HEART FAILURE

Determinants of Late-Onset Heart Failure in Myocardial Infarction Survivors: GISSI Prevenzione Trial Results

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Introduction and objectives. Improvement in the early phase of myocardial infarction (MI) is associated with a higher rate of late complications, including late-onset heart failure (LHF). The factors predicting LHF are not well understood. Our aims were to identify the factors predicting LHF and to determine the survival rate in these patients.

Patients and method. The GISSI-Prevenzione trial involved 11 323 low-risk patients (NYHA class ≤II) who had had a recent MI (<3 months). It was a multicenter, open-label, clinical trial of the efficacy of treatment with polyunsaturated fatty acids, vitamin E, both, or neither. Patients with heart failure at baseline and those whose ejection fraction was unknown (n=2908) were excluded from the present analysis. Late-onset heart failure was defined prospectively as hospital admission due to heart failure. A Cox regression model adjusted for major covariates was used for risk analysis.

Results. The study included 8415 patients. During 3.5 years of follow-up, 192 (2.3%) developed LHF. The risk of LHF could be predicted from readily available parameters: age (per year; RR=1.07; 95% CI, 1.05-1.09), ejection fraction (per 1% increment; RR=0.96; 95% CI, 0.94-0.97), heart rate (≥74 beats/min; RR=1.62; 95% CI, 1.21-2.16), white blood cell count (≥8900 per ml; RR=1.42; 95% CI, 1.05-1.94), diabetes (RR=1.62; 95% CI, 1.17-2.24), hypertension (RR=1.76; 95% CI, 1.33-2.34), peripheral artery disease (RR=2.11; 95% CI, 1.32-3.37), and reinfarction (RR=2.09; 95% CI, 1.28-3.39). LHF was associated with poor survival: (RR=2.34; 95% CI, 1.63-3.36).

Conclusions. The risk of LHF in post-MI patients can be predicted from readily available parameters. LHF was associated with a poor prognosis.

Key words: *Heart failure. Myocardial infarction. Prognosis.*

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Determinantes de insuficiencia cardíaca tardía postinfarto de miocardio: resultados del estudio GISSI Prevenzione

Introducción y objetivos. La mejoría pronóstica de la etapa inicial del infarto conlleva un mayor número de complicaciones a largo plazo. Entre éstas destaca la insuficiencia cardíaca tardía (ICT). Los factores relacionados con la ICT no son del todo conocidos. El objetivo es determinar qué factores pronósticos se relacionan con la ICT y cuál es la supervivencia de estos pacientes.

Pacientes y método. El estudio GISSI Prevenzione fue multicéntrico, abierto, aleatorizado y se estudió a 11.323 pacientes postinfarto reciente (< 3 meses) de bajo riesgo (NYHA ≤ II) para evaluar la eficacia del tratamiento con ácidos grasos poliinsaturados, vitamina E, ambos o ninguno. Para este análisis se excluyó a los pacientes con insuficiencia cardíaca durante el ingreso y a aquellos sin determinación de la fracción de eyección (FE) (n = 2.908). La ICT se definió previamente como la necesidad de hospitalización por insuficiencia cardíaca. La predicción de riesgo se realizó con el modelo de Cox ajustado por diversas covariables.

Resultados. Se incluyó a 8.415 pacientes. Durante 3,5 años de seguimiento, 192 pacientes (2,3%) desarrollaron

ABREVIATIONS

AMI: acute myocardial infarction.
LOHF: late-onset heart failure.
EOHF: early-onset heart failure.
ACEI: angiotensin converting enzyme inhibitors.

ICT. Variables fácilmente asequibles permiten predecir el riesgo de ICT: edad (por año), riesgo relativo [RR] = 1,07; intervalo de confianza [IC] del 95%, 1,05-1,09), FE (por cada 1% de incremento, RR = 0,96; IC del 95%, 0,94-0,97), frecuencia cardíaca ≥ 74 lat/min (RR = 1,62; IC del 95%, 1,21-2,16), recuento de leucocitos ≥ 8.900/ml (RR = 1,42; IC del 95%, 1,05-1,94), diabetes (RR = 1,62; IC del 95%, 1,17-2,24), hipertensión (RR = 1,76; IC del 95%, 1,33-2,34), vasculopatía periférica (RR = 2,11; IC del 95%, 1,32-3,37) e infarto recurrente (RR = 2,09; IC del 95; 1,28-3,39). La ICT presentó mayor mortalidad alejada (RR = 2,34; IC del 95%, 1,63-3,36).

