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Prognostic impact of precipitated cardiac decompensation in symptomatic heart failure with reduced ejection fraction and severe secondary mitral regurgitation.

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Graphical Abstract

Graphical Abstract

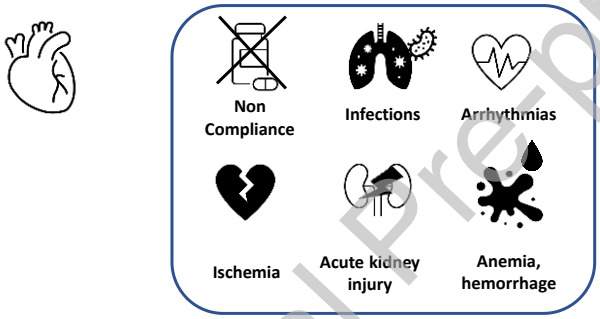
Acute Heart Failure Decompensations in the Mitra.Fr Study

Objective : what is the distribution & relationship with death of primary and secondary HF decompensations?

- 304 patients with symptomatic HFrEF, severe mitral regurgitation and GDMT
- 59 % patients had at least one HF decompensation within 24-months
- Total of 340 HF decompensations over 24-months

Primary HF Decompensations (PHF) without trigger (n=249)

Secondary HF Decompensations (SHF) related to a trigger (n=91)



Results

- PHF decompensaitons were 3-times more frequent than SHF decompensations
- No significant difference between PHF and SHF relationship to death (HR=1.82, 95%CI [0.93, 3.58]; p=0.082)
- Each HF decompensation recurrence was associated with a 25% increased risk of death (HR=1.27, 95%CI [1.08; 1.50]; p=0.005)

Abstract

BACKGROUND: Our aim was to assess the distribution of primary (with no trigger) and secondary (with a decompensation trigger) heart failure events in a severe heart failure population and their association with two-year all-cause mortality in the Mitra.Fr study.

METHODS: We included 304 patients with symptomatic heart failure, and severe mitral regurgitation and guideline directed medical therapy randomized to medical therapy alone or medical therapy with percutaneous mitral valve repair. According to the follow-up, we defined three categories of events: follow-up without any heart failure event, at least one decompensation starting with a primary heart failure decompensation or starting with a precipitated secondary heart failure event. The primary outcome was 2-years all-cause mortality.

RESULTS: 179 patients (59 %) had at least one heart failure decompensation within 24-months of follow-up. 129 heart failure decompensations (72%) were a first primary heart failure and 50 (28%) were a first secondary decompensation. Finally, 30 patients had both types of decompensations but these were not taken into account for the comparison of primary and secondary decompensations. Primary decompensations were 3-times more frequent than secondary decompensations, but the mean number of heart failure decompensations was similar in the “Primary heart failure group” compared to the “Secondary heart failure group”: (1.94±1.39 versus 1.80±1.07 respectively; p=0.480).

Compared to patients without heart failure decompensation, patients with “Only primary decompensation” or with “Only secondary decompensation” had a significantly increased risk of death (HR=4.87, 95%CI [2.86, 8.32] and 2.68 95%CI [1.64, 4.37] respectively). All-cause mortality, was not significantly different between these two type of decompensations (HR=1.82, 95%CI [0.93, 3.58]; p=0.082), but each additional heart failure recurrence was associated with a significant increase in mortality risk (HR=1.27, 95%CI [1.08; 1.50]; p=0.005).

CONCLUSIONS: In heart failure with reduced ejection fraction and severe secondary mitral regurgitation patients, primary heart failure decompensations were three-times more frequent compared to precipitated decompensations with a non-significant trend in increased risk of all-cause mortality. Our results fail to support the differentiation between primary and secondary decompensations as they seem to portend the same outcome impact.

Key Words: reduced ejection fraction heart failure; percutaneous mitral valve repair; heart failure decompensation; secondary mitral regurgitation; advanced heart failure; guideline directed medical therapy.

Introduction

Heart failure (HF) is a major cause of morbidity and mortality, and an increasing public health burden in industrialized countries[1,2]. It is the leading cause of hospitalization among adults older than 65 years. It is also associated with frequent hospital readmissions[3]. The clinical course of chronic congestive HF is characterized by frequent exacerbations requiring hospitalizations, increasing in frequency in the final stages and leading ultimately to death[4].

