

# Participation of Argentina in the European Registry of Heart Failure

## *Participación de la Argentina en el Registro Europeo de Insuficiencia Cardíaca*

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### ABSTRACT

**Background:** Heart failure is a globally expanding disease and the available therapeutic tools are still insufficient.

**Objectives:** The aim of this study was to know the epidemiological and clinical characteristics of patients with diagnosis of heart failure in the Argentine Republic, as well as the treatments implemented and their prognosis, in both outpatients and hospitalized patients due to disease recurrence.

**Methods:** An observational, prospective, multicenter study of outpatients with chronic heart failure and hospitalized patients admitted due to decompensated heart failure was performed in the Argentine Republic from August 2012 to March 2013, in order to participate in the long-term Heart Failure Registry organized by the European Society of Cardiology. To facilitate recruitment, the study design contemplated inclusion only one day per week. Patients were followed up for one year.

**Results:** A total of 492 patients were included: 122 with decompensated heart failure and 370 with chronic heart failure. In both groups, women accounted for 30%. Compared with outpatients, hospitalized patients were older [72.5 years (IQR 64-80) vs. 63 years (IQR 54-71);  $p < 0.0001$ ] and with a higher risk clinical profile. Atrial fibrillation and preserved ejection fraction were more frequent in hospitalized patients. Median hospitalization time was 5 days and in-hospital mortality was 2.5%. At one year follow-up, 20.8% of patients recruited at hospital admission and 10.3% of outpatients died. The rate of readmission for decompensated heart failure was 45.6% and that of hospitalization for chronic heart failure was 28%.

**Conclusions:** Hospitalized and outpatient populations were not homogeneous; hospitalized patients were older and heart failure with preserved ejection fraction was more prevalent. The rate of events at the 12-month follow-up period was elevated and even higher for those with decompensated heart failure.

**Key words:** Heart Failure - Registries - Argentina/epidemiology

### RESUMEN

**Introducción:** La insuficiencia cardíaca es una patología que se encuentra en expansión a nivel global y las herramientas terapéuticas disponibles aún son insuficientes.

**Objetivos:** Conocer las características epidemiológicas y clínicas de los pacientes con diagnóstico de insuficiencia cardíaca en la República Argentina, así como las terapéuticas implementadas y su pronóstico, tanto en pacientes ambulatorios como en internados por una reagudización.

**Material y métodos:** Se realizó un relevamiento observacional, prospectivo multicéntrico de pacientes con insuficiencia cardíaca crónica ambulatorios e internados por insuficiencia cardíaca descompensada en la República Argentina durante el período agosto 2012-marzo 2013, reclutados para participar en el Registro a largo plazo de Insuficiencia Cardíaca organizado por la Sociedad Europea de Cardiología. Para facilitar el reclutamiento, el diseño contempló la inclusión solamente un día semanal. Se realizó seguimiento al año de los pacientes.

**Resultados:** Se incluyeron 492 pacientes, de los cuales 122 correspondieron a insuficiencia cardíaca descompensada y 370 a insuficiencia cardíaca crónica. En ambos grupos, las mujeres representaron el 30%. Comparados con los ambulatorios, los internados tuvieron mayor edad [72,5 años (RIC 64-80) vs. 63 años (RIC 54-71);  $p < 0,0001$ ] y un perfil clínico de mayor riesgo. La fibrilación auricular y la fracción de eyección preservada fueron más frecuentes en los internados. La mediana de internación fue de 5 días y la mortalidad hospitalaria fue del 2,5%. Al año de seguimiento fallecieron el 20,8% de los reclutados en la internación y el 10,3% de los ambulatorios. La tasa de readmisión para insuficiencia cardíaca descompensada fue del 45,6% y la de hospitalización para insuficiencia cardíaca crónica fue del 28%.

REV ARGENT CARDIOL 2017;85:332-339. <http://dx.doi.org/10.7775/rac.v85.i4.10972>

Received: 06/09/2017 - Accepted: 08/29/2017

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**Conclusiones:** Las poblaciones de pacientes internados y ambulatorios no fueron homogéneas; los hospitalizados tuvieron mayor edad y fue más prevalente la insuficiencia cardíaca con fracción de eyección preservada. La tasa de eventos en el seguimiento a 12 meses fue elevada y aun mayor para aquellos con insuficiencia cardíaca descompensada.