Conclusiones. Elementos fácilmente asequibles en la consulta permiten predecir el riesgo de ICT en pacientes postinfarto. La ICT se asocia con un mal pronóstico.

Palabras clave: *Insuficiencia cardíaca. Infarto de miocardio. Pronóstico.*

INTRODUCTION

The short-term prognosis of patients with acute myocardial infarction (AMI) has improved over recent years. Pharmacological treatment with aspirin, beta-blockers and angiotensin converting enzyme inhibitors (ACEI), along with better pharmacological and non-pharmacological revascularization techniques, have led to improved initial survival rates,[1-3] particularly in younger patients. However, this improvement exposes them to a greater risk of developing late-onset complications.[4]

The number of patients hospitalized for heart failure has increased by 155% in recent years,[5] probably because of improved initial survival following an AMI.[6,7] Indeed, late-onset heart failure (LOHF) in AMI survivors has become an important public health problem. Although the predictors of early-onset heart failure (EOHF) in AMI survivors are well known,[8] relatively little is known about long-term risk indicators, and those studies that have addressed the subject[2,9,10] have involved populations with lifestyles and food habits very different from those of Mediterranean Europe.

The main aim of the present work was to determine the indicators of LOHF in a large population of low risk survivors of AMI and to determine the prognosis of patients with this complication once diagnosed. The secondary aim was to determine the predictors of the composite event of death/LOHF.

PATIENTS AND METHODS

A detailed description of the GISSI Prevenzione study and the demographic characteristics of the patient population involved are available elsewhere.[11] Briefly, the study initially included 11 323 patients who had recently suffered a low risk (class ≤II on the New York Heart Association [NYHA] scale) AMI (<3 months; median, 16 days). Using a randomized, open study design, the efficacy of treatment with polyunsaturated fatty acids (n3PUFA) (1 g/day), vitamin E (300 U/day), both, or neither, was studied over a period of 3.5 years. Apart from the experimental interventions, the same criteria were applied to all patients with regard to pharmacological and non-pharmacological treatment.

Those patients with a diagnosis of heart failure at the beginning of the study (based on a clinical diagnosis made by a cardiologist and/or the prescription of ACEI, diuretic drugs or beta blockers for heart failure; n=1331) were excluded. Also excluded were those patients for whom this condition could neither be confirmed nor ruled out (n=90), as well as those whose ejection fraction had not been determined (n=1487). The final number of patients included was therefore 8415. The suffering of a previous AMI was not an exclusion criterion.

Late-onset heart failure was defined as the need to be hospitalized owing to a clinical diagnosis of heart failure any time after randomization to the different treatment regimens.

Statistical Analysis

The characteristics of patients who developed and who did not develop LOHF were compared using the χ^2 test for categorical variables and the Student t test for continuous variables (the latter variables showed a normal distribution). Numerical variables were analyzed both in a continuous manner and via the use of quartiles. Their introduction into the final model in either continuous format or through the use of cut-off points depended on the observations made using the quartile system. In multivariate analysis, the numerical variables were entered in continuous format if the use of quartiles revealed no category in which the risk was any different (e.g., for EF and age). However, they were entered with respect to a cut-off point when the quartiles showed a distinctly different risk above and below that point (e.g., for heart rate and leukocyte count).

Multivariate analysis was performed using the Cox proportional risk model, taking into account age, sex, electrical instability (defined as ≥10 ventricular extrasystoles per hour or frequent or sustained ventricular arrhythmia as determined by Holter monitoring [24 h]), the presence of residual ischemia (angina or positive stress test), use of tobacco, medication (ACEI, beta-blockers, diuretic drugs, and anticoagulants), and prior AMI and experimental treatment (n3PUFA and vitamin E). The predictive power of the model was analyzed by plotting the corresponding ROC curve.