Recently, the Mitral Valve Academic Research Consortium (MVARC)[5] proposed a differentiation of acute heart failure (AHF) re-hospitalizations depending on their underlying cause. In their consensus, the definition for HF hospitalization requires: 1) a hospital stay for worsening heart failure for >24 h; and 2) administration of intravenous or mechanical HF therapies. An emergency room stay for >24 h would qualify as a HF hospitalization endpoint, even absent formal hospital admission, as such a prolonged stay represents a severe episode of heart failure. Patients hospitalized with HF are further subclassified as: IA. Primary (cardiac related) HF hospitalization and IB. Secondary (noncardiac related) HF hospitalization. Primary HF may be due to any cardiac cause, including primary LV dysfunction with or without medication or dietary noncompliance, acute myocardial infarction (MI), arrhythmias, and worsening valve dysfunction. Secondary HF is present when a noncardiac primary condition is present such as pneumonia, urinary tract infection, or renal failure, which results in fluid overload or myocardial failure.[5] To our knowledge, this differentiation and its significance has never been assessed in a clinical study.

Several precipitating factors leading to HF hospitalization have been identified in prior studies[6-10]. The most frequent precipitating factors include infections, arrhythmias, acute coronary syndromes, worsening renal function, uncontrolled hypertension and non-compliance with medications or diet[7,8]. Current recommendations for the management of HF, recommend identifying precipitants of AHF in order to treat the cause(s) of the acute episode[1,11].

There is heterogeneous data on the relationship between these precipitating factors and long-term morbidity and mortality, including recurrent hospitalizations[8,9,12,13]. Some reports suggested that acute coronary syndromes and infections induced HF decompensations were associated with higher mortality and readmission rates compared to other precipitating factors[7-9]. However, most of these studies reported data from registries where only up to 50% patients had an history of chronic HF. Therefore, it is not clear that primary HF (PHF) and precipitated or secondary HF (SHF) decompensations have a different predictive value on recurrent AHF decompensations and all-cause death in a reduced left ventricular ejection fraction (LVEF) chronic HF patient population.

Our main objective was to assess the distribution of PHF and SHF decompensations in the Mitra.fr study population and their association with clinical outcomes and with two-year all-cause mortality.

Methods

Study population

The study population was derived from a secondary analysis of the MITRA.fr study database. Mitra.fr was a multicenter, randomized, controlled, prospective, open-label phase III trial comparing percutaneous mitral valve repair (PMVR) with guideline directed medical treatment (GDMT) alone in chronic reduced LVEF patients with severe secondary mitral regurgitation. The study design, patient population characteristics and primary results have already been reported[14-16].

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

This study was funded by the French Ministry of Health and Research National Program 2012 grant number 12-027-0355 and additional funding by Abbott Vascular.

Written informed consent was obtained from all the patients before the initiation of trial procedures. The trial was approved by a central ethics committee and the French National Agency for Medicines and Health Products Safety and was conducted in accordance with the provisions of the Declaration of Helsinki.

Briefly, from December 2013 through March 2017, 304 patients were included from 37 trial centers in France. Eligible patients had a severe secondary mitral regurgitation, a left ventricular ejection fraction between 15% and 40% and chronic HF symptoms (assessed as New York Heart Association [NYHA] functional class II, III, or IV). All eligible patients received medical treatment for chronic HF with reduced left ventricular ejection fraction, according to the European guidelines that were current at the time of the trial[2]. For this study, both study groups were pooled together, as the effect of intervention on primary outcome was neutral[16].

In the Mitra.fr study, an independent centralized adjudication committee reviewed all HF decompensations. Each HF decompensation was reviewed by two independent experienced adjudicators and classified as HF, as well as underlying type of HF category depending on the presence of a predominant precipitating factor. In case of discrepancy between these two adjudicators, a third adjudicator was requested, and the event was classified according to the consensual agreement between 2 out of 3 adjudicators.

The following definition was used for HF hospitalization and have already been reported: an hospitalization for worsening heart failure for ≥24 h with worsening signs of congestion requiring mandatory administration of intravenous diuretics or mechanical heart failure therapies (including inotropic drugs)[15].

Time-dependent covariates were considered in this survival analysis, with multiple records for everyone. Each record corresponding to an interval of time (hospital stays) during which all covariates remain constant. Four type of hospital stays were defined throughout the follow-up, associated with the occurrence of primary HF (PHF) and secondary HF (SHF) decompensations.

