

Why and when do patients with heart failure and normal left ventricular ejection fraction die? Analysis of >600 deaths in a community long-term study

Lilian Grigorian-Shamagian, MD, PhD, Fernando Otero Raviña, MD, PhD, Emad Abu Assi, MD, Rafael Vidal Perez, MD, Elvis Teijeira-Fernandez, MD, Alfonso Varela Roman, MD, Laura Moreira Sayagues, MD, and Jose Ramon Gonzalez-Juanatey, MD, PhD *Santiago de Compostela, Spain*

Background The aim of the study was to examine the causes of the death of patients with heart failure (HF) and evaluate the differences in this respect between patients with and without depression of left ventricular ejection fraction (LVEF).

Method All patients hospitalized with HF between 1995 and 2002 in the cardiology service of a tertiary hospital were assessed. LVEF was evaluated by echocardiography during hospitalization and was considered normal when it was $\geq 50\%$. After a mean follow-up time of 3.7 ± 2.8 years, 615 cases had terminated in death.

Results The most common cause was refractory HF, both in the whole group (39%) and in both the subgroups defined with respect to LVEF (normal and depressed). There was no statistically significant difference between the normal and depressed subgroups as regard the distribution of deaths, although the depressed group showed a somewhat greater incidence of sudden death (21% as against 16% in the normal group) and a somewhat smaller incidence of death due to refractory HF (37% as against 47%). However, in the depressed LVEF group, the cumulative risk of death due to acute myocardial infarction in the first 1.5 years first increased rapidly and then more slowly, whereas the reverse pattern was held in the normal left ventricular systolic function group, in which it was the cumulative risks of death from noncardiovascular or vascular noncardiac causes that initially increased more rapidly than later.

Conclusions The spectrum of causes of death among patients with HF who have been hospitalized is independent of LVEF in the long term. In the short term, there are differences between patients with normal LVEF and depressed LVEF as regard the dynamics of the risks of death from acute myocardial infarction, noncardiac vascular causes, and noncardiovascular causes. These results may help orient the short-term and long-term management of HF, especially for patients with normal LVEF, for whom there is still no well-established consensus strategy. (*Am Heart J* 2008;156:1184-90.)

Heart failure (HF) is the most lethal of cardiovascular pathologic conditions. Although the annual death rate among patients with HF included in the most recent clinical trials is $<10\%$,^{1,2} much higher rates are observed among unselected patients,³⁻⁵ who on average are generally older and more likely to present comorbidity, although the survival of unselected patients has also improved in recent years.^{4,6-11}

On the other hand, community studies of patients with HF suggest that patients who present normal left ventricular systolic function (LVSF) survive significantly longer

than those who do not.¹²⁻¹⁵ By contrast, recent studies of hospitalized patients by our group and other authors^{16,17} have found that there is no difference in mortality between these 2 types of HF and that whereas survival has improved in recent years among patients with depressed left ventricular ejection fraction (LVEF), there has been no such improvement among patients with normal LVEF.^{6,18}

The main causes of death among patients with HF and depressed LVSF have been reported to be sudden death and refractory HF,^{19,20} although most data supporting this view come from controlled clinical trials involving selected patients who are usually younger and have less comorbidity than the generality of patients with HF. Importantly, nothing is really known for sure about the relative incidences of a different cause of death spectrum and/or different cause-specific mortality profiles. Any such differences might have implications for the therapeutic approach to these patients, on which no consensus has so far been reached.^{21,22}

In the study described here, we examined causes of death and cause-specific mortality profiles in a large

From the Cardiology Department and Coronary Unit, University Clinical Hospital of Santiago de Compostela, Santiago de Compostela, Spain.

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Reprint requests: Jose Ramon Gonzalez-Juanatey, MD, PhD, FESC, Servicio de Cardiología, Hospital Clínico Universitario de Santiago de Compostela, Travesía Choupana s/n, 15706 Santiago de Compostela, Spain.