The same procedures were used to predict the composite event of LOHF/death; the factors derived from the Cox regression were examined to see whether they were related to this. The calculation of the number of risk factors affecting each patient was performed by simply counting each of the categorical variables that predicted LOHF or death. Numerical variables were considered to be present if their values were above the corresponding cut-off point (60 years for age, <48% for EF, ≥74 beats per min for heart rate, and ≥8900/mL for the leukocyte count). This approach underestimated the risk obtained with the original multivariate analysis, but is practical and aids in the understanding of the results.

All *P* values were two-tailed. All calculations were performed using the SAS statistical package.

RESULTS

Of the 8415 patients eventually included, 192 (2.28%) developed LOHF. The median time for the appearance of this complication was 8.9 months. The incidence of events was distributed asymmetrically over time. In the first year the incidence of LOHF was 1.4%, after which it was close to 0.3% per year.

Among those who developed LOHF, 18 (9.4%) suffered a recurrence of AMI before this complication arose. Among those who did not develop LOHF, 341 (4.2%) suffered a new AMI during follow-up (*P*=.0004).

Table 1 shows the main characteristics of the patients who developed and who did not develop LOHF. Those who developed the complication were older and more commonly women. The other risk factors were also distributed asymmetrically: diabetes, high blood pressure, peripheral vascular disease and prior AMI were more common among those who developed LOHF. In addition, those who developed the complication had lower total cholesterol levels, higher leukocytes counts, and a lower EF (Table 1).

Table 2 shows the results of the univariate analysis. Only cholesterol level, dyspnea functional class and prior AMI were non-significant in the multivariate analysis.

Multivariate analysis identified eight independent predictors of LOHF (Table 3) (all of which can easily be measured in the consulting room during an

TABLE 1. **Baseline Characteristics of the Patients Who Developed and Did Not Develop Late-Onset Heart Failure**

	Without LOHF, n (%)	With LOHF, n (%)	*P*
N	8.223	192	
Women	1.130 (13.7)	41 (21.3)	.003
Age, years, mean±SD	58.2±10.4	66.0±9.0	<.0001
High blood pressure	2.864 (34.8)	104 (54.2)	<.0001
Smoking habit	3.699 (45.0)	61 (31.8)	.004
Diabetes	1.067 (13.0)	51 (26.6)	<.0001
Prior AMI	852 (10.4)	31 (16.2)	.0098
Intermittent claudication	325 (4.0)	20 (10.4)	<.0001
Anterior AMI site	2.496 (30.4)	66 (34.4)	.23
AMI with no Q wave	1.431 (17.4)	29 (15.1)	.41
Post-infarction angina	912 (11.1)	25 (13.0)	.40
Angioplasty	271 (3.3)	2 (1.0)	.08
Revascularization surgery	163 (2.0)	3 (1.6)	.68
Recurrent AMI	341 (4.2)	18 (9.4)	.0004
NYHA			
0	3.222 (39.2)	78 (40.6)	.69
I	4.608 (56.0)	96 (5.0)	.10
II	393 (4.8)	18 (9.4)	.004
Heart rate, beats/min			
(mean±SD)	68±10	71±1	<.0001
Ejection fraction, %			
(mean±SD)	54±9.8	49±10.1	<.0001
Total cholesterol, mg/dL			
(mean±SD)	212±41	202±38	.001
HDL-C, mg/dL			
(mean±SD)	41±1	41±12.2	.83
Fibrinogen, mean±SD	390±138	403±154	.25
Leukocyte count,			
mean±SD	7.7±2.2	8.1±2.6	.08
Creatinine, mg/dL			
(mean±SD)	1.1±0.3	1.1±0.3	.10
Uric acid, mean±SD	5.7±1.6	5.8±1.6	.63
ACEI	3483 (42.4)	107 (55.7)	.0002
Diuretics	314 (3.8)	25 (13.0)	<.0001
Beta-blockers	3.940 (47.9)	72 (37.5)	.0043
Anticoagulants	7.645 (93.0)	172 (89.6)	.08
Statins	1.695 (21.3)	38 (19.8)	.62

*LOHF indicates late-onset heart failure; NYHA, New York Heart Association; HDL-C, high density lipoprotein cholesterol; ACEI, angiotensin converting enzyme inhibitors.

outpatient appointment) that allow the risk of developing LOHF to be predicted: age (a demographic variable), high blood pressure, diabetes and peripheral vascular disease (cardiovascular disease risks), the EF (an instrumentally measured variable), the leukocyte count (a blood analysis variable), heart rate (determined during physical examination), and finally, recurrent AMI during follow-up (Table 3).