The selected predominant precipitating factors for HF hospitalization were:

- Infection: in the presence of fever and/or other evidence of infection at presentation (leucocytosis, elevated inflammatory parameters, clinical or microbiological evidence of infection)
- Atrial arrhythmia: atrial fibrillation, atrial flutter, supraventricular tachycardia, new-onset or recurrent with ventricular response > 110/min
- Noncompliance with medications or diet (specific mention of noncompliance, missed medications, or salty foods by the admitting physicians)
- Severe anemia as defined according to the World Health Organization's definition by an hemoglobin level < 8 g/dL[17]
- Ventricular arrhythmia: wide complex (QRS duration greater than 120 milliseconds) tachyarrhythmia at a heart rate greater than 100/min
- Acute kidney injury[18]: acute or exacerbation of chronic kidney dysfunction as defined by the Class I and F of the RIFLE classification with an increase in the serum creatinine level ≥ 2.0-fold baseline

- Acute coronary syndrome: presence of ECG alterations and/or dynamic elevation of standard troponin levels, according to the criteria of the European Society of Cardiology (ESC)[19]

Primary Outcome

The primary outcome of the study was all-cause mortality. Patients were censored at 730 days of follow-up after the randomization date.

Data collection

The Clinical Investigation Center of Lyon, an academic research organization within Hospices Civils de Lyon (INSERM 1407), conducted, coordinated the trial, and collected the trial data. Standardized definitions were used to abstract clinic data. Demographic and clinical characteristics, medical history, previous treatments, and outcomes were among the variables collected. Reported data were double checked to ensure they were correct, and that completeness and accuracy of data quality were monitored. The data, methods and study materials are available upon reasonable request.

Statistical Analysis

Since the occurrence of HF is time dependent, multiple records for each individual patient were defined, with each record corresponding to an interval of time (hospital stays) during which all covariates remain constant. Four type of hospital stays were defined throughout the follow-up: no event since the hospitalization ("No previous event"); only primary HF decompensations ("Only PHF events"); only secondary HF decompensations where HF decompensation was related to a precipitating factor ("Only SHF events"); and both type of events since the beginning of hospitalization ("PHF & SHF events"). All patients started in the "No previous event" group and moved to the PHF (SHF) when the first primary (secondary) decompensation occurred. A patient who presented a primary decompensation then a secondary HF decompensation had three records and contributed sequentially to the three curves within the following periods: [0; Time of first PHF event], [Time of first PHF event; Time of first SHF event] and [Time of first SHF event; end of follow-up].

Cox regression modelling with time-dependent covariates, adjusted on the precipitating factors for HF hospitalization, was used to quantify the adjusted risk of each type of event (Table 3). Unadjusted survival was also calculated with Kaplan-Meier method (Figure 1).
In the survival analysis, only the first occurrence of each type of events was considered to define the type of hospital stay.

Adjusted hazard ratio with their 95% confidence interval were estimated without adjustment for multiple comparisons. All analyses were performed using R statistical software 3.5.0 or SAS 9.4 software.

The confounding variables included in the regression models were selected among baseline variables with significantly different distributions between the different HF decompensations subgroups and with known associations with 24-months mortality: age, NYHA status, estimated glomerular filtration rate (eGFR), mitral regurgitation grade >2 and the number of HF-event recurrence (Table 1).

In addition, for description purposes, patients were classified in three sub-groups depending on the first occurrence and type of HF decompensation during the 24-months follow-up. These groups only serve to describe the characteristics of the study population (Table 1): the “Reference group” of no HF decompensation; the “Patients with a first primary decompensation”, with the first decompensation being a primary HF event, the “Patients with a first secondary decompensation ”, with the first decompensation being a secondary HF event. Patient with both type of events were not included in this descriptive analysis. Quantitative variables were expressed as mean (SD) or median (interquartile range, IQR) as appropriate and qualitative variables were expressed as number (percentage).

Results

Heart Failure Event Distribution and Recurrence

Overall, patient population was 70.5±10.2 years, with 75.1% males, with a 33±6% mean left ventricular ejection fraction. Mean glomerular filtration rate was 49±19 ml/min/m2; 72.3% had a NYHA ≥ 3 and median NTproBNP level was 3324 [1934; 6387] ng/L (Table 1).

Among the 304 patients included in our study, 179 patients (59%) had at least one HF decompensation within two years of follow-up. In 129 patients (72%) the first event was a PHF decompensation, and in 50 patients (28%) the first event was a SHF decompensation (Table 2). The distribution of precipitant factors in SHF decompensations is reported in Table 2. The two principal precipitating factors in this patient sub-group were infections and supraventricular arrhythmias (mainly atrial fibrillation).

Overall, over a two-year period, 125 (41%) patients had no HF decompensation, 90 (30%) patients had only one HF event, and 89 (29%) patients had two or more HF decompensations. Finally, 30 (17%) patients presented both types of HF decompensations.

We identified a total of 340 HF decompensations over two years. PHF decompensations (n=249) were 3-times more frequent than SHF decompensations (n=91). The mean number of HF decompensations was similar in the “Primary HF group” compared to the “Secondary HF group”: (1.94±1.39 versus 1.80±1.07 respectively; p=0.480).

