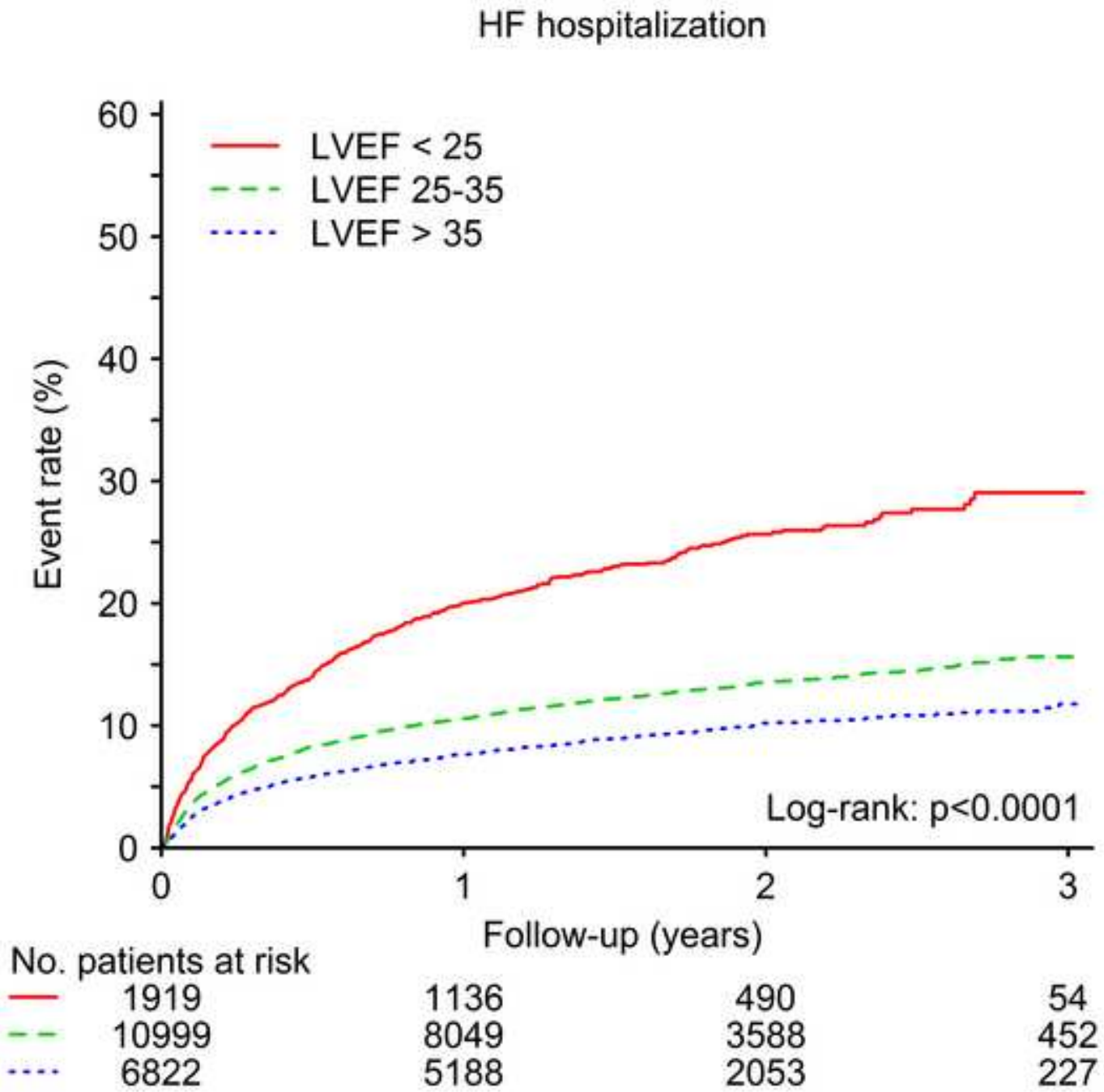

Figure 1B high res panel
