

## Heart failure in real world

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### ABSTRACT

The heart failure (HF) is one of the greatest problems of public health with increasing epidemiological importance. In the present study we analyzed a population of 299 patients, consecutively admitted to hospital, whose diagnosis of HF was verified retrospectively. In our analysis we considered underlying heart diseases, comorbidities, ejection fraction, presence of atrial fibrillation and pleural effusion, values of NT pro-BNP and causes of destabilization precipitating HF. The mean age of our population was 81 years. Patients with preserved systolic function were 145 (61% of the total, 59 male and 86 female). 166 patients (69% of the total) had hypertensive heart disease and 211 had hypertension (88% of the total). Patients with pleural effusion were 108 (46% of total). In the total population 102 patients (43%) had from 3 to 5 comorbidities, 169 patients (71%) had at least 2 comorbidities and only 4 patients (1.7%) had no comorbidities. The collected data highlight the complexity of patients with HF, often due to advanced age and a high number of comorbidities.

### Introduction

Heart failure (HF) is one of the most important problems of public health with an increasing epidemiological impact in recent years. HF represents a disease with incidence and prevalence still rising, characterized by high morbidity and mortality and heavy burden in terms of costs for public health system.

HF can be defined as an alteration of the structure or function of the heart leading to inability to ensure an appropriate tissue perfusion or to permit it only through a filling pressure increase.<sup>1</sup> Clinically, HF presents as a syndrome with characteristic symptoms

(dyspnea and orthopnea in particular, asthenia and fatigue) and signs (peripheral edema, jugular venous distension, rales). However, the diagnosis of HF is not always easy, since many of the symptoms are also common to many other diseases. The demonstration of underlying heart disease is therefore crucial both for diagnostic and for therapeutic approach.

The prevalence of HF in the general adult population is between 2% and 3% and increases significantly in patients over 75 years of age (the prevalence of HF in the age group between 70 and 80 years ranges between 10 and 20%).<sup>2</sup> The increase in the overall prevalence is justified mainly by the ageing of the population and the prolonged survival of patients with hypertension and ischemic heart disease. HF causes 5% of total hospitalization, it is found in 10% of hospitalized patients and is source of 25% of the cost of the National Health System (a large part of this cost is due to hospitalizations).<sup>3</sup> Patients with HF have a 5-year mortality of about 55%, non-cardiovascular causes of death are rising especially in patients with preserved systolic function.<sup>4</sup>

There are many conditions that can lead to HF and they have a different distribution in different parts of the world. Approximately 50% of patients with HF have a reduced left ventricular ejection fraction (LVEF). Ischemic heart disease, that is often associated with hypertension and diabetes mellitus, leads to about two-thirds of HF with reduced LVEF. The valvular diseases account for about 10% of the causes of HF with reduced LVEF with a decreasing incidence in Western countries because of the always easier identification and subsequent surgical treatment. There are also many other conditions leading to HF with reduced LVEF: myocarditis, alcohol abuse, cardio-toxicity chemother-

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apy in addition to idiopathic dilated cardiomyopathy.<sup>5</sup> The HF with preserved LVEF, also called diastolic HF, presents a different etiology, epidemiology and prognosis.<sup>6</sup> Patients with diastolic HF are more likely to be older, female, obese and are less likely to have ischemic heart disease but are more often affected by high blood pressure and atrial fibrillation.<sup>7</sup>

The diagnosis of HF can be difficult, especially in the early stages of disease. In fact many of its symptoms are non-specific. Symptoms that are more specific for HF (orthopnea and paroxysmal nocturnal dyspnea) are often present only in patients with clear clinical pictures.<sup>8</sup> Many of the signs of HF are correlated to sodium and water retention (especially pitting ankle edema) and are often non-specific or non-detectable if the patient is already receiving diuretics.<sup>9</sup> In any case, symptoms and signs of HF are often difficult to identify and this is even more difficult in obese patients, patients with chronic lung disease and in elderly.<sup>10</sup> It is therefore important to use the anamnestic information in order to detect the presence of risk factors or past medical conditions that might have led to an alteration in the structure or function of the heart and their consistency with the patient's symptoms. There are several laboratory and instrumental investigations useful in the diagnosis of HF. Electrocardiogram, echocardiogram and chest x-ray are the most useful tools in patients with suspected HF. In particular echocardiogram allows to obtain useful information regarding volumes, left ventricular systolic and diastolic function, wall thickness and presence of valvular disease.<sup>11</sup> Among laboratory investigations, measurement of natriuretic peptide (BNP, NT pro-BNP) has acquired a certain value in the differential diagnosis of HF. In the presence of natriuretic peptide's values within the normal limits it is allowed to rule out diagnosis of HF with an accuracy of 95%.<sup>12</sup> Several other laboratory tests including blood count and renal function are important to guide therapeutic approach and determinate the severity of the HF.