The same model was useful for predicting the composite event of LOHF/death by any cause (Table 3).

The LOHF risk prediction model had an area under the curve (AUC) of 0.787 (95% confidence interval

TABLE 2. **Univariate Analysis***

	N (%)	Mean±SD	Events (%)	RR	95% CI	*P*
Age (risk increase per year)	–	–	–	1.08	1.07-1.10	<.0001
Women	1171 (13.9)		41 (3.5)	1.16	0.82-1.65	.40
Men	7244 (86.1)		151 (2.1)	1.00	–	
Ejection fraction (continuous)				0.96	0.94-0.97	<.0001
≥60%	2523 (30.0)	65±5	33 (1.3)	1.00	–	
≥54% and <60%	1786 (21.2)	56±2	29 (1.6)	1.22	0.74-2.01	.44
≥48% and <54%	2086 (24.8)	50±1	43 (2.1)	1.44	0.91-2.27	.12
<48%	2020 (24.0)	41±5	87 (4.3)	2.81	1.88-4.20	<.0001
Prior AMI†	883 (10.5)	–	31 (3.5)	1.52	1.03-2.24	.033
No prior AMI	7526 (89.5)	–	161 (2.1)	1.00	–	
NYHA						
0	3300 (39.2)	–	78 (2.4)	1.00	–	
I	4704 (55.9)	–	96 (2.0)	0.90	0.67-1.21	.48
II	411 (4.9)		18 (4.4)	1.51	0.91-2.53	.11
Heart rate†				1.03	1.02-1.05	<.0001
<60	1358 (16.2)	53±4	20 (1.5)	1.00	–	
≥60 and <68	2617 (31.2)	62±2	39 (1.5)	0.98	0.57-1.68	.94
≥68 and <74	2186 (26.0)	70±1	53 (2.4)	1.47	0.88-2.47	.14
≥74	2233 (26.6)	80±6	79 (3.5)	2.10	1.29-3.45	.003
Total cholesterol (continuous)†				0.996	0.993-1.00	.04
<184	2090 (24.9)	162±17	63 (3.0)	1.45	0.95-2.21	.08
≥118-<209	2065 (24.6)	196±7	56 (2.7)	1.43	0.93-2.19	.10
≥209-<237	2145 (25.5)	222±8	38 (1.8)	0.97	0.61-1.54	.91
≥237	2100 (25.0)	265±27	35 (1.7)	1.00	–	
Leukocyte count†				1.10	1.04-1.16	.001
<6.2	1981 (23.7)	5.2±0.7	45 (2.3)	1.00	–	
≥6.2-<7.4	2087 (25.0)	6.8±0.3	43 (2.1)	0.98	0.64-1.49	.92
≥7.4-<8.9	2108 (25.2)	8.0±0.4	43 (2.0)	1.047	0.69-1.59	.83
≥8.9	2182 (26.1)	10.7±1.9	61 (2.8)	1.55	1.05-2.28	.028
Diabetes	1118 (13.3)		51 (4.6)	1.97	1.43-2.73	<.0001
No diabetes	7297 (86.7)	–	141 (1.9)	1.00		
High blood pressure	2968 (35.3)	–	104 (3.5)	1.76	1.32-2.34	.0001
No high blood pressure	5447 (6.7)	–	88 (1.6)	1.00		
Intermittent claudication	345 (4.1)	–	20 (5.8)	2.35	1.47-3.74	.0004
No intermittent claudication	8070 (95.9)	–	172 (2.1)	1.00		
Recurrent AMI	359 (4.3)	–	18 (5.0)	2.13	1.31-3.46	.002
No recurrent AMI	8.056 (95.7)	–	174 (2.2)	1.00		

*SD indicates standard deviation; RR, relative risk; CI, confidence interval; NYHA, New York Heart Association.
†Some variables do not add up to 8415 due to a lack of data.

