Heart Failure Etiologies and Clinical Factors precipitating for Worsening Heart Failure: findings from BIOSTAT-CHF

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Running title: Etiologies and precipitants in patients with symptomatic heart failure

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Highlights

- Patients with HF of an ischemic etiology had the highest rate of death and/or HF hospitalization.
- Patients with worsening HF precipitated by renal failure were associated with highest risk of death and/or HF hospitalization.
- There was no interaction between HF etiologies and precipitating factors for worsening HF with regards to the study outcomes.
- Treatment up-titration likely benefits patients irrespective of their etiology and/or precipitant factor.

Abstract

Background

Knowledge on the association between heart failure (HF) etiologies, precipitant causes and clinical outcomes may help in ascertaining patient's risk and in selecting tailored therapeutic strategies.

Methods

The prognostic value of both HF etiologies and precipitants for worsening HF were analyzed using the index cohort of BIOSTAT-CHF. The studied HF etiologies were: a) ischemic HF; b) dilated cardiomyopathy; c) hypertensive HF; d) valvular HF; and e) other/unknown. The precipitating factors for worsening HF were: a) atrial fibrillation; b) non-adherence; c) renal failure; d) acute coronary syndrome; e) hypertension; and f) Infection. The primary outcome was the composite of all-cause death or HF hospitalization.

Results

Among 2,465 patients included in the study, 45% (N=1102) had ischemic HF, 23% (N=563) dilated cardiomyopathy, 15% (N=379) other/unknown, 10% (N=237) hypertensive and 7% (N=184) valvular HF. Patients with ischemic HF had the worst prognosis, whereas patients with dilated cardiomyopathy had the best prognosis. From the precipitating factors for worsening HF, renal failure was the one independently associated with worse prognosis (adjusted HR (95%CI)=1.48 (1.04-2.09), p<0.001). We found no interaction between HF etiologies and precipitating factors for worsening HF with regard to the study outcomes (p interaction>0.10 for all). Treatment up-titration benefited patients regardless of their underlying etiology or precipitating cause (p interaction>0.10 for all).

Conclusions

In BIOSTAT-CHF, patients with HF of an ischemic etiology, and those with worsening HF precipitated by renal failure (irrespective of the underlying HF etiology), had the highest rates of death and HF hospitalization, but still benefited equally from treatment up-titration.

Keywords: Heart failure; etiology; precipitating factor; prognosis

Introduction

Heart failure (HF) therapies have improved patient outcome over the last decades, however those with worsening symptoms and/or signs of HF still have a poor prognosis [1, 2]. Both the etiology of HF and the factors leading to its decompensation may influence outcomes and drug response [3-7]. Previous studies have shown that patients with HF of an ischemic etiology have worse prognosis than those with non-ischemic etiology [8, 9], and patients with worsening HF precipitated by infection or worsening renal function had worse prognosis than those with worsening HF precipitated by hypertension or noncompliance [7, 10, 11]. Nonetheless, the prognostic assessment of the HF etiologies and the worsening HF precipitating factors as well as their interaction and response to treatment, is yet to be determined. The systems BIOlogy study to Tailored Treatment in Chronic Heart Failure (BIOSTAT-CHF) allows the study of the associations between the HF etiologies, precipitants for worsening HF, treatment up-titration and clinical outcomes.

The main aims of the present study were; 1) to describe the clinical characteristics of the patients with regard to their HF etiologies and worsening HF precipitants; 2) to study the association between HF etiologies and worsening HF precipitants with outcomes; 3) to assess whether the prognostic implications of the precipitating factors may be modified by the HF etiologies (and vice-versa); 4) to assess whether the potential benefits of treatment up-titration are influenced by the HF etiology and/or precipitant.

Methods

Patient Population

The BIOSTAT-CHF was an international study and its main features have been previously described [12, 13]. Included patients were ≥18 years of age with symptoms of new onset or worsening HF, confirmed either by a left ventricular ejection fraction (LVEF) of ≤40% or a B-type natriuretic peptide or N-terminal pro–B-type natriuretic peptide (NT-proBNP) plasma levels>400pg/ml or>2,000 pg/ml, respectively. Patients needed to be treated with either oral or intravenous furosemide ≥40 mg/day or equivalent at the time of inclusion. From the 2,516 patients, we selected the 2,465 patients who had

specific information on the HF etiologies (**Figure 1**). Patients were receiving <50% of the target doses of at least one of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEi/ARBs) and beta-blockers at the time of inclusion. The first 3 months of treatment were considered to be a treatment optimization phase. During the optimization phase, initiation or up-titration of ACEi/ARB and/or beta-blocker was done according to the routine clinical practice of the treating physicians, who were encouraged to follow the European Society of Cardiology guideline [14]. Patients reaching at least 50% of the recommended dose of ACEi/ARB and/or beta-blocker at the 3-month visit were considered successfully up-titrated.