The prognosis of HF is influenced by several factors among which the most important appear to be age and comorbidity.<sup>13</sup> The assessment of the prognosis and, in particular the identification of comorbidities, have a primary importance for the classification of patients with HF and for the management of therapies.<sup>14</sup> The aim of treatment is to reduce symptoms and signs of HF, improve the quality of life, reduce mortality and prevent hospitalization.<sup>15</sup> The therapy of HF is based, wherever possible, on removing underlying diseases (myocardial revascularization in ischemic heart disease, corrective valvular surgery, *etc.*). The therapeutic approach must be based on educational measures (salt and water intake, *etc.*). Drug therapy includes both symptomatic drug treatment (diuretics) and treatment with drugs that can improve survival [ $\beta$ -

blockers, angiotensin converting enzyme-inhibitors (ACE-I) an renin-angiotensin-aldosterone system (RAAS) blockers]. In selected cases minimally invasive treatments (myocardial resynchronization with pacemaker) can be used or, in younger patients with particularly severe heart disease, heart transplantation may be performed.

### Aim of the study

In this study we wanted to analyze a real population of patients consecutively admitted to hospital whose diagnosis of HF was verified retrospectively. The aim was to obtain an image from the real world of a disease that will have an increasing importance in terms of care as well as costs for our National Health System. We wanted to verify in a more homogeneous cohort of patients compared to those of previous multicentric studies, the *real* characteristics of patients with heart failure hospitalized in a Department of Medicine.

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### Materials and Methods

Our work is based on a retrospective survey conducted on a population of patients consecutively admitted to the Department of Internal Medicine of a proximity hospital, with diagnosis of HF in the calendar year 2012. To gather data we analyzed all clinical records as well as discharge letters of every single patient. The diagnosis of HF was verified including in the analysis only patients who had either symptoms and signs characteristic of HF as well as instrumental findings that confirm the presence of underlying structural heart disease. All patients with NT-proBNP values below 500 pg/mL were excluded.

Regarding underlying heart disease we have included: ischemic heart disease, hypertensive heart disease, valvular heart disease and idiopathic dilated cardiomyopathy.

We considered as ischemic heart disease all patients who had history of previous acute coronary events or episodes of angina pectoris.<sup>16</sup> As part of hypertensive heart disease we have included patients with history of hypertension and instrumental findings documenting the presence of concentric left ventricular hypertrophy with evidence of diastolic dysfunction.<sup>17</sup> In the group of idiopathic dilated cardiomyopathy we considered patients with echocardiographic finding of ventricular dilatation associated with impaired left ventricular function and with previous coronary angiography negative for ischemic heart disease.<sup>18</sup> In the group of valvular heart disease we considered aortic and mitral stenosis and regurgitation. In our analysis we included severe and moderate degree of valvular disease documented by

echocardiogram performed during hospitalization or within 12 months before admission. For aortic stenosis was considered the trans-valvular gradient equal or greater than 30 mmHg. For mitral stenosis was considered mean trans-valvular gradient equal or greater than 5 mmHg. For aortic and mitral regurgitation we included almost ++/++++ color-doppler-degrees.

Among comorbidities we considered: hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), anemia and kidney failure.

For hypertension we considered history of hypertension and/or treatment with antihypertensive drug. For diabetes we considered patients who had previous diagnosis of diabetes made according to the universally accepted criteria and/or antidiabetic treatment or with glycated hemoglobin measurement during the hospitalization greater than 6.5%. For COPD we considered only patients who had a diagnosis established by spirometric tests according to the criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) project. Anemia was defined according to the World Health Organization (WHO) criteria: hemoglobin less than 12.5 g/dL in males and less than 11.5 g/dL in females. Renal failure was considered with a glomerular filtration rate less than or equal to 45 mL/min/1.73 m<sup>2</sup> corresponding to a stage 3B according to National Kidney Foundation produces clinical practice guidelines through the National Kidney Foundation/Disease Outcomes Quality Initiative (NKF/DOQI).