Heart Failure decompensation categories and outcomes at two-years

At two-years, there were 105 (34.5%) death events in the whole study population. Figure 1 shows the Kaplan Meier survival curves for all-cause death for each situation. All patients begin without decompensation, and along time patients experiencing a first PHF or SHF join the respective curve.

The survival without HF decompensation events was associated with a low 6.1% rate of death at 2 years. In comparison, the survival with only primary decompensations was associated with a significant increased rate of death at 2 years of 60.4% compared to survival without heart failure (p<0.001). The survival with only secondary decompensations was like that of only primary decompensations with a 2-year death rate of 58.7%. This death rate was also significantly worse than the survival without HF decompensation (p<0.001). Finally,

survival combining primary and secondary HF decompensations was associated with the worst 2-year death rate of 84.3%.

Univariate and multivariate analyses for confounding variables

All univariate and multivariate analysis results are presented in Table 3. In the univariate Cox analysis accounting for HF types, the clinical variables that were significantly associated with increased mortality were age, NYHA >2 and GFR.

There was no significant difference in survival of patients associated with the PMVR intervention: HR=0.95; 95%CI [0.65; 1.40]; p=0.800. This factor was included in the multivariate analysis, but the effect of the PMVR intervention remained non-significant (data not shown).

Compared to patients with no previous event since the hospitalization “No previous event”, patients with a history of event, whatever the category “Only PHF events” or “Only SHF events”, had a significantly increased risk of death over the follow-up: adjusted HR were (HR=4.87, 95%CI [2.86, 8.32]) and (HR=2.68, 95%CI [1.64, 4.37]). All-cause mortality, was not significantly increased in the “Only PHF events” compared to “Only SHF events” (HR=1.82, 95%CI [0.93; 3.58]; p=0.082). Each additional HF recurrence was associated with a significant increase in mortality risk (HR=1.27, 95%CI [1.08; 1.50]; p=0.005).

Discussion

In an advanced chronic HF patient population with significant secondary mitral valve regurgitation and guideline directed medical therapy, our study shows that HF decompensations are a major predictor of all-cause death at two years, whatever their background setting. Primary HF decompensations were significantly more frequent than secondary HF decompensations but were not associated with a higher risk in all-cause mortality after adjustment on main confounding variables. Recurrence rates were similar between primary and secondary HF events and each recurrence was associated with a consistent 25% relative risk increase in all-cause mortality. Finally, the absence of difference in SHF compared to PHF events in terms of mortality do not support the differentiation between PHF and SHF as they seem to portend the same outcome impact.

In a homogeneous selected population of severe HF patients with reduced ejection fraction, with close prospective follow-up, our study demonstrates once again that HF decompensations are a major predictor of all-cause death at two-years. This is consistent with previous studies by Rudiger et al. (HR 2.6 95% CI [1.5-4.8])[20] and Nunez et al.[21]. This remains true despite the severity of our patient population with a two-year mortality rate of one third and an optimal GDMT. In addition, our results show that each individual HF decompensation is associated with a 25% increase in relative risk of death at 2 years. These results are at odds with the hypothesis that HF decompensations in severe HF patient populations are independent of death events, as this was suggested in recent reports[22].

The second finding of our study concerns the differences between HF events related to precipitating factors and HF events related to primary LV pump failure in a patient population with severely reduced ejection fraction HF. Current recommendations for the management of acute HF (AHF) advise identification of precipitants of HF to treat specifically the cause(s) of the acute episode[11]. We identified seven precipitating factors in accordance with the literature. Infections and supra-ventricular arrhythmias were shown to be the most common with more than half of cases. This is in accordance with previous reports in acute HF patient populations. In this patient population primary HF events related to LV

dysfunction and the severity of the underlying heart disease were the main cause of all HF events, with 78% of all HF events. This is different from AHF registries in the emergency departments, where up to 61% of HF events were related to at least one precipitating factor[9]. This difference is likely related to differences in study populations, since less than 50% of patients included in these registries had a previous history of chronic HF. These registries also included high proportions of HF with preserved ejection fraction patients.