E-mail: jose.ramon.gonzalez.juanatey@sergas.es

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group of patients admitted to hospital for HF for an 8-year period, and we looked for differences in these respects between patients with and without LVSF dysfunction.

Methods

Study group

We studied all informed consenting patients admitted with HF between January 1, 1995, and December 31, 2002, in the cardiology service of a northwest Spanish tertiary hospital serving a population of about 400,000. Heart failure was defined by modified Framingham criteria: satisfaction of ≥ 2 major criteria (paroxysmal nocturnal dyspnea, orthopnea, rales, jugular venous distension, third sound, and radiologic signs of pulmonary congestion and/or cardiomegaly) or of one major criterion together with ≥ 2 minor criteria (effort dyspnea, peripheral edema, hepatomegaly, and pleural effusion); in the latter case, other possible causes of the clinical signs and symptoms were ruled out using appropriate tests. Patient selection and inclusion in the study was performed during hospitalization by 2 staff cardiologists with ample experience of treating patients with HF. For patients admitted to the service on >1 occasion during the study period, only the data pertinent to the first admission were evaluated in this study. For all included patients who had at any time been hospitalized for HF before the start of the study period, any such hospitalization had occurred at least 4 years before the start of the study, that is, before 1991; in view of this time interval, it was assumed that the risks of these patients at first admission during the study were essentially similar to those of patients admitted for the first time during the study.

Study protocol and variables' definitions

Data on patients included in the study were stored in a predefined data base. The information considered included demographic data and variables relating to cardiovascular risk factors, etiology, clinical situation upon admission, supplementary examinations performed during admission (electrocardiography, radiography, echocardiography, coronary angiography), drugs prescribed upon discharge, and duration of hospitalization. Inclusion in the study did not imply any deviation from the protocols in force in our center or any alteration of the criteria or actions of the patients' clinicians. In particular, echocardiography was performed whenever it was deemed necessary by the cardiologist responsible for the patient, and only on these occasions; when performed, LVEF was determined by the modified Simpson method, and a cutoff of 50% was used to define LVSF dysfunction.

Data on survival and causes of death were obtained in August 2004 and January 2006, mainly by consultation of our hospital records for these patients. When no unambiguous information was obtained in this way, resort was had to the patient's primary care physician, followed, if necessary, by direct telephonic contact with the patient or some relative. Records of death were examined by an end point committee in a blinded fashion; in all cases in which the cause of death could be established unequivocally, it was classified in 1 of 5 categories, as follows.

- *Sudden death*, defined as the sudden, unexpected death of a patient who until then had been considered stable. Sudden deaths could be either witnessed (with or without documentation of arrhythmia) or unwitnessed (if the patient had

been seen within the 24 hours preceding death but had shown no premonitory HF, myocardial infarction, or other clear cause of death).

- *Refractory HF*, defined as death with decompensated HF that failed to respond to treatment, in the absence of any other cause of death.
- Acute myocardial infarction, if infarct caused electrical or mechanical complications leading to early death.
- Noncardiac vascular causes if death was due to cerebrovascular accidents, to vasculorenal diseases (kidney failure in the absence of glomerulopathy or other parenchymatic alterations), or to burst aneurysms.
- Noncardiovascular causes.

Statistical analyses

Data for categorical or dichotomous variables are expressed as percentages and were compared using a χ^2 test. Data for continuous variables are expressed as means \pm SDs and were compared using Student *t* tests or analyses of variance, as appropriate. Kaplan-Meier survival curves were compared using log-rank tests. Mortality curves adjusted for age and sex were constructed by Cox analysis following justification of the assumption of proportional hazards by means of log-log survival plots for each variable; relative risks and their 95% CIs were estimated using the Cox regression coefficients. The criterion for statistical significance was $P < .05$.

Results

Characteristics of the study groups during admission

Tables I and II summarize the clinical characteristics and treatments of the 1,360 patients (mean age 71 years) who were included in the study. Echocardiography had been performed in 1,101 cases, and systolic function had been normal in 42% of the 1,062 in which it had been possible to determine LVEF.