We also evaluated the number of comorbidities present simultaneously in hospitalized patients with HF.

Ejection fraction was calculated by using the biplane Simpson method and in agreement with the literature data we have defined as preserved systolic function LVEF values greater than or equal to 50%.

In the group of Atrial fibrillation we included patients whose AF had not appeared during hospitalization but it was pre-existing or already diagnosed as chronic or permanent AF.

We analyzed the presence of pleural effusion diagnosed by chest X ray and thoracic ultrasound.

The values of NT pro-BNP was measured during the admission to the emergency department or within the first two days of hospitalization.

We also analyzed, when detectable, the causes of destabilization that had precipitated the HF.

## Results

The total hospitalized admissions with diagnosis of HF were 299. The total number of patients was 238 (108 male and 130 female; mean age 81 years old). Patients hospitalized two or more times were 38 (16% of the total population). Patients with preserved LVEF were 145 (61% of the total population) including 59 male and 86 female. Patients with reduced LVEF were

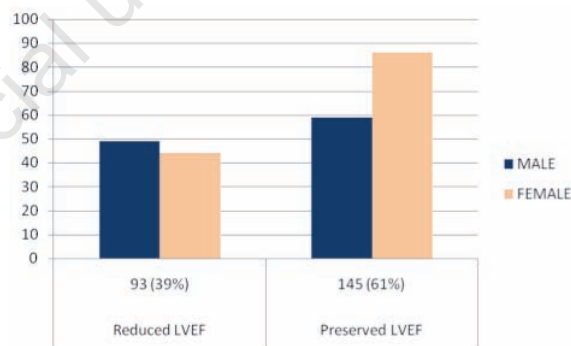
93 (39% of the total population) including 49 male and 44 female (Figure 1).

Among the underlying heart disease: patients with ischemic heart disease were 51 (21% of the total), those with hypertensive heart disease 166 (69 of the total), those with ischemic-hypertensive heart disease 40 (17% of the total), those with idiopathic dilated cardiomyopathy 12 (5% of the total) (Figure 2). Patients with valvular disease of at least moderate severity were 90 (38% of the total) of which 24 with aortic stenosis, 57 with mitral regurgitation, 4 with mitral stenosis and 5 with aortic regurgitation.

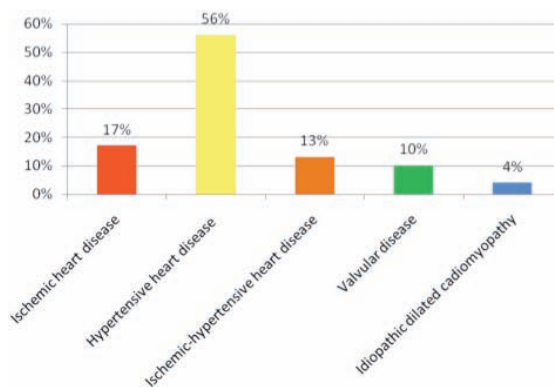
Among comorbidities we found 211 patients with hypertension (88% of the total), 68 with diabetes mellitus (28% of the total), 66 with COPD (28% of the total), 112 with anemia (47% of the total) and 99 with renal failure (41% of the total) (Figure 3).

Patients with permanent AF were 102 approximately 43% of the total (Figure 3).

Patients with pleural effusion were 108 (46% of



**Figure 1. Distribution of the population according to sex and systolic function. LVEF, left ventricular ejection fraction.**



**Figure 2. Percentage distribution of the population according to underlying heart disease.**

the total) of which 74 had a bilateral pleural effusion (Figure 4).

The mean value of NT pro-BNP result 6425 pg/mL in patients with preserved LVEF and 8670 pg/mL in patients with reduced LVEF.

The cause of destabilization was indeterminate in 50% of patients. The detected cause was distributed as follows: 13% infections, 10% arrhythmias, 10% acute exacerbation of COPD, 8% poor compliance, 4% acute coronary syndrome, 3% anemia and 2% acute renal failure.

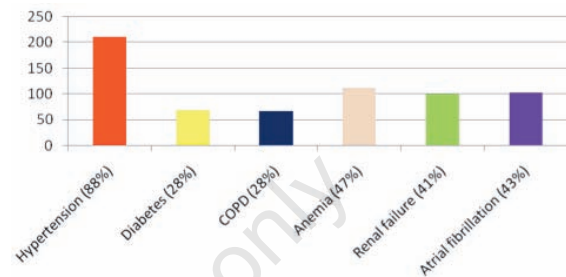
In the total study population 102 patients (43% of the total) had 3 to 5 comorbidities, 169 patients (71% of the total) had at least 2 comorbidities and only 4 patients (1.7% of the total) had no comorbidity (Figure 5).