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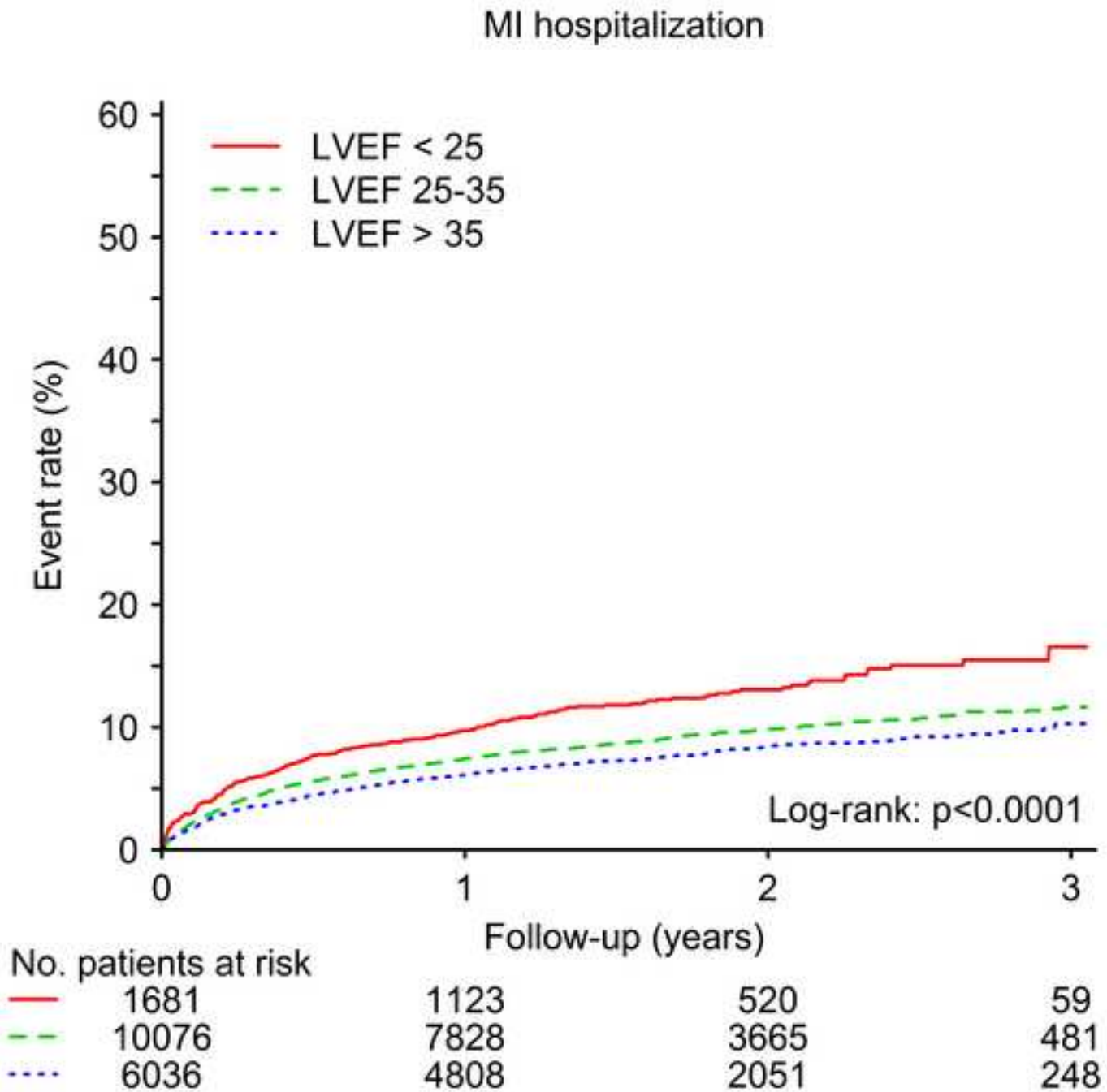