Several reports in AHF populations suggested different mortality outcomes depending on the presence as well as the type of precipitating factor[7]. In our homogeneous study population with severe reduced EF chronic HF with secondary mitral regurgitation, our results show that there is similarly increased risk of death in PHF events compared to SHF events. Because of the limited number of SHF events, we did not have sufficient statistical power to assess the possible differences in outcomes according to the underlying precipitating factors. Other studies have reported poorer outcomes with HF events related to ischemic events and pulmonary infections[8,9,12] and better outcomes for atrial fibrillation triggered events[12]. This data is heterogenous, since reports have also shown the absence of influence of any precipitating factor on subsequent mortality[13,23]. To standardize endpoints for clinical trials with PMVR devices, the MVARC proposed a differentiation of AHF decompensations depending on their underlying cause[5]. Type A HF re-hospitalization corresponds to HF with a primitive cardiac cause. Type B corresponds to an episode caused by an extra-cardiac precipitating factor that can be clearly identified[5]. This MVARC proposed not to include type B events in the primary endpoint definition of HF events. Our data challenges this assertion, showing that primary HF events are the main cause for decompensations, and that both types of events have a similar prognostic impact on all-cause mortality. Therefore, there does not appear to be a strong rationale to separate both type of events. However, we must acknowledge that our analysis showing that PHF and SHF decompensations confer similar prognoses is not warranted given a probable lack of statistical power for this specific comparison. There was a trend towards a two-time increased risk of death when comparing PHF and SHF that did not reach statistical significance. Also, as recommended in the recent ESC guidelines[1] and consensus papers on the management of acute HF[11], therapeutic management of patients with HF decompensation should always investigate and control or correct the underlying triggers.

Finally, this study raises the hypothesis that primary HF decompensations are more frequent towards the end stages of disease as opposed to HF related to precipitating factors at the beginning in the evolution of HF with reduced ejection fraction. The evolution in time of HF is known to present an increased frequency in HF events, but to our knowledge there is very little data on the nature of these events[24]. Previous reports in all-comer AHF patients showed that two thirds of HF events were related to at least one precipitating factor[9]. In our patient population with advanced chronic HF, 78% of events were not related to a precipitating factor. Moreover, a major and independent factor of mortality was HF recurrence. In our patient population, the average recurrence was of 1 HF event per year in each one of the two thirds of patients presenting with a HF decompensation. Each HF decompensation was associated with a relative increase in 25% of mortality. This is consistent with similar increase in mortality in an observational study report by Setoguchi et al[25]. Then someone will say what is lost can never be saved; but on the contrary, for us, this is a reminder that in patients with symptomatic advanced HF features, the therapeutic management should be re-assessed carefully following recent therapeutic guidelines[1] whether there is a precipitating factor or not.

Limitations

Our study has limitations:

First, this was a secondary, post hoc, analysis, therefore our results are by nature hypotheses generating, could be influenced by confounders and need further confirmation in larger groups of patients.

Second, we had a limited sample size which increases the risk of chance findings and limits the statistical power to assess individual precipitating factors. However, the homogeneous patient population, the two-year follow-up period and the high rate of HF and death events with prospective data and event adjudication committee are characteristics to strengthen our findings. Also, we arbitrarily decided to limit the explanatory variables included in our analysis to limit the risk alpha inflation. Because of this, well-established prognosticators in the general HF population such as sex, prior admission for acute HF or systolic blood

pressure at admission were not included. Furthermore, there are inherent limitations related to the simplistic single-factor analysis. Each secondary HF decompensation could be related not only to one precipitating factor but several. This induces a limitation in our analysis of the data.

Third, our patient population was a highly selected and advanced HF population with severe secondary mitral valve regurgitation, therefore the findings in this population might not be generalizable to the larger group of reduced ejection fraction HF population. The selected nature of our HF population might limit the external validity of our study results.

Fourth, the distinction between PHF and SHF decompensations and defining underlying triggers of HF decompensation is arbitrary. One will argue that arrythmias have of cardiac origin and could be a symptom of a PHF. We a priori and specifically decided to count them as secondary, because other published reports have, and because arrythmias have specific treatments that are independent of HF drugs. In addition, all HF decompensation cases were carefully adjudicated by two or three expert cardiologists, blinded to the other's assessment. To retain the presence of a trigger and retain the SHF adjudication. For all SHF decompensations, two independent adjudicators had to agree.

Finally, as in any observational study, unrecorded precipitating factors may have confounded the results. However, we had a precise list of precipitating factors to look for, and it was double checked by an expert adjudication committee, to avoid unobserved variables and improve precipitating factor standardization.

Conclusion

In an advanced chronic heart failure patient population, primary HF decompensations and HF decompensations related to a precipitating factor (secondary HF) were significantly associated with an increased 2-year mortality. There were no significant death rate differences between both types of events and their rates of recurrence were similar. Therefore, out data do not support the rationale for separating SHF from PHF decompensations in the classification of HF hospitalization events in patients with severe symptomatic HF and secondary mitral regurgitation. HF decompensations are a major independent predictor of death in this population even after adjustment on HF recurrence

and other clinical predictors. Further studies are needed to confirm these results and assess the individual impact of precise cardiac or extra-cardiac precipitating factors.