BIOSTAT-CHF was conducted in concordance with the declaration of Helsinki, national ethics and legal requirements, as well as relevant EU legislation. The study was approved by national and local ethics committees and all patients recruited in BIOSTAT-CHF were given written informed consent to participate in the study.

Precipitating Factors and Heart Failure Etiology

HF etiology was characterized according to the specified cases in the case report form (CRF) in categories of ischemic etiology, dilated cardiomyopathy, hypertensive, valvular etiology, and other/unknown according to the treating clinical physicians (**Supplementary table 1**).

In the BIOSTAT-CHF protocol/CRF, there were six different classifications of worsening HF precipitating factors from which clinicians could choose ("tick box"): acute coronary syndrome (ACS), atrial fibrillation (AF), hypertension, renal failure, infection and non-adherence (diet, medications or iatrogenic). These factors were collected in the CRF, as per investigator clinical judgement according to the ESC guidelines [14] (**Supplementary table 1**). More than 1 factor could be selected (whenever applicable). These factors were identified by the local investigators for each patient. The definitions provided by the above referenced guidelines were encouraged, where: ACS, would require elevation of troponin I above the 95th percentile and dynamic electrocardiographic alterations suggestive of acute myocardial ischemia [15]; AF, presence of AF on the electrocardiogram; hypertension, office systolic blood pressure (SBP)>140 mmHg; renal failure, creatinine >1.5 mg/dl and or deterioration (>20% eGFR drop)of renal function compared with the last available

measurement; and infection, with elevated inflammatory parameters, *e.g.*, leucocyte, c-reactive peptide or procalcitonin.

Statistical Analysis

Categorical variables are described as frequencies (percentages) and continuous variables are described as means ± standard deviation or median [25th and 75th percentiles] depending on their distribution. Comparisons of demographic, clinical and biological parameters among HF etiologies were conducted using χ^2 tests for categorical variables and Kruskal-Wallis test or Mann-Whitney test for continuous variables.

The primary outcome was the composite of all-cause mortality or HF hospitalization. Time-to-event comparisons were analyzed using log rank test and Cox proportional hazards models. Survival probabilities were estimated using the Kaplan-Meier method and plotted as survival curves with HF etiologies and worsening HF precipitants at 400 and 60 days, respectively, due to violation of proportional hazards after these time-points (the Kaplan-Meier curves during overall term follow-up are shown in the **Supplementary figure 1**).

Cox proportional-hazards models for HF etiologies and worsening HF precipitating factors were then used to obtain unadjusted and covariate adjusted hazard ratios (HRs) (with dilated cardiomyopathy and non-adherence as the reference groups, respectively). Multivariable models were adjusted for BIOSTAT-CHF risk model [16]. The risk model for the composite outcome included age, HF hospitalization in the year before inclusion, presence of edema, NT-proBNP, SBP, hemoglobin, high-density lipoprotein levels, serum sodium concentration, and absence of beta-blocker. The risk model for all-cause mortality or cardiovascular mortality included age, higher blood urea nitrogen and NT-proBNP, lower hemoglobin and failure to prescribe a beta-blocker [16]. Furthermore, we performed multivariable analyses after adjusting for ischemic etiology/renal failure in addition to aforementioned covariates. An interaction test was performed to determine whether the effect of respective precipitants would be influenced by the HF etiology, and whether the response to treatment could be influenced by either HF etiology or precipitant.

All analyzes were performed using R version 3.4.0. (R Development Core Team, Vienna, Austria). P-value<0.05 was considered statistically significant.