**Palabras clave:** Insuficiencia cardíaca - Registros - Argentina/epidemiología

## Abbreviations

<b>SBP</b>	Systolic blood pressure	<b>IQR</b>	Interquartile range
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## INTRODUCTION

In the last decades, heart failure has become a globally expanding disease, with approximately 26 million adults who suffer from this condition. (1) According to 2016 updated data, its prevalence in the adult population of the United States is 2.2%, and the risk of developing heart failure after 40 years of age is 20%. (2)

It is a disease with a high mortality rate. Average survival is 5 years with marked impairment in the quality of life, making the disease the center of these patients' life. Approximately 80% require at least one hospitalization due to decompensation, which represents a negative breaking point in patient evolution.

In Argentina we do not have epidemiological data providing information on the number of patients with heart failure, but extrapolating its prevalence according to the number of adults in the country, around 660,000 individuals would suffer from this disease. (3) According to data from the Ministry of Health of Argentina, the mortality rate for heart failure has been for 20 years above that for other cardiovascular conditions, with 121/100,000 inhabitants in 1991 and 67.8/100,000 inhabitants in 2006; with an annual reduction of 3.3%. (4)

During the years 2012-2013, the Argentine Society of Cardiology participated in the Heart Failure Registry of the European Society of Cardiology, simultaneously recruiting patients with stable chronic heart failure and decompensated heart failure.

The aim of the following publication was to analyze the information collected from the 492 patients included in Argentina.

## METHODS

A survey of heart failure patients was carried out in Argentina between August 2012 and March 2013, with the purpose of participating in the EURObservational Research Program (EORP) organized by the European Society of Cardiology. It was a prospective, observational, multicenter study focused on acquiring information about patients with heart failure.

The aim of the registry was to simultaneously know the characteristics of both outpatients and hospitalized patients suffering from heart failure with a new control at one year.

Chronic heart failure was considered for all patients who consulted on an outpatient basis with this diagnosis according to the clinical judgment of the participating center cardiologist, without exclusion criteria except for those under 18 years of age. Conversely, acute heart failure was considered in all patients admitted to hospital for heart failure who

required intravenous treatment with diuretics, inotropic agents or vasodilators. Patients with heart failure in the context of an acute coronary syndrome were excluded.

To facilitate recruitment, the design considered inclusion of patients admitted with the main diagnosis of heart failure only one day per week or of those outpatients who that day consulted for the same diagnosis. The recruitment day was at the center's discretion. The registry design considered a visit or else a telephone contact at 12 months to collect information related to their vital status and the state of their illness.

Patients were controlled from the diagnostic and therapeutic point of view according to each center's standards. Drug prescriptions and indications to reach a diagnosis and treatment were decided by the participating physicians.

The primary endpoint was to describe the epidemiological characteristics of outpatients and hospitalized patients with heart failure and provide data related to diagnosis and treatment.

## Statistical Analysis

Quantitative variables were expressed as mean and standard deviation or median and 25%-75% interquartile range (IQR), depending on whether or not the distribution was parametric.

Statistical significance between groups was determined by the t test or the Wilcoxon test depending on whether or not the distribution was parametric.

In the case of 3 or more groups, ANOVA or the Kruskal Wallis test was used, respectively.

Qualitative variables were expressed as percentage and statistical significance was established through the chi-square test or Fisher's exact test for binary variables and in case of more than two possibilities through Monte Carlo estimation for the exact p value.

A two-tailed  $p < 0.05$  was considered significant.

To compare the evolution at one-year follow-up, the cumulative incidence of mortality and rehospitalization was analyzed by Kaplan-Meier curves; divided between outpatients and hospitalized patients and compared with the log rank test.

SAS 9.3 statistical software (SAS Institute, Inc., Cary, NC, USA) was used for statistical analyses.

## Ethical Considerations

The study was evaluated and approved by the Ethics Committee and the Scientific Committee of the participating institutions.

## RESULTS

During the 8-month recruitment period, 492 patients were included, 122 with decompensated heart failure,

and 370 with chronic heart failure.

At one-year follow-up, 87% (106 of 122) of hospitalized patient data and 94% (349 of 370) of outpatient data was available.

Twenty-one centers, 13 corresponding to the metropolitan area of the Federal Capital of Argentina and 8 from other provinces participated in the study (see Appendix).