The subgroups with normal and depressed LVSF exhibited the same differences as have been reported in previous studies (Tables I and II).

The only statistically significant difference between the 298 patients for whom LVEF could not be determined and those for whom it could was that a smaller proportion of the former were in New York Heart Association functional class IV upon admission.

Survival

Reliable survival data were available for 90.4% of the whole study group. Mean follow-up after discharge from hospital was 3.7 years (range 0.0-11.2 years), and in 615 cases terminated in death. Mean survival time was 6.0 years (range 5.7-6.3 years).

There was no significant difference between the normal and depressed LVSF groups as regard either follow-up time ($P = .17$) or survival time (mean 5.9 years [95% CI 5.4-6.4 years] among those with normal LVSF, mean 6.3 years [95% CI 5.9-6.8 years] among those with depressed LVEF, $P = .33$). Although patients without an LVEF measurement survived for a shorter time than those

Table I. Demographic and clinical characteristics of the whole study group and the subgroups defined by LVEF status

| Characteristic | Whole group (N = 1360) | LVEF ≥50% (n = 443) | LVEF <50% (n = 619) | Unknown LVEF (n = 298) | P* | P† |
|---------------------------------|---------------------------|------------------------|------------------------|---------------------------|-------|-------|
| Age (y) | 70.5 ± 11.8 | 72.9 ± 10.1 | 67.6 ± 12.2 | 72.9 ± 12.7 | <.001 | <.001 |
| Age ≥75 y (%) | 37.6 | 44.0 | 29.3 | 45.3 | <.001 | <.001 |
| Hospital stay (d) | 13.6 ± 10.7 | 12.8 ± 10.7 | 14.5 ± 11.3 | 12.9 ± 9.2 | .018 | .013 |
| Male sex (%) | 60.7 | 50.6 | 69.1 | 58.1 | <.001 | <.001 |
| Ischemic cardiopathy (%) | 50.7 | 42.4 | 54.6 | 55.0 | <.001 | <.001 |
| Valvular cardiopathy (%) | 18.6 | 32.1 | 12.3 | 11.7 | <.001 | <.001 |
| Dilated cardiomyopathy (%) | 8.5 | 0 | 16.3 | 4.4 | <.001 | <.001 |
| Other cardiopathy (%) | 22.1 | 25.1 | 16.8 | 28.9 | <.001 | <.001 |
| History of hypertension (%) | 54.9 | 61.9 | 51.8 | 51.0 | .002 | .001 |
| History of diabetes (%) | 27.8 | 26.1 | 28.8 | 28.2 | .612 | .365 |
| History of hyperlipidemia (%) | 32.9 | 33.2 | 34.3 | 29.5 | .343 | .742 |
| History of smoking (%) | 29.3 | 24.0 | 36.1 | 22.9 | <.001 | <.001 |
| NYHA class IV (%) | 37.6 | 36.2 | 42.0 | 30.4 | .003 | .065 |
| Left bundle branch block (%) | 15.9 | 7.3 | 21.5 | 17.1 | <.001 | <.001 |
| Atrial fibrillation (%) | 32.3 | 37.9 | 30.2 | 28.0 | .007 | .010 |
| Third sound at auscultation (%) | 9.9 | 3.0 | 17.2 | 5.0 | <.001 | <.001 |
| Alveolar edema at admission (%) | 11.4 | 6.9 | 14.4 | 11.9 | .001 | <.001 |

NYHA, New York Heart Association.

*For comparisons between the groups with LVEF ≥50%, LVEF <50%, and unknown LVEF.

†For comparisons between the groups with LVEF ≥50% and LVEF <50%.