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Conflicts of Interest

None related to the subject of the manuscript.

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Figure Legends

Figure 1. Kaplan Meier survival curves for all-cause death events at two years depending on the history of HF events

Time-dependent covariates were considered in this survival analysis. Multiple records for each individual, with each record corresponding to an interval of time (hospital stays) during which all covariates remain constant. Four type of hospital stays were defined throughout the follow-up: no previous event since the hospitalization “No previous event” (red curve); only primary heart failure decompensations “Only PHF events” (green curve); only secondary HF decompensations “Only SHF events” (blue curve); and both type of decompensations since the beginning of hospitalization “PHF & SHF events” (brown curve). All patients started in the “No previous event” group and moved to the PHF (SHF) when the first primary (secondary) event occurred. A patient who presented a primary event then a secondary HF event had three records and contributed sequentially to the three curves within the following periods: [0; Time of first PHF event], [Time of first PHF event; Time of first SHF event] and [Time of first SHF event; end of follow-up].

Figure 2. Survival curves for all-cause death events at two years depending on the number of HF decompensations

Time-dependent covariates were considered in this survival analysis. Multiple records for each individual, with each record corresponding to an interval of time (hospital stays) during which all covariates remain constant. Each heart failure decompensation whatever the type counted as one heart failure event. All patients started in the “No previous event” group and moved to the first HF event when a heart failure decompensation occurred (“One Previous Event”). If another or more events occurred, the patient moved to the multiple HF event group (“Two + HF event”).