#### General characteristics of the patients included in the study

Table 1 shows the comparative characteristics of the patients admitted for decompensated heart failure and of patients with chronic stable heart failure.

Median age of the hospitalized group was 9.5 years higher than that of the outpatient group: 72.5 (IQR 64-80) vs. 63 (IQR 54-71) years,  $p < 0.0001$ . In both groups, gender distribution was 70/30 with a higher prevalence of men.

The presence of atrial fibrillation at the time of recruitment was significantly higher in hospitalized patients (44.3%) than in outpatients (27%) ( $p < 0.005$ ).

Among outpatients, etiology was distributed as follows: 38% ischemic, 32% idiopathic, 4.6% valvular heart disease, 6.8% secondary to arterial hypertension and 38.4% due to other etiologies. Among hospitalized patients, the distribution of etiology was 41.8% ischemic, 17.2% idiopathic, 17.2% valvular heart disease, 9.8% hypertensive and 13.9% due to other etiologies. The ischemic origin of heart disease was present only in 39% of the overall population, and was significantly higher among hospitalized patients ( $p < 0.0001$ ).

At the time of recruitment, ejection fraction was significantly higher in hospitalized patients than in outpatients: 0.38 (IQR 0.30-0.50) vs. 0.31 (IQR 0.25-0.40);  $p = 0.0004$ . Only 13% of outpatients had pre-

served ejection fraction ( $> 0.45$ ) vs. 36% of hospitalized patients ( $p < 0.0001$ ) (see Table 1).

The presence of comorbidities was common in both groups of patients, and with no significant differences between them, except that there were more diabetics (30.3% vs. 21.4%  $p: 0.04$ ) and more patients with  $Hb < 12$  mg/dl (52.2 vs. 23.3%;  $p = 0.0001$ ) among hospitalized patients. Regarding vital signs on admission, hospitalized patients presented higher systolic blood pressure (SBP) than outpatients: 128.5 mmHg (IQR 110-150) vs. 110 mmHg (IQR 100-129);  $p < 0.0001$ . Heart rate was also higher: 90 beats/minute (IQR 75-110) vs. 70 beats/minute (IQR 62-75) ( $p < 0.0001$ ) between hospitalized and outpatients, respectively.

#### Hospitalized patients with heart failure.

Regarding the presentation of heart failure at the time of hospitalization, a marked prevalence of congestive forms was observed, whereas the presentation with low cardiac output syndrome and/or shock was very scarce: Congestive 65.6%, acute pulmonary edema 21.3%, hypertensive 7.4%, right ventricle failure 3.3% and cardiogenic shock or low cardiac output 2.5%.

Median hospital stay was 5 days (IQR 3-9) and mortality was 2.5% (3 patients). Echocardiogram was performed in 85% of the population and 5% of patients underwent pulmonary artery catheterization to measure pulmonary pressures. Treatment consisted in intravenous diuretics in 96.7% of cases, intravenous vasodilators in 59.8% and inotropic agents in 14.8% of patients.

At the time of discharge, the rate of neurohormonal antagonist use was 60.7%, 75.4% and 49.2% for angiotensin II converting enzyme inhibitors/angiotensin II receptor blockers, beta-blockers and antialdosterone agents, respectively.

**Table 1.** Baseline comparative characteristics between hospitalized patients and outpatients

	Hospitalized patients (n = 122)	Outpatients (n = 370)	p
Age, years, median (IQR)	72.5 (64-80)	63 (54-71)	<0.0001
Females, %	30.3	30	0.9
Functional class III-IV, %	96.7	17	<0.0001
Admission systolic blood pressure, mmHg (IQR)	128.5 (110-150)	110 (100-129)	<0.0001
Heart rate, bpm (IQR)	90 (75-110)	70 (62-75)	<0.0001
Ejection fraction, % (IQR)	38 (0.30-0.50)	31 (0.25-0.40)	0,0004
Ejection fraction $\geq 45\%$ , n (%)	44 (36)	49 (13.3)	<0.0001
Atrial fibrillation, n (%)	54 (44.3)	101 (27.3)	0.0005
Ischemic etiology, n (%)	51 (41.8)	141 (38.1)	<0.0001
Valvular etiology, n (%)	21 (17.2)	17 (4.6)	<0.0001
Hemoglobin $< 12$ g/dl, n (%)	64 (52.2)	86 (23.3)	<0.0001
Diabetes, n (%)	37 (30.3)	70 (21.4)	0.04
Hypertension, n (%)	73 (59.8)	211 (57)	ns
Chronic renal failure, n (%)	25 (20.5)	57 (15.4)	ns
COPD, n (%)	15 (12.3)	45 (12.2)	ns

IQR: Interquartile range. COPD: Chronic obstructive pulmonary disease. ns: Non-significant.