Results

Patient Characteristics by Heart Failure Etiology

Of the 2,465 patients included in this study, the mean age was 68.4±12.0 years old, 73.2% was male, the mean LVEF was 31.0±10.5%, and 67.1% of patients were hospitalized. With regard to the HF etiology, 45% (N=1102) had ischemic HF, 23% (N=563) dilated cardiomyopathy, 15% (N=379) other/unknown, 10% (N=237) hypertensive and 7% (N=184) valvular HF (**Table 1**). Compared to patients with non-ischemic HF, patients with ischemic HF were older (mean age 70 vs 67 years), more often male (80 vs 68%) and had more cardiovascular comorbidities and poorer renal function (all P<0.001). Amongst all etiologies, patients with dilated cardiomyopathy were the youngest, had fewest comorbidities, best renal function and highest prescription rates of ACEi/ARB and mineralocorticoid receptor antagonist (MRA) prescriptions.

Distribution of Precipitating Factors According to Heart Failure Etiology

Patients with ischemic HF were more often precipitated by ACS (**Table 2**). Patients with hypertensive HF were mainly precipitated by both hypertensive crisis and AF, and the latter was also a major precipitant in patients with valvular HF and dilated cardiomyopathy. The patient characteristics according to the respective precipitating factors are depicted in the **Supplementary table 2**.

Association of Heart Failure Etiologies with Outcomes

The primary outcome occurred in 46.7%, 45.6%, 42.2%, 35.9% and 29.3% of patients with valvular, ischemic, hypertensive HF, other/unknown etiology and dilated cardiomyopathy, respectively. Kaplan-Meier curves showed worse prognoses for valvular and ischemic HF (**Supplementary figure 2**). Ischemic HF remained the worst prognosis in the survival analyses adjusted for BIOSTAT-CHF risk model (**Figure 2**); with a corresponding adjusted HR (95%CI) =1.34 (1.12-1.60), p<0.001 (**Table 3**). Patients with ischemic HF retained the worst prognosis after adjusting for aforementioned risk

model plus renal function; adjusted HR (95%CI)=1.34 (1.12–1.60), p=0.001, and there was no interaction between ischemic HF and renal failure as a precipitant (p=0.30). Similar association between HF etiologies and primary outcome was observed in patients with a LVEF of ≤40% (**Supplementary table 4**). Furthermore, patients with ischemic HF tended to be associated with higher incidence of cardiovascular mortality (p=0.08), but no specific HF etiology was associated with all-cause mortality (all P-value>0.1). As a sensitivity analysis, the associations of HF etiologies with the primary outcome in ambulatory and hospitalized patients are shown in the **Supplementary table 3**.

Association of Worsening HF Precipitating Factors with Outcomes

The primary outcome occurred in 68.0%, 45.3%, 40.3%, 39.1%, 36.8% and 36.3% of the patients precipitated by renal failure, infection, hypertension, AF, ACS and non-adherence, respectively. After adjusting for BIOSTAT-CHF risk model and ischemic etiology, renal failure was associated with higher incidence of the primary outcome; adjusted HR (95%CI)=1.49 (1.05-2.10), p=0.003 (**Table 4**). Renal failure also tended to be associated with higher risk of all-cause mortality; adjusted HR (95%CI)=1.44 (0.96-2.15), p=0.08. With regard to the primary outcome, there was no significant interaction between HF etiology and the worsening HF precipitants (p=0.95).

Association and Interaction with Treatment Up-Titration

Patients with HF of hypertensive etiology had more often successful treatment up-titration, whereas patients with valvular HF were less often up-titrated (**Table 1**).

Interaction tests for the primary outcome did not show treatment up-titration heterogeneity with regard to HF etiologies and/or precipitant factors (all P-value>0.10) (**Table 5**).

Discussion

In ambulant and hospitalized patients with worsening HF, we assessed the clinical characteristics and outcome of different etiologies and precipitating factors. We found that patients with ischemic HF and worsening HF precipitated by renal failure had the worst prognosis. These findings suggest that both

the HF etiology and the precipitating factors provide relevant and independent prognostic information, and that treatment up-titration was not influenced by HF etiologies and precipitating factors.

Heart Failure Etiologies

Our results align with previous reports suggesting that the most common HF etiology was ischemia [6, 17]. Patients with ischemic HF were older, had more cardiovascular risk factors, comorbidities and were associated with higher risk at cardiovascular mortality and morbidity [8, 9, 18, 19]. In particular, patients with a LVEF ≤40% of an ischemic etiology had worse prognosis, which is consistent with previous studies [4, 18].