FIGURE 1

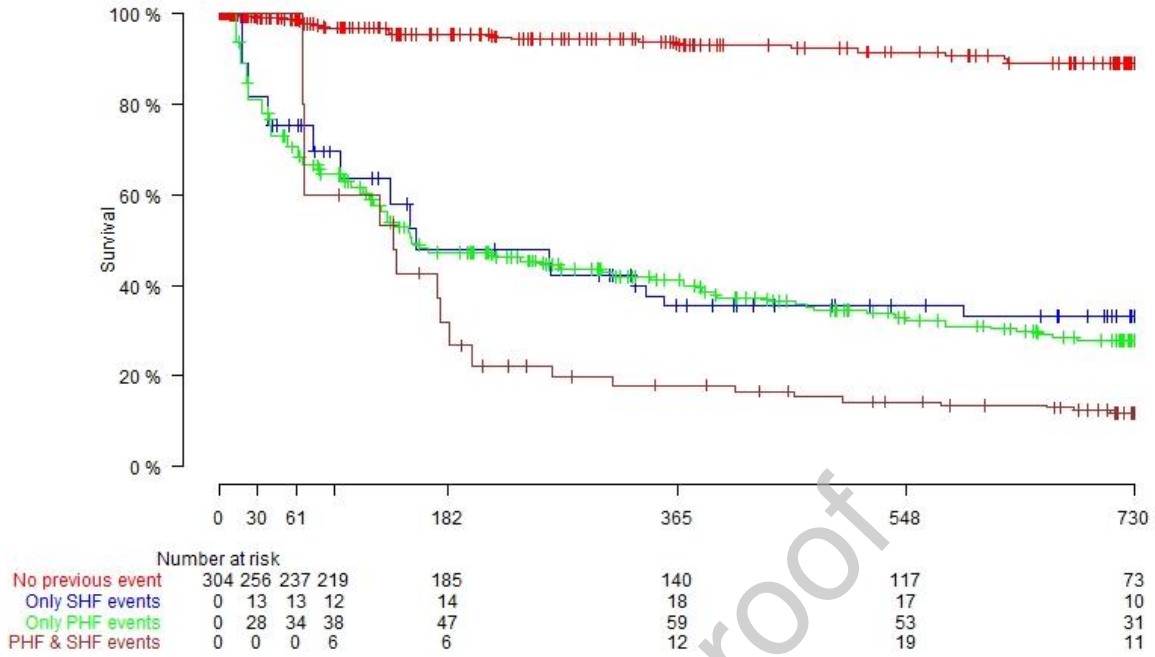

FIGURE 2

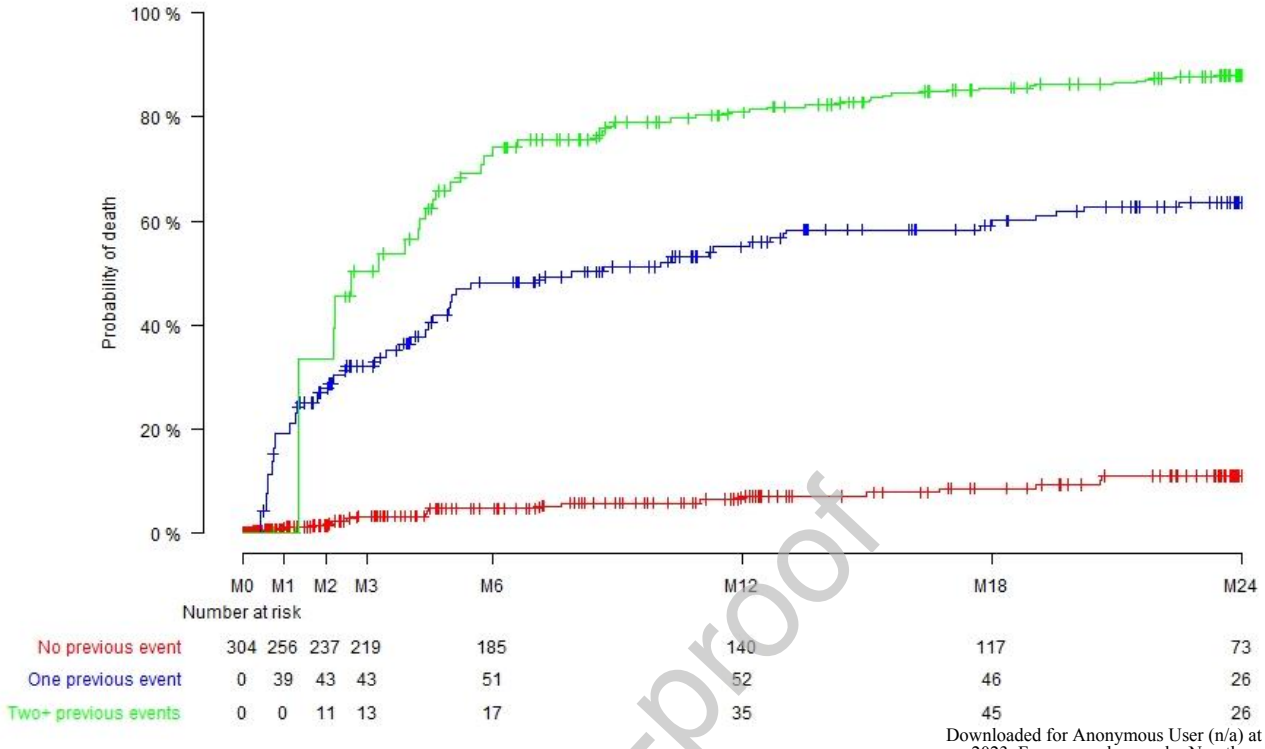

***Table 1*. Baseline characteristics of the study population according to the type of first HF event, whenever it occurred during the 2-year follow-up.**

	Patients with no decompensation	Patients with a first primary decompensation	Patients with a first secondary decompensation
	n=125	**n=129**	**n=50**
Age - years	70.2 (10.0)	70.2 (10.4)	71.1 (8.9)
Age ≤ 75 years	79 (62.7)	84 (65.6)	31 (62.0)
Male sex - no. (%)	93 (73.8)	98 (76.6)	36 (72.0)
Medical history - no. (%)			
Ischemic cardiomyopathy	82 (65.1)	72 (56.3)	26 (52.0)
Atrial fibrillation	40 (33.1)	39 (32.5)	18 (37.5)
Diabetes	37 (29.4)	38 (29.7)	14 (28.0)
Number of HF hospitalization within 1 year ≥2	40 (31.7)	59 (46.1)	19 (38.0)
NYHA class - no. (%)			
II	48 (38.1)	36 (28.1)	16 (32.0)
III or IV	78 (61.9)	92 (71.9)	33 (68.0)
Systolic Blood Pressure - mmHg	109.5 (18.8)	106.8 (15.7)	110.6 (15.3)
Heart Rate - beats/min	71.6 (11.6)	73.7 (13.6)	71.9 (12.2)
Median EUROSCORE II (IQR)	5.4 [3.3, 10.4]	6.6 [3.9, 11]	6.3 [3.4 ; 12.0]
HF MAGGIC Score	25.2 (5.8)	27.1 (5.7)	27.1 (5.8)
LVEF - %	33.8 (6.1)	32.8 (7.0)	32.0 (6.7)
LVEDD - mm	68.5 (7.8)	68.4 (7.5)	70.2 (8.7)
Median BNP (IQR)	524 [309, 1009]	881 [501, 1275]	800 [632, 1017]
Median NT-proBNP (IQR)	2251 [1443, 3543]	5118 [3002, 8397]	3815 [2564, 7334]
GFR - ml/min	51.5 (19.3)	49.6 (21.5)	44.3 (16.0)
Heart Failure Medical Treatment no. (%)			
RAS-inhibitor	105 (83.3)	106 (82.8)	38 (76.0)
Beta-blocker	113 (89.7)	112 (87.5)	47 (94.0)
MRAs	74 (59.2)	68 (53.1)	24 (48.0)
Diuretics	124 (98.4)	126 (98.4)	49 (100.0)
Antiplatelet Therapy	72 (57.6)	60 (46.9)	22 (44.0)
Anticoagulant Therapy	71 (56.3)	78 (60.9)	37 (74.0)
CRT and/or ICD	72 (57.1)	82 (64.1)	32 (64.0)
PMVR procedure	68 (54.0)	56 (43.8)	28 (56.0)