### Ambulatory heart failure patients

With a prevalence of 87% of patients with systolic impairment and 83% in functional class I/II, 88.9% of patients were prescribed angiotensin II converting enzyme inhibitors, 94.6% beta-blockers and 72.2% antialdosterone agents (Table 2) at the time of recruitment. The rate of diuretic use was 67.8%. Digoxin was prescribed in 17% of patients, while amiodarone was indicated in 30% of patients. Ivabradine was prescribed in 2.7 of patients. The rate of electrical therapy with implantable cardioverter defibrillator and/or resynchronization device reached 29.3%, (23.6% only cardioverter defibrillator and 5.7% cardioverter defibrillator with resynchronizer) in a population where half of the patients had ejection fraction  $\leq 0.30$ .

### One-year follow-up

Among the 106 hospitalized patients, 22 (20.8%) died at one-year follow-up, in 45.5% (n=10) of cases from cardiovascular causes and in 54.5% (n=12) of cases from extracardiac causes. Readmission rate was 45.6% (n = 47), 68% due to heart failure (Figure 1).

Of the 370 outpatients recruited, with a population predominantly in functional class I-II, mortality at one year reached 10.3% and the cause of death was cardiovascular in 75% of cases. Twenty-eight percent of patients were hospitalized during the one-year follow-up, 65% due to heart failure (see Figure 1).

The comparative analysis between the two groups showed that the outcome was clearly worse among patients who were recruited at the time of admission:  $p < 0.001$  for hospitalization and  $p = 0.045$  for mortality (Figures 2 and 3).

### DISCUSSION

In the last 25 years, numerous registries of heart

failure have been carried out in Argentina. Although most have been in decompensated patients, there is also information from outpatients with chronic heart failure, although this is less updated. (5)

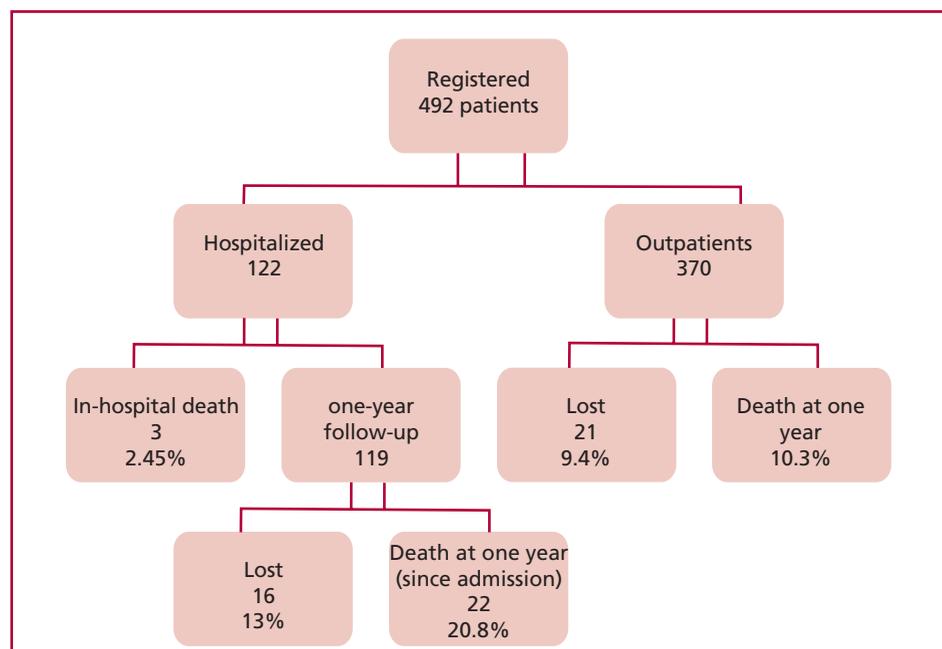
What is the contribution of the present registry? To our understanding, it has several added values. It is the first one that has recruited simultaneously and in the same centers stable and decompensated patients at a national level, thus allowing a comparison between them. On the other hand, it is the first registry that has performed a one-year follow-up after recruitment, providing information in our country on the poor evolution of heart failure patients.