Table II. Management of the whole study group and the subgroups defined by LVEF status

| Characteristic | Whole group (N = 1360) | LVEF ≥50% (n = 443) | LVEF <50% (n = 619) | Unknown LVEF (n = 298) | P* | P† |
|-------------------------|---------------------------|------------------------|------------------------|---------------------------|-------|-------|
| Echocardiography (%) | 81.0 | 100 | 100 | 13.1 | <.001 | 1.000 |
| Coronariography (%) | 39.5 | 29.6 | 46.2 | 40.3 | <.001 | <.001 |
| ACE inhibitors (%) | 61.9 | 52.1 | 73.9 | 49.8 | <.001 | <.001 |
| ARBs (%) | 5.4 | 5.0 | 5.3 | 6.0 | .871 | .884 |
| β-Blockers (%) | 29.2 | 24.7 | 34.1 | 24.9 | .002 | .002 |
| Spirolactone (%) | 12.1 | 8.6 | 16.0 | 8.6 | <.001 | .001 |
| Diuretics (%) | 73.9 | 66.0 | 82.2 | 67.4 | <.001 | <.001 |
| Digoxin (%) | 26.8 | 19.9 | 33.2 | 23.2 | <.001 | <.001 |
| Calcium antagonists (%) | 19.9 | 31.7 | 10.5 | 22.7 | <.001 | <.001 |
| Antiaggregants (%) | 57.2 | 51.6 | 59.9 | 61.8 | .013 | .012 |
| Anticoagulants (%) | 26.2 | 28.5 | 27.0 | 20.2 | .060 | .660 |

ACE, Angiotensin converting enzyme; ARB, angiotensin receptor blocker.

*For comparisons between the groups with LVEF ≥50%, LVEF <50%, and unknown LVEF.

†For comparisons between the groups with LVEF ≥50% and LVEF <50%.

for whom LVEF was determined (mean 5.2 [95%CI 4.6-5.8] years as against 6.2 [95% CI 5.8-6.5] years, $P = .003$), this difference was not significant when age was taken into account (age-adjusted hazard ratio 0.86 [95% CI 0.71-1.04], $P = .125$).

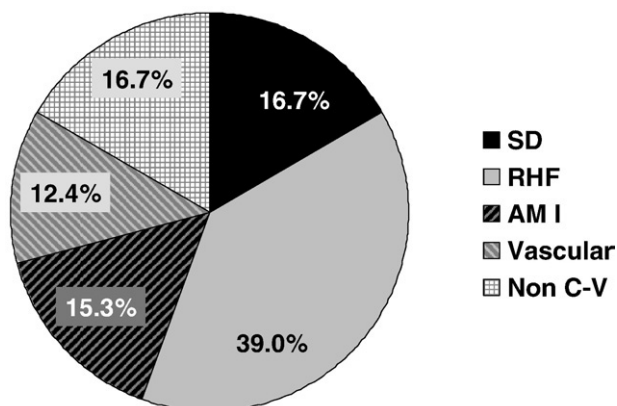
Causes of death

Cause of death could be established unequivocally in 516 cases. The most common cause was refractory HF (39%), other deaths being distributed quite similarly among sudden death, acute myocardial infarct, noncardiac vascular causes, and noncardiovascular causes (Figure 1). There was no statistically significant difference

between the normal LVEF and depressed LVEF subgroups as regard the distribution of deaths among the 5 types of cause distinguished in this study, although the latter group showed a greater incidence of sudden death (21% as against 16%) (Figure 2) and a smaller incidence of death from refractory HF (37% as against 41%), which as in the whole group was the most common cause of death in both subgroups. There were no significant differences between patients with and without an LVEF measurement as regard cause of death.

Rather different patterns were observed during the first 1.5 years of follow-up, especially among patients with normal LVEF (Figure 3). During this period, 50% of deaths

Figure 1

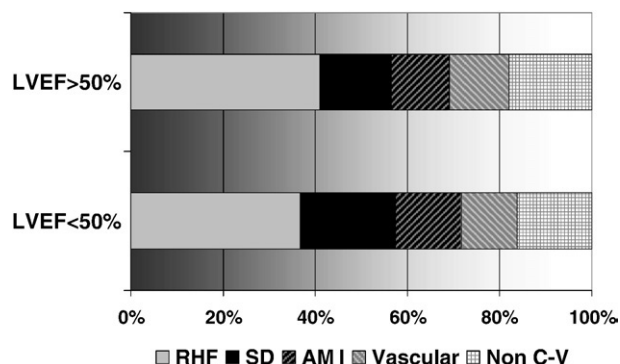


Distribution of deaths of patients with HF among 5 types of cause during the whole follow-up period, in the whole study group. SD, Sudden death; RHF, refractory HF; AMI, acute myocardial infarction; V, noncardiac vascular origin; NCV, noncardiovascular origin.