Among patients with non-ischemic HF, valvular HF has also been associated with worse prognosis [4], as also confirmed in the present study. Progressive valvular degeneration may increase the volume and/or pressure overload associated with an increased rate of HF hospitalization and death [20, 21]. Indeed, in our study, patients with a valvular HF had worse clinical status, illustrated by high proportion of anemia and impaired renal function, which may contribute to worse outcomes. In contrast, dilated cardiomyopathy was associated with better outcomes. Favorable trends in optimal treatments and low prevalence of comorbidities have been recently documented, potentially leading to lower rates of adverse outcomes [22, 23]. In the present analysis, patients with a dilated cardiomyopathy were the youngest, had good renal function, and higher baseline MRA prescriptions, which may be associated with their improved prognosis among HF etiologies [24-26].

Patients with HF of a hypertensive etiology might have been more often successfully up-titrated, while those with HF of a valvular etiology were less likely to be up-titrated. However, treatment up-titration, when it occurred, likely benefited patients irrespective of their HF etiology [27].

Precipitating Factors

With regard to the worsening HF precipitating factors, our results were also consistent with the previously published studies. Patients with HF precipitated by renal failure were elderly, had more frequent prior HF admission, more comorbidities, more severe congestion and worse prognosis [10, 28-31]. Renal failure as a precipitant may be determined by clinical deterioration and by therapeutic approach such as diuresis and renin angiotensin aldosterone system inhibitors [3]. In the present analysis, patients with renal failure were not likely to receive ACEi/ARB, MRA and diuretics, suggesting that renal

failure in this setting may not be considered to be a subsequent deterioration. Moreover, our results show that the occurrence of renal failure may discourage physicians from up-titrating ACEi/ARB and be associated with worse prognosis irrespective of treatment up-titration. Therefore, our observations may further increase the clinician's awareness for patients with worsening HF precipitated by renal failure, who might need closer surveillance.

Patients with HF precipitated by non-adherence were younger, had lower LVEF and more frequent prior HF admissions [5, 11], whereas patients with hypertension had less comorbidities and less severe congestion [5, 32]. Both of the precipitants, non-adherence (used as referent variable in our analyses) and hypertension, have been associated with more favorable outcomes [5]. Conversely, our results did not show worse prognosis of either ACS or infection as a precipitant. ACS and infection have been reported to be associated with worse short-term outcomes [5], prognostic implication of these precipitants may vary thus with term follow-up. In addition, anemia is also presumably considered as a precipitant in clinical practice. In the present analysis, however, <1.0 % of patients (N=21) were precipitated by anemia, which is concordant with previous reports [5, 10, 28, 29].

Interplay between Heart Failure Etiologies and Precipitating Factors

ACS was a frequent precipitant in patients with ischemic HF, whereas hypertension was a frequent precipitant in patients with hypertensive HF, both of which were consistent with previous literature [32, 33]. In contrast, patients with valvular HF were more likely to be precipitated by AF and renal failure. The disappearance of atrial contraction in AF or extensive fluid volume overload in renal failure, may contribute to be decompensated phase in patients with valvular HF [20, 21, 34, 35].

To the best of our knowledge, this is the first report to study and relate the HF etiologies to the worsening HF precipitating factors. We found no statistical interaction between the HF etiology and the worsening HF precipitants with regard to the study outcomes, suggesting that both entities may have independent prognostic value. Our observations may help potentially clinicians in better identifying the worsening HF precipitants in the light of the patient's history and also in identifying those patients at higher risk of subsequent events.

Limitations

Our study has several limitations. This is a post-hoc analysis of the BIOSTAT-CHF, hence the limitations inherent to observational data are present herein, as a consequence we cannot infer causality nor exclude residual confounders. By design, BIOSTAT-CHF enrolled patients who had no optimal guideline medical therapy or no anticipated need for cardiac transplantation or ventricular assist device. Although, this condition is frequent, results may not be generalizable to these patients. The HF etiologies and precipitants were ascertained by the treating physicians in their routine clinical practice. The detailed clinical information of HF etiologies such as valvular HF and dilated cardiomyopathy were not available, while the number of precipitants might have been underreported; for example, dietary factors such as excessive salt intake and concomitant drugs such as steroidal and non-steroidal inflammatory drugs. We selected patients with single precipitant in survival analysis regarding respective precipitants. Therefore, the number of each individual precipitant was small, potentially having limited power of the associations. Our results, however, were consistent with previous reports, reinforcing the external validation of our findings. After adjustment, patients with ischemic HF was not associated with all-cause mortality (but tended to be associated with cardiovascular mortality), suggesting that the associations with all-cause death alone, might have been diluted by death of non-cardiovascular causes. In BIOSTAT-CHF, the number of patients with preserved LVEF was small, leading to difficulty in survival analysis across LVEF strata. Finally, interaction analyses may lack statistical power, however, these analyses are exploratory and only if some strong between-group difference was present, that interaction could be observed.