Rehospitalized patients were 38 (16% of the total), with an average age of 83 years. 50% of these patients had a reduced LVEF (19 patients), 68% had 3 to 5 comorbidities and 89% had at least two comorbidities. Any patient had no comorbidity. The average values of NT pro-BNP were 10,619 pg/mL in patients with preserved LVEF and 13,975 in patients with reduced LVEF.

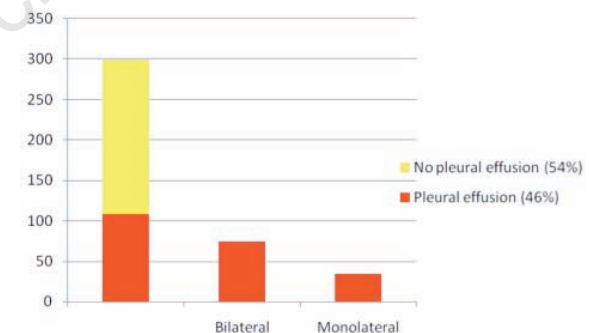
## Discussion

Epidemiological data regarding HF are often ambiguous mainly due to the heterogeneity of the populations studied (hospital statistics, longitudinal or transverse community analysis, clinical trials) and also the lack of a widely accepted definition of HF. In addition, many studies do not allow estimating the actual complexity of the patient suffering from HF (comorbidities and older age are often exclusion criteria from the analysis). In our study we wanted to check whether the literature data could find a match in a real population of patients admitted with diagnosis of HF in a Department of Internal Medicine. We therefore performed a retrospective analysis using the tool of the computerized medical records that allowed us to easily find a vast amount of reliable data regarding the patients examined. In many cases there were also the checklist for diseases whose compilation was scheduled for the most frequently encountered diseases (HF, COPD, stroke, pneumonia, gastrointestinal bleeding). The first observation that emerges from the analysis is that our population is considerably older than the populations considered in most works in the literature including the study TEMISTOCLE<sup>19</sup> with 89% of patients older than 70 years of (in TEMISTOCLE study the percentage of patients older than 70 years admitted to medical division for HF was 76.2%). Conversely, there was a distribution between gender which provides a slight predominance of the female sex. The highest prevalence of patients with preserved LVEF (61% in our study compared to 40.8% in the Medicine-subpopulation of TEMISTO-

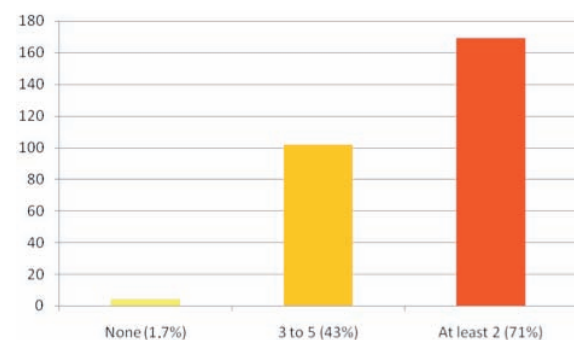
CLE study), of hypertensive heart disease (69% in our study compared to 45.5% in CONFINE study) and of hypertension (88% in our study compared to 62.8% in CONFINE study) appears to be justified only by the more advanced average age of our population and by the typical profile of HF with preserved systolic function. With regard to comorbidities, if we compare data obtained from our population with



**Figure 3. Comorbidity in the general population (absolute number and percentage). COPD, chronic obstructive pulmonary disease.**



**Figure 4. Distribution of the population according to the presence of pleural effusion (monolateral or bilateral).**



**Figure 5. Number of comorbidities (absolute number and percentage).**



those of other studies such as the study CONFINE,<sup>20</sup> we notice a lower percentage of patients without comorbidity (only 1.7% in our study compared to the 10% in the CONFINE study) and significantly higher percentage of patients with two or more comorbidities (43% in our study). The permanent atrial fibrillation in our population showed a prevalence comparable to that reported in the literature. One interesting observation that emerges from our study is the high prevalence (45%) of pleural effusion (68% bilateral pleural effusion). This finding may be useful in the differential diagnosis of HF also because of the ease of detection through the use of ultrasound. The pro-BNP was used primarily to exclude the diagnosis of HF although we detected average values of pro-BNP significantly higher in rehospitalized patients with reduced systolic function. Retrospective analysis did not provide significant data about the causes of destabilization but showed a high prevalence of indeterminate cause. By analyzing rehospitalized patients separately we noted a higher prevalence of comorbidities (89% of patients with at least two comorbidities) and average values of pro-BNP significantly higher than the rest of the population.