in this group were due to refractory HF, 17% to sudden death, 14% to noncardiac vascular accidents, 11% to noncardiovascular causes, and 9% to acute myocardial infarction. In the group with depressed LVEF, the main difference with respect to the whole follow-up period was a slightly higher incidence of sudden death (24%). However, as in the case of the whole follow-up period, the differences between the normal and depressed LVEF subgroups were not statistically significant.

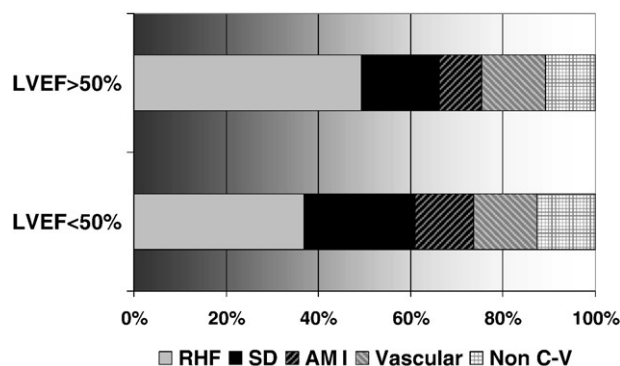
Although the normal and depressed LVEF groups did not differ significantly in cause of death spectrum for either the first 1.5 years or the whole follow-up period, there were nevertheless differences between them as regard the evolution of mortality due to specific causes. In the depressed LVEF group, after adjustment for age and sex, the probability that a death due to myocardial infarction during the first 1.5 years would occur during the first month was almost 50%, whereas for all the other causes of death the cumulative probability was about 25% after 1 month and increased linearly thereafter, reaching 50% after about 8 months (Figure 4, middle panel). By contrast, in the normal LVEF group, there was greater variety in this respect (Figure 4, left panel); for sudden death or death due to refractory HF within 1.5 years, the cumulative probability increased virtually linearly, taking about 8 months to reach 50%; for noncardiovascular and noncardiac vascular deaths, the 50% level was reached earlier (after about 4 months in the former case and 5 months in the latter), whereas for deaths due to acute myocardial infarction the 50% level was reached later, after about 14 months. Among patients for whom no LVEF measurement was obtained, the pattern observed was for all causes of death rather similar to that of

Figure 2



Distribution of deaths of patients with HF among 5 types of cause during the whole follow-up period in the groups with LVEF \geq 50% and LVEF <50%. Abbreviations as for Figure 1.