Results are mean (standard deviation) or median and interquatile range (IQR).

Primary HF: primary acute HF decompensation without any precipitating factor; secondary HF : AHF decompensation related to at least one precipitating factor. HF: heart failure, LVEF: left ventricular ejection fraction, LVEDV: left ventricle end diastolic volume, BNP: brain natriuretic peptid, NT pro BNP: N terminal pro brain natriuretic peptid, NYHA: New York heart association, GFR: glomerular filtration rate, LVEDD: left ventricular end-diastolic diameter, RAS-inhibitor: renin angiotensin system inhibitor, MRA: mineralo-corticoid receptor antagonist, CRT: cardiac resynchronization therapy, ICD: intra cardiac defibrillator, PMVR: percutaneous mitral valve repair, MAGGIC risk score: Meta-Analysis Global Group in Chronic Heart Failure Risk score.

***Table 2*. Principal precipitating factors for heart failure decompensations (cause of secondary HF decompensation)**

Precipitating Factor	n=156 (%)
Infection*	52 (33)
Atrial arrhythmia	37 (24)
Acute coronary syndrome	16 (10)
Non-compliance with medications or diet	16 (10)
Anemia	11 (7)
Ventricular arrhythmia	9 (6)
Worsening renal function	8 (5)
Other	6 (4)

*Data are presented as n and (%). *The most frequent infections were pneumonia, followed by urinary tract infections and then miscellaneous sites (skin, digestive sepsis…). Repeated SHF events are included in this table.*

***Table 3.* Univariate and multivariate Cox models for all-cause death analyses.**

	Univariate HR (95% CI)	*P* value	Multivariate HR (95% CI)	*P* value
PHF event	7.25 (4.69 ; 11.20)	<0.001	4.87 (2.86 ; 8.32)	<0.001
SHF event	3.05 (1.97 ; 4.71)	<0.001	2.68 (1.64 ; 4.37)	<0.001
HF recurrence	1.25 (1.05 ; 1.48)	0.010	1.27 (1.08 ; 1.50)	0.005
Age (for 10 years)	1.65 (1.30 ; 2.08)	<0.001	1.64 (1.26 ; 2.13)	<0.001
NYHA class > 2	1.57 (0.99 ; 2.48)	0.054	1.12 (0.69 ;1.81)	0.640
GFR (for 15 ml/min)	0.87 (0.74 ; 1.04)	0.124	1.00 (0.83 ;1.22)	0.970
LVEF (for 10%)	0.90 (0.67 ; 1.21)	0.487	--	--
MR Grade ≥4	1.26 (0.79 ; 1.98)	0.330	--	--
LVEDD (for 10 mm)	1.09 (0.86 ; 1.39)	0.478	--	--
SPAP (for 10 mmHg)	0.92 (0.78 ; 1.08)	0.290	--	--
PMVR intervention	0.95 (0.65 ; 1.40)	0.800	--	--

PHF: primary AHF events without any precipitating factor; SHF: AHF events related to at least one precipitating factor.
HF: heart failure, MR: mitral regurgitation grade, LVEF: left ventricular ejection fraction, SPAP: systolic pulmonary artery pressure, LVEDD: left ventricular end diastolic diameter, GFR: glomerular filtration rate, NYHA: New York Heart Association.

PHF: primary AHF events without any precipitating factor; SHF: AHF events related to at least one precipitating factor.
HF: heart failure, MR: mitral regurgitation grade, LVEF: left ventricular ejection fraction, SPAP: systolic pulmonary artery pressure, LVEDD: left ventricular end diastolic diameter, GFR: glomerular filtration rate, NYHA: New York Heart Association.