In the process of center selection, high and low complexity centers were included in different provinces of the country. This adds the value of having information from centers with different levels of resources and in different areas of urbanization.

**Table 2.** Chronic heart failure. Treatment at time of recruitment

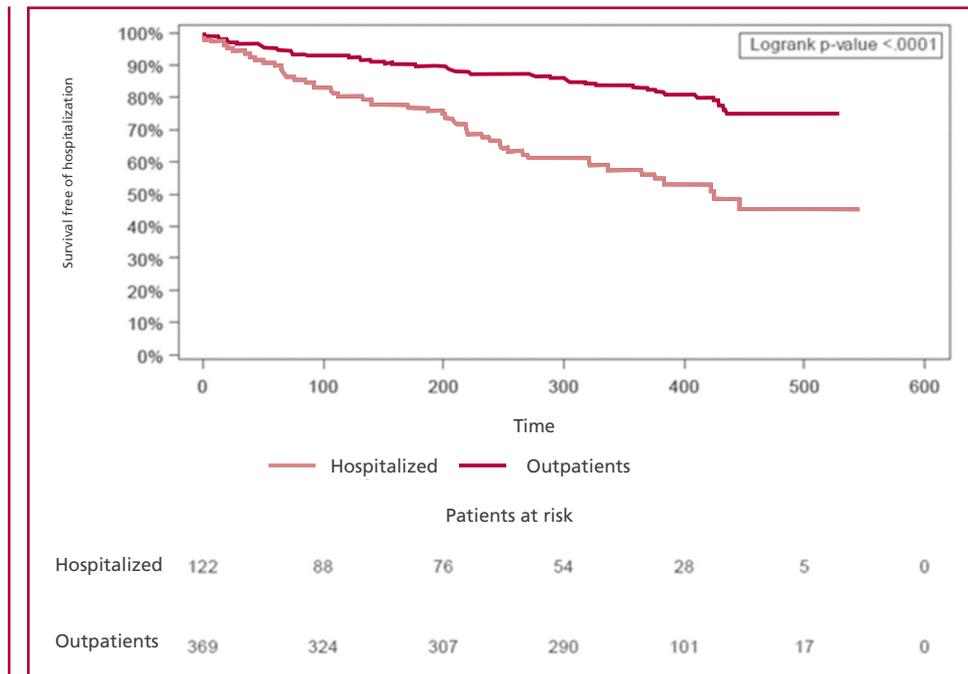
Medication	%
ACEI/ARB II	88.9
Betablockers	94.6
Antialdosterone agents	72.2
Diuretics	67.8
Digoxin	17.3
Statins	47.6
Antiplatelet agents	51.6
Nitrates	5.1
Anticoagulants	40.3
Amiodarone	30
Ivabradine	2.7

ACEI/ARB II: Angiotensin II converting enzyme inhibitors/angiotensin II receptor blockers