Figure 1C high res panel
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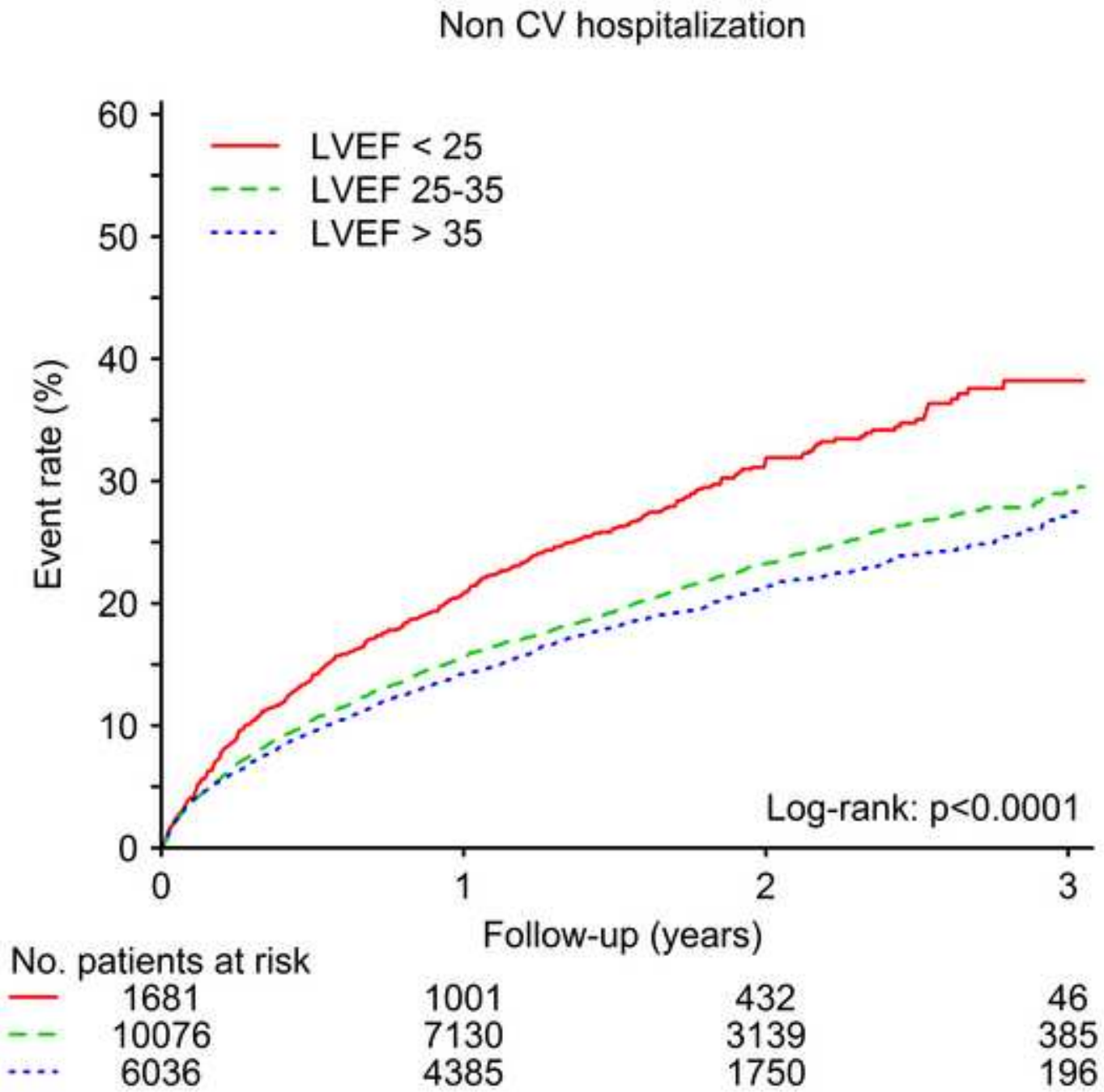

Supplementary Table 1

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Supplementary Table 2

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Supplementary Table 3

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