[CI], 0.757-0.817; *P*<.0001), and of 0.748 (95% CI, 0.729-0.766; *P*<.0001) for the prediction of risk of LOHF/death.

The development of LOHF was associated with high mortality—16.7% (n=32) compared to 6.7% in those who did not develop this complication (n=544 cases) (hazard ratio [HR]=2.34; 95% CI, 1.63-3.36; *P*<.0001). Figure 1 shows the difference in mortality for these 2 groups.

The number of risk factors affecting each patient was related to the probability of developing LOHF and of dying. Compared to patients who had none of the risk factors identified, those who had 1 or 2 factors, 3 or 4 factors, or 5 or more had an overall increased risk of 188%, 676%, and 1549% respectively (Table 4, Figure 2).

DISCUSSION

This *post hoc* analysis of the GISSI Prevenzione study results identifies the variables that predict the risk of developing LOHF, even in populations at low risk of complications. All of these variables are easily measured during an outpatient appointment. When LOHF is diagnosed, the prognosis of a patient is severely affected; mortality becomes nearly double that recorded among patients who do not develop this complication.

Although the factors related to the appearance of EOHF following an AMI are well known,[8] relatively little is known about the factors influencing the development of LOHF. Such information would be valuable since it is believed that the increase in the

TABLE 3. **Multivariate Analysis for the Prediction of Late-Onset Heart Failure**

	Risk of LOHF			Risk of Death or LOHF		
	RR	95% CI	*P*	RR	95% CI	*P*
Age (risk increase per year)	1.07	1.05-1.09	<.0001	1.07	1.06-1.07	<.0001
High blood pressure	1.76	1.32-2.34	.0001	1.33	1.15-1.54	.0001
Diabetes	1.62	1.17-2.24	.004	1.43	1.20-1.70	<.0001
Intermittent claudication	2.11	1.33-3.37	0.002	2.01	1.57-2.57	<.0001
Recurrent AMI	2.09	1.28-3.39	.003	1.65	1.25-2.17	.0004
Ejection fraction (for each of 1%)	0.96	0.94-0.97	<.001	0.97	0.96-0.98	<.0001
Heart rate ≥74	1.62	1.21-2.16	.001	1.54	1.33-1.79	<.0001
Leukocyte count ≥8.9	1.42	1.05-1.94	.02	1.30	1.11-1.53	.001

*RR indicates relative risk; CI, confidence interval; LOHF, late-onset heart failure.

incidence of heart failure is related to the increased survival now achieved after an initial AMI.[6,7] The work performed in this area to date has involved patients at a much higher overall risk of cardiovascular disease than that faced by populations of Mediterranean charateristics.[2,9,10] The Framingham study reported an annual incidence of LOHF of 2% in a cohort of patients without documented heart disease (with a wide diagnostic range for this complication).[2] Other North American studies (also with an ample diagnostic margin for LOHF) in patients with prior AMI report a much higher rate, reaching as high as 41% in 6.5 years.[10] The event rate is much lower, however, when the patients studied are those involved in clinical trials. Analysis of the CARE database, which employs diagnostic criteria for LOHF similar to those used in the present study, shows an incidence of 1.3% per year.[9] It is noteworthy that the population involved was at much greater risk

than the European population, and that the median follow-up time was five years. The SAVE study, which involved patients with at least moderate deterioration of systolic function, reported an incidence of LOHF of 15% after 3.5 years of follow-up, and that the mortality of patients with this complication was 6 times greater than in those without this problem.[12]