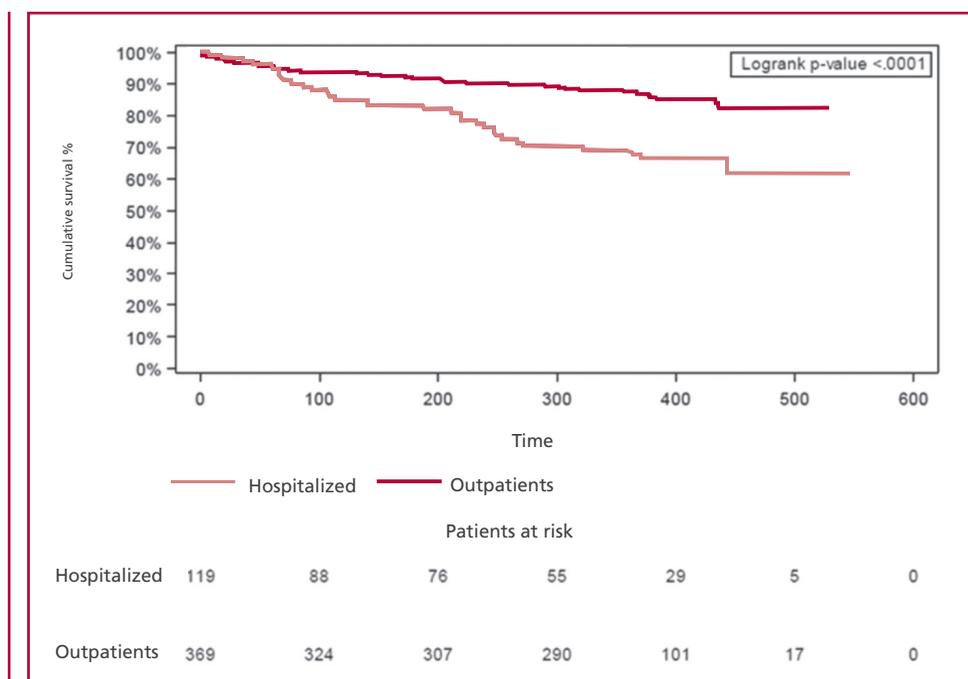


**Fig. 1.** In-hospital and one-year evolution.

**Fig. 2.** Kaplan-Meier curve for survival free of hospitalization at follow-up



**Fig. 3.** Kaplan-Meier curve for mortality at follow-up



**Outpatients vs. hospitalized patients. Are they the same population?**

Comparing hospitalized patients with outpatients, it is clear that they present different characteristics. Clearly, hospitalization for heart failure not only includes decompensated chronic patients, but also another population with no history of heart failure. On average, hospitalized patients are almost 10 years older, which probably does not represent a bias due to more severely ill patients, but a disease that affects older patients, with a consistent notorious higher prevalence of preserved systolic function. While in

decompensated patients it is close to 50%, in chronic patients it is only 13.5%. According to the registry, 65% of cases were chronic patients who became decompensated. Thus, we can infer that just over one-third of hospitalizations for heart failure correspond to patients without history of heart failure, which probably explains the differences found in age and ejection fraction.

**Characteristics of hospitalized patients**

Among hospitalized patients, baseline characteristics were similar to those of previous registries in terms

of old age, predominance of congestive heart failure and high prevalence of comorbidities. (6, 7) However, in-hospital mortality was significantly lower. It is interesting to observe how, over more than 20 years and 12 registries, there is a great heterogeneity in the mortality rate, without a pattern (8-16) to explain these differences. It is possible that the low mortality rate of the present registry is simply a consequence of this dynamic, since there have been no therapeutic differences to explain it. As in previous registries, the congestive form was the most usual type of presentation, with very low prevalence of patients admitted with low cardiac output syndrome. It should be noted that, similarly to most registries, patients with heart failure secondary to an acute ischemic event were not included.

Hypertension was very common on admission. Median SBP was 128.5 mmHg, but in 25% of the patients it was over 150 mmHg, coinciding with almost all the registries of acute heart failure, either of Argentina or of other regions. (17) However, the rate of intravenous vasodilator use is greater in Argentina than in registries from other countries. (18) In the present registry, the rate of use was 60%, whereas in the European and Mediterranean countries registry it was 20%, despite there were no significant differences in the admission SBP. Although there is no evidence to support administration of vasodilators, (19, 20) their use seems reasonable, both due to the elevated SBP as for pathophysiological reasons to optimize loading conditions.

#### Long-term prognosis of hospitalized patients

According to the results of the registry, the therapeutic measures implemented in the acute phase have been efficient to achieve low in-hospital mortality. However, the most interesting fact of the registry is the poor prognosis at one year: 1 out of 5 discharged patients (i.e. which survived hospitalization) died within a year. This is consistent with the information provided by the 2007 SAC registry, (7) reporting 12.8% mortality at 90 days among discharged patients.

This information exhibits the greatest challenge that decompensation due to heart failure raises: To improve the outcome of patients once they leave the hospitalization phase.

Could an intervention in the acute phase improve the outcome in the post-hospitalization phase? Although the hypothesis is very attractive, it has not yet been demonstrated. (21) However, it is important to emphasize the need to optimize post-discharge management in the vulnerable phase.