Figure 3



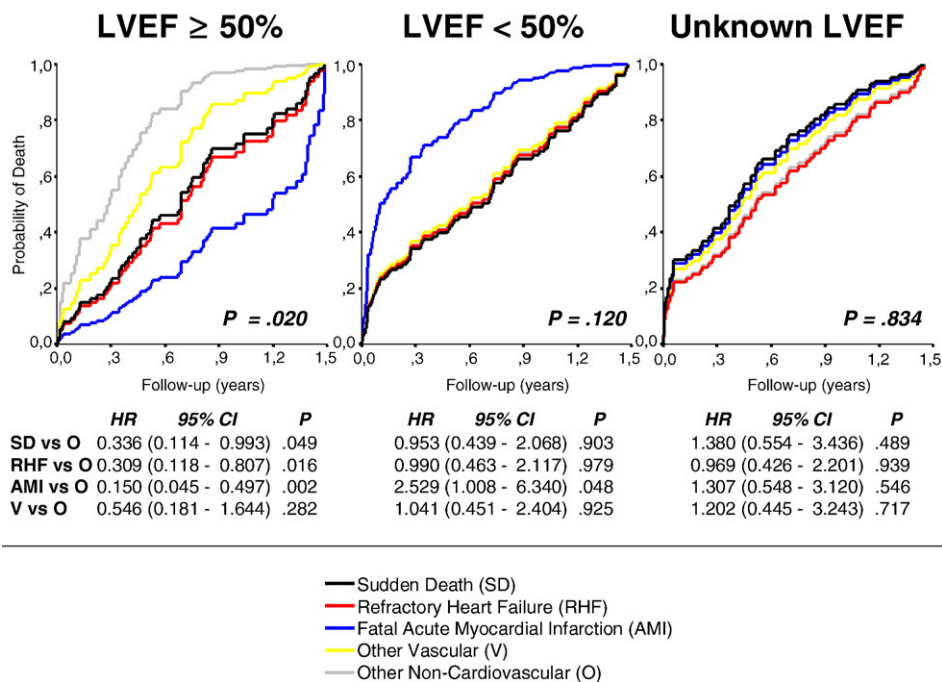
Distribution of deaths of patients with HF among 5 types of cause during the first 18 months after hospital admission, in the groups with LVEF \geq 50% and LVEF <50%. Abbreviations as for Figure 1.

nonmyocardial infarction deaths in the depressed LVEF group (Figure 4, right panel).

Discussion

In this study of patients admitted to a university hospital with HF during an 8-year period, we observed no statistically significant overall differences in causes of death between those with depressed and preserved LVEF. In both groups, the most common cause of death was refractory HF during both the whole follow-up period and for the first 1.5 years after hospitalization. However, the normal and depressed LVEF groups differed as regard the evolution of the cumulative probabilities associated with deaths due to specific causes during the first 1.5 years. If

Figure 4



Cause-specific mortality curves adjusted for age and sex for patients with HF and LVEF <50% (middle panel), LVEF \geq 50% (left panel), and unknown LVEF (right panel) who died within 18 months of hospitalization.

the age and sex distributions in the normal and depressed LVEF groups had been the same, then in the depressed group, 50% of those dying of acute myocardial infarction in this period would have died within little for a month, as against about 14 months for the normal LVEF group, and 50% of those dying of noncardiovascular or noncardiac vascular causes would have died within about 8 months, as against about 4 and 5 months, respectively, in the normal LVEF group.

Patients with HF and normal LVEF are still being managed without their differential characteristics being taken into account on a scientifically sound basis.^{21,22} As far as we know, this is the first published investigation of causes of death among patients with HF and normal LVEF who have not undergone any preselection process. Our findings help clarify the prognosis of such patients and have significant implications for their management.

As regard patients with HF and deteriorated LVSF, our findings broadly coincide with those of recent clinical trials and other studies of such patients.^{19,20} Refractory HF and sudden death are the 2 main causes of death regardless of whether HF is of ischemic origin. However, considerably more of our patients died of refractory HF than sudden death, whereas the reverse was found in 2 recent clinical trials (EPHESUS [Eplerenone Post-AMI Heart Failure Efficacy and Survival Study] and the low-LVEF arm of

CHARM [Candesartan in HF Assessment of Reduction in Mortality and morbidity]).^{19,20} This discrepancy may have been due to differences in sex ratio and/or to our patients being older and having more comorbidities (anemia, kidney failure, and others) and a lower prevalence of ischemic cardiopathy. These same differences may well explain why the incidence of noncardiovascular deaths was higher in this study than in other clinical trials.