The dissociation between the incidence of heart failure reported in epidemiological studies and clinical trials is not surprising. The former usually base the diagnosis of LOHF on hospital administration records, which make use of the International Classification of Diseases (ICD). Although the importance of these records is based on the very large numbers of patients they contain, it should be remembered that the use of ICD codes is based on the practice of the institution collecting the data, and that this lack of uniformity could lead to bias.[13] It has also been reported that to
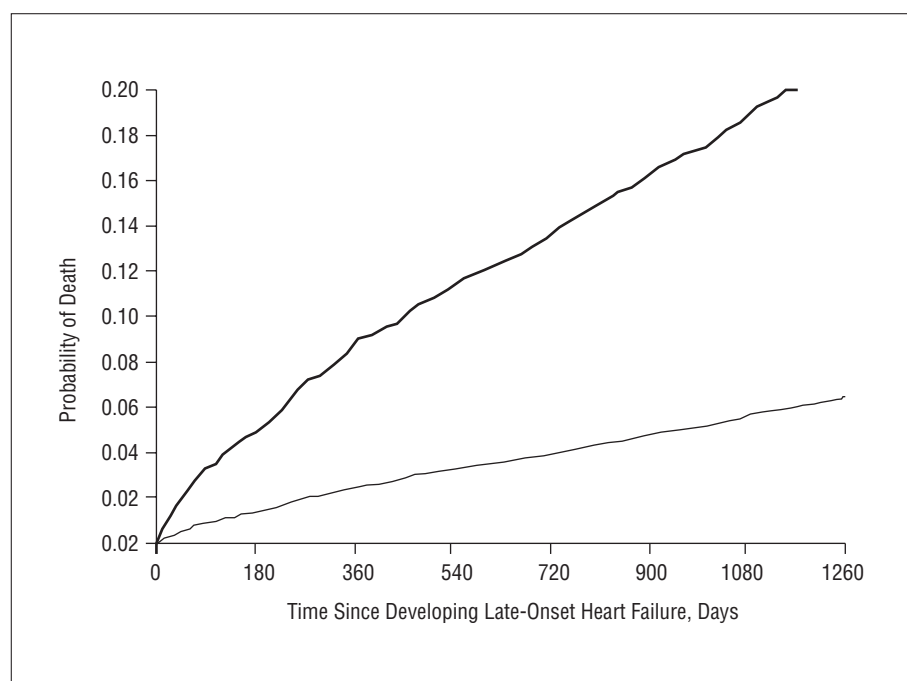

Figure 1. Probability of death for patients with no late-onset heart failure (LOHF) (thin lower line) and for those diagnosed with LOHF (upper thick line). Patients without LOHF; relative risk =1.0 (reference category); patients with LOHF: relative risk =2.34 (1.63-3.36); *P*<.01. Corrected for age and sex.

TABLE 4. **Multivariate Analysis for the Prediction of Death or Late-Onset Heart Failure According to the Number of Affecting Risk Factors**

|	N	Events (%)	RR	95% CI	*P*
No risk factor	1259	29 (2.3)	1.00	–	
1 or 2 risk factors	4861	316 (6.5)	2.88	1.97-4.22	<.0001
3 or 4 risk factors	2023	334 (16.5)	7.76	5.31-11.34	<.0001
5 or more risk factors	195	61 (31.3)	16.49	10.6-25.7	<.0001

*RR indicates relative risk; CI, confidence interval.

ensure health insurance payments there is a tendency to include more serious diagnoses. This leads to poor classifications and the overestimation of serious diseases such as heart failure.[14] Consequently, relying on diagnoses of heart failure based solely on ICD codes (i.e., without additional confirmation from medical histories) could overestimate the incidence of this complication. The information reported in clinical trials is therefore likely to be more accurate. However, it should also be remembered that clinical trials commonly include patients with characteristics that are not representative of everyday practice. Moreover, even when focusing on clinical trial data there are differences in the incidence and prognosis associated with LOHF depending on the population in question. In populations with lifestyles different to those of Mediterranean Europe, such as those involved in the CARE[9] and SAVE[12] studies, the event rates and associated prognoses differ strongly with those reported in the present study. These discrepancies may be largely explained by the baseline seriousness of the conditions of the CARE and SAVE patients, and in part by the longer follow-up times of these studies. Certainly the GISSI Prevenzione study included patients at lower risk of cardiovascular disease (the restrictions regarding inclusion were few); the clinical study method used was pragmatic with the idea that everyday practice should be represented.[15] In any event, and as with any clinical trial, it cannot be ruled out that the lower rate of events observed reflects a bias towards the selection of patients at lower risk. A further factor that may have contributed to the relatively low incidence of LOHF in the present study is the restrictive definition of LOHF used (i.e., the need to be *hospitalized* for LOHF).