The other interesting fact is that only half of the deaths were due to a cardiac cause. This shows the great vulnerability of these patients, in whom although death is not due to heart failure, the latter determines the poor tolerance to any other disease, turning necessary the reinforcement of a multidisciplinary approach. It can also be assumed that comorbidities cause death in patients with heart failure.

Beyond mortality, the high rate of re-hospitalization that these patients presented during the follow-up year is also of concern; 46% of discharged patients, i.e. almost half, required readmission during the year. In this case, the main cause was heart failure recurrence.

#### Outpatient characteristics

It is usually stated that patients from randomized studies are unrepresentative of real life because they are a selected population with less comorbidities and this is generally attributed to younger age compared with that of registries. However, our records showed an outpatient median age more comparable to that of interventional studies than other registries. Beyond the easy explanation of recruitment bias, there are probably other reasons that may explain it. In this sense, the clear separation of decompensated patients (who are older) decreases the average age. On the other hand, although the inclusion criteria did not require it, the high proportion of patients with systolic dysfunction who are generally younger also draws age to a lower average; nevertheless, it is likely that this data is more representative of reality. (22)

It is also very likely that, since it is a population exclusively registered by cardiologists, many elderly patients with more comorbidities, who are followed-up by general practitioners or clinicians, have been excluded.

Another interesting, albeit not surprising, fact was the low prevalence of heart failure with ejection fraction >45% among outpatients. This information reinforces the explanation for the relatively low age of patients. With a relatively undemanding recruitment criterion, where biomarkers were not required to confirm the diagnosis, it is evident that the clinical criteria used were demanding for inclusion in the registry, which also explains the low prevalence of patients with preserved ejection fraction. Regarding pharmacological prescription, although we do not have the doses administered to each patient, we can in general assume that outpatients were adequately medicated considering the rate of neurohormonal antagonist use. (23)

Although the rate of device implantation for electrical therapy (cardioverter defibrillators and resynchronizers) is lower than suggested by the management guidelines, it is superior to the general data of the European registry. (18)

Regarding prognosis, the observed results show that even in stable patients, heart failure remains a disease with a worrying prognosis. Among outpatients, the vast majority (83%) was in functional class I-II, and correctly medicated. However, mortality at one year was 10%, and 28% required hospitalization. As in acute patients, heart failure was the cause of hospitalization in only half of the patients.

#### Limitations

The diagnosis of heart failure was done according to

clinical parameters and at the discretion of the treating physician, without the requirement of biomarkers or any other confirmatory tool. Neither was there a centralized validation, so we cannot rule out the presence of unduly recruited patients.

As in most registries, the participation was voluntary both on the part of the recruiting centers, as well as of patients, so the existence of some bias cannot be excluded.

As previously mentioned, recruitment was performed only by cardiologists, so it is not possible to know if the characteristics of patients with heart failure treated by clinicians or general practitioners are similar.

The rate of patients lost to follow-up exceeds the usual, which may limit the validity of the observation.

## CONCLUSIONS

Hospitalization for heart failure exceeds the mere decompensation of chronic patients. It also includes a population of elderly people with preserved ejection fraction, where hypertension is the most frequent denominator at the time of decompensation. The treatment and outcome during hospitalization are acceptable; however, the prognosis at one year is very poor. At least in this registry, the number of ambulatory patients with preserved ejection fraction was much lower than estimated. Despite having an acceptable rate of therapeutic prescription, mortality remains high.

## Conflicts of interest

None declared. (See authors' conflicts of interest forms on the website/Supplementary material).

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**APPENDIX**

## Participating centers and number of recruited patients

Center	N° of patients
Fundación Favaloro	165
Instituto de Cardiología "J. F. Cabral" Corrientes	51
Hospital Churruca	41
Sanatorio Modelo de Quilmes	38
ICBA	32
Sanatorio Pasteur - Catamarca	31
Hospital Italiano de Córdoba	31
Hospital Italiano de Buenos Aires	21
Hospital César Milstein	20
Clínica Bazterrica	19
Hospital Rivadavia	16
Hospital Escuela de Corrientes	13
Hospital Diego Paroissien de Mendoza	13
INCOR - La Rioja	9
Clínica San Jorge - Ushuaia	9
CEMIC	8
Sanatorio de la Trinidad de Palermo	7
Hospital Zonal del Tórax Dr. Antonio A. Cetrángolo	7
Sanatorio Anchorena	6
Hospital Italiano de Mendoza	5