Several recent studies have reported that the death rate among patients with HF and normal LVSF, who now constitute 30% to 50% of all patients with HF,^{23,24} is not, as was once supposed, significantly lower than that of patients with depressed LVSF and that the above-noted decline in the annual death rate among patients with and HF depressed LVSF has not been paralleled among patients with normal LVSF.^{6,18} However, very little has been published concerning the relative frequencies of different causes of death among patients with normal LVSF HF. Because patients with normal LVSF are older than patients with depressed LVSF, more likely to be hypertensive and female and less likely to have ischemic cardiopathy,^{12,17} the cause-of-death spectra of the 2 groups may well differ. In particular, the association of normal LVSF HF with hypertension might suggest that this particular type of HF is fundamentally a clinical manifestation of vascular and kidney disease of hypertensive origin and that the

causes of death of these patients should be more varied and exhibit a higher incidence of stroke, aortic aneurysm, and other causes directly related to hypertension than those associated with depressed LVSF HF. This hypothesis is indeed in keeping with the results of the CHARM-Preserved study, in which a large proportion of deaths among patients with normal LVSF were of noncardiovascular origin.²⁰ However, it must be borne in mind that the total annual death rate in this arm of CHARM was only 4%, much lower than in this and numerous other studies of patients with normal LVSF HF.²⁵ In fact, there are grounds for thinking that the preserved arm of CHARM may have included patients who did not have HF, in which case these patients without HF may have inflated the proportion of noncardiovascular deaths in that study. In the present study, the main cause of death in both the normal and depressed LVSF groups was refractory HF, which in the former group caused >50% of all deaths during the first 1.5 years of follow-up.

The finding that the spectrum of causes of death among patients with normal LVSF HF is very similar to that of patients with reduced LVSF has implications for the management of patients of the former kind, for whom the recommendations of current clinical guidelines are essentially based on speculation.^{21,22} In combination with the finding that the survival of patients with normal LVSF could benefit from angiotensin-converting enzyme inhibitor treatment to a similar extent to that of patients with depressed LVSF,^{12,26} it implies that, pending more comprehensive studies, the therapeutic approach to the normal LVSF group should include angiotensin-converting enzyme inhibitors alongside diuretics to alleviate congestion and control blood pressure.

In this study, we found that the normal and depressed LVEF groups differed as regard the evolution of the cumulative probabilities associated with deaths due to specific causes during the first 1.5 years. After hospitalization, the cumulative probability of a death due to acute myocardial infarction during this period initially increased rapidly among patients with depressed LVSF but relatively slowly among those with normal LVSF, among whom it was the cumulative probability of a death due to noncardiovascular or noncardiac vascular causes that initially increased most rapidly (Figure 4). These differences may be due to differences in the etiology of HF or in the causes of the HF decompensation leading to hospitalization—among patients with depressed LVEF, ischemic heart disease, whether acute coronary syndromes or chronic ischemic disease, is both a common etiology and determinant of hospitalization, whereas the etiologies and determinants of hospitalization of patients with normal LVEF are more diverse.²⁷ These results suggest that the HF etiology and the hospitalization determinants are important clinical conditions related

with the prognosis particularly in the early period after hospital admission.

Limitations

Although in this study retrospective classification of deaths in accordance with their cause was effected by a panel of clinicians with ample experience of HF, it is possible that some cases may have been misclassified. In particular, it is possible that deaths due to acute myocardial infarction occurring soon after discharge from hospital may in some cases have been interpreted as sudden death, which may have distorted our results very slightly. However, distortion seems unlikely to have been introduced by its not having been possible to determine the cause of 16% of deaths because these deaths were distributed proportionally between the normal LVSF and depressed-LVSF groups.

A factor that may have prevented the study group as a whole from being fully representative of the general HF population is all patients had been hospitalized in the cardiology service of a university hospital. In particular, this may have been responsible for them being, on average, slightly younger than those involved in certain community studies or studies of patients hospitalized in other kinds of hospital or service, and for a greater prevalence of men and of ischemic heart disease and a smaller prevalence of comorbidity.

In conclusion, not only is the long-term death rate among patients hospitalized with HF and normal LVSF similar to that found among patients with depressed LVSF but also the causes of death are similar in the long term in these 2 groups. In the short term (<1.5 years after hospitalization), there are differences between patients with normal LVEF and depressed LVEF as regard the dynamics of the risks of death from acute myocardial infarction, noncardiac vascular causes, and noncardiovascular causes. These results may help orient the short-term and long-term management of HF, especially for patients with normal LVEF, for whom there is still no well-established consensus strategy.

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