The collected data confirm the complexity of patients with HF, often due to advanced age and a high number of comorbidities. These findings are not very different from what has already been demonstrated in previous epidemiological studies on HF as those previously mentioned.<sup>19,20</sup> In order to compare the collected data with those of other multicenter studies it is right to point out some differences in the method of data collection. In our single-center study we were able to define the comorbidities with greater accuracy (*e.g.*, diagnosis of COPD made only with spirometric tests according to the criteria of the GOLD project, diagnosis of renal failure according to NKF/DOQI). The percentage of COPD, even excluding patients without a diagnosis made by spirometry, was anyway higher than that found in other studies (28% in our study compared to 26.7% in the CONFINE study). In our study, in addition to considering comorbidity taken by itself, we also evaluated the number of comorbidities present simultaneously in hospitalized patients with HF. This index allowed us to highlight more strongly the complexity of patients with HF. Separate analysis of rehospitalized patients (which noted a greater number of comorbidities simultaneously present) confirmed that the greater presence of a lot of comorbidities makes more complex the management of patients with HF. In this sense, it would be interesting to evaluate in patients with HF a *score of comorbidities* in order to select patients with higher risk as that require more complex management (*e.g.*, follow-up, more attention in the treatment of single comorbidity).

## Conclusions

Much progress has been made in recent years in the diagnosis and treatment of patient with HF and this is confirmed by literature data showing increased survival of patients with HF.<sup>21</sup> However, the comparison with the *real world* shows us a population of patients with different characteristics compared with those provided by the majority of epidemiological studies and clinical trials in which the advanced age and the presence of comorbidities represent criteria for exclusion from the study. The longer life-expectancy of all the major industrialized countries such as ours, as is clear from our study, results in an higher prevalence of a profile of HF patients who have an advanced average age and a higher number of comorbidities. We therefore confirm the usefulness of the systematic data collection on real populations and the creation of registries of pathology in order to have a more truthful picture of HF patients.<sup>22</sup> This mode has not only an epidemiological purpose but it is useful for both a correct diagnostic and prognostic classification as well as for management of therapies. In fact the presence of several comorbidities makes more difficult the management and the physician must carefully balance advantages and disadvantages of the different drugs within each comorbidity and the HF. If we just think of the implications of renal failure in the proper management of diuretic therapy and of the use of certain medications such as ACE-I and blockers of the RAAS.<sup>23</sup> Similarly the presence of anemia, often associated with chronic renal failure, represents a condition of refractoriness to treatment for HF.<sup>24</sup> COPD, which is also a very common comorbidity in our population (28% of total), may create difficulties in the diagnosis of HF and also in the management of therapies (*e.g.*,  $\beta$ -blockers and  $\beta$ -stimulants).<sup>25</sup> In the differential diagnosis of dyspnea we must consider that there is a high prevalence of COPD in patients with HF such as of HF in COPD patients.<sup>26</sup> For this reason it is important in all patients with dyspnea to have a comprehensive approach that includes, in addition to the examinations of the first level, echocardiogram and spirometry. Therefore it is necessary a comprehensive approach to the patients with HF to highlight and also treat the associated comorbidities, bearing in mind that often the management of various therapies can be complex. The increase in prevalence of subject with HF of older age and with a high number of comorbidities could justify the fact that the rate of rehospitalization of patients with HF does not appear to have significantly decreased in recent years despite the progress made in terms of diagnosis and treatment.<sup>27</sup> A greater understanding of the characteristics of real population of patients suffering from HF will therefore be useful for a better classification of the patient and to calibrate the therapy with the purpose to

optimize the treatment and reduce rehospitalization. Our study demonstrates how HF can be more and more a reason for hospitalization and consequently of health care. In a population of patients with an increasing average age the role of comorbidity is more important. All this requires us to provide a careful personalization of treatment and avoid a straightforward application of the guidelines.

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