In addition, in some patients no echocardiogram could be performed to determine the EF; theoretically the loss of these patients could have had some impact on the results. Although the event rate was lower, the factors related to the appearance of LOHF were similar. The confirmation that patients at different risk can share similar prognostic factors agrees with that

Figure 2. Probability of death or late-onset heart failure (LOHF) in patients with no risk factors (lower line), in those with 1 or 2 factors (second line from bottom), in those with 3 or 4 factors (third line from bottom), and in patients with 5 or more factors (thick upper line). Table 4 shows the number of patients in each group, their relative risk and the 95% confidence interval.
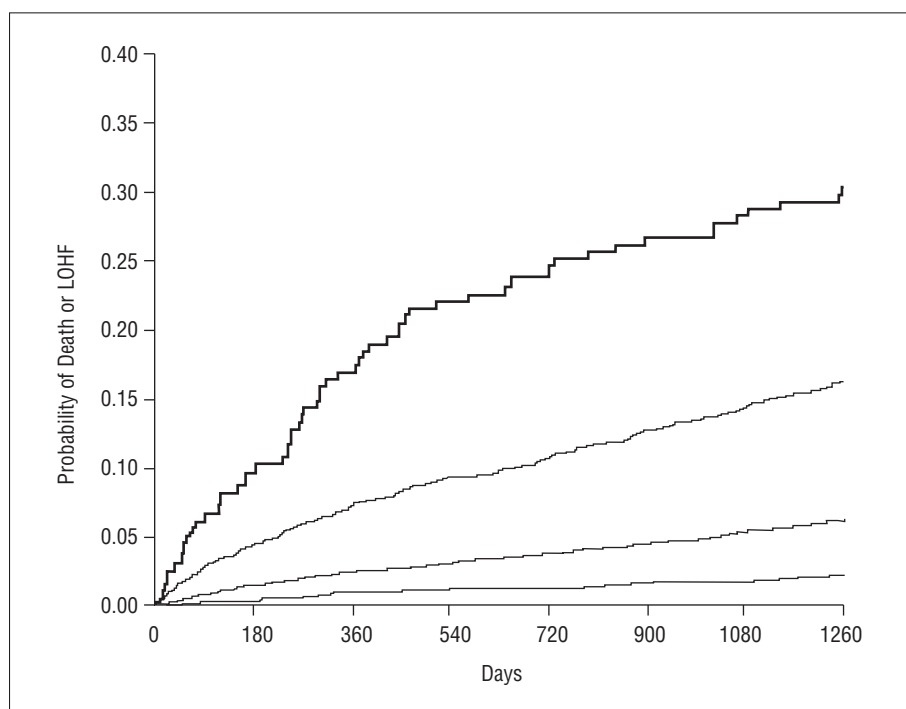
reported in a recent study regarding the "globalness" of risk factors,[16] and emphasizes the need to monitor and aggressively treat these factors.

The rate of heart failure at admission varies from 20 to 40%[8]; the factors related to EOHF are more associated with mechanical dysfunction and less with remodeling and neurohormonal activation, which are more characteristic of LOHF.[8] In fact, in the present patients, the site of the AMI—an important predictor of EOHF—appeared to have no importance in the prediction of LOHF. The factors identified in the present study with respect to LOHF appear to be related to remodeling and late neurohormonal activation. It should be noted that these factors affect overall risk in a multiplicative fashion, and that neurohormonal activation does not act in an all-or-nothing manner but with a scale of activation. The presence of different risk factors in a patient might therefore lead to a greater neurohormonal response, and reveal the need to embark on more aggressive treatment. In the present work, the presence of 3 or more factors allows the increased risk of LOHF or all-cause death to be discerned rapidly and easily. The factors identified predict the risk of LOHF independent of pharmacological treatment.

In conclusion, in a large, low risk, European population whose members had survived an AMI, the risk of developing LOHF was low compared to that reported in studies from other countries. Nonetheless, patients with a firm diagnosis of LOHF showed a mortality rate twice that of those who did not develop this complication. The identified factors can all be easily monitored during outpatient appointments, and allow physicians to rapidly discern the risk of LOHF or death.

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