Conclusions

Both etiology and precipitating factors for worsening HF may provide independent prognostic information. Patients with HF of an ischemic etiology, and those with worsening HF precipitated by renal failure had the worst clinical prognosis. Treatment up-titration likely benefits patients irrespective of their etiology or precipitant factor. These findings may help in better identifying patient's risk based both on their HF etiology and the factor that led to the visit, and should encourage the up-titration of life-saving therapies irrespective of the HF etiology and/or a precipitant.

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Table 1. Patient Characteristic according to the Heart Failure Etiologies

Values are Mean ± SD, n (%) or median (25th to 75th percentile)

BMI, body mass index; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; NYHA, New York Heart Association; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal prohormone brain natriuretic peptide.

Table 2. Prevalence of Precipitating Factors according to the Heart Failure Etiologies

Table 3. Cox Proportional Hazard Models of the Heart Failure Etiologies for the Clinical Outcomes

HR, hazard ratio; CI, confidence interval; HF, heart failure.

Table 4. Cox Proportional Hazard Models of Precipitating Factors for the Clinical Outcomes

HR, hazard ratio; CI, confidence interval; HF, heart failure.

Table 5. Cox Proportional Hazard Models for the Primary Outcome according to Successful Up-titration of ≥50% of Guideline-Recommended Target Doses

Table 1. Patient Characteristic according to the Heart Failure Etiologies

	Global (N=2465)	Ischemic HF (N=1102)	Non-ischemic HF					P-value between ischemic vs non-ischemic	P-value among all etiologies
			Overall (N=1363)	Hypertensive HF (N=237)	Valvular HF (N=184)	Dilated Cardiomyopathy (N=563)	Other/Unknown (N=379)		
Age, yrs	68.4 ± 12.0	70.0 ± 10.6	67.1 ± 12.8	72.9 ± 10.3	71.7 ± 11.5	62.3 ± 12.7	68.1 ± 12.5	**<0.001**	**<0.001**
Male, N (%)	1805 (73.2 %)	883 (80.1 %)	922 (67.6 %)	135 (57.0 %)	103 (56.0 %)	425 (75.5 %)	259 (68.3 %)	**<0.001**	**<0.001**
BMI, kg/m²	27.9 ± 5.5	28.1 ± 5.3	27.8 ± 5.6	28.4 ± 5.6	26.5 ± 4.9	27.6 ± 5.3	28.2 ± 6.3	0.09	**0.003**
Medical history									
Hypertension, N (%)	1539 (62.4 %)	767 (69.6 %)	772 (56.6 %)	230 (97.0 %)	101 (54.9 %)	251 (44.6 %)	190 (50.1 %)	**<0.001**	**<0.001**
Diabetes mellitus, N (%)	798 (32.4 %)	447 (40.6 %)	351 (25.8 %)	87 (36.7 %)	32 (17.4 %)	136 (24.2 %)	96 (25.3 %)	**<0.001**	**<0.001**
Myocardial infarction, N (%)	940 (38.1 %)	838 (76.0 %)	102 (7.5 %)	19 (8.0 %)	12 (6.5 %)	25 (4.4 %)	46 (12.1 %)	**<0.001**	**<0.001**
Stroke, N (%)	231 (9.4 %)	135 (12.3 %)	96 (7.0 %)	20 (8.4 %)	17 (9.2 %)	27 (4.8 %)	32 (8.4 %)	**<0.001**	**<0.001**
PAD, N (%)	267 (10.8 %)	169 (15.3 %)	98 (7.2 %)	26 (11.0 %)	16 (8.7 %)	26 (4.6 %)	30 (7.9 %)	**<0.001**	**<0.001**
COPD, N (%)	423 (17.2 %)	204 (18.5 %)	219 (16.1 %)	38 (16.0 %)	29 (15.8 %)	88 (15.6 %)	64 (16.9 %)	0.11	0.59
Valvular surgery, N (%)	176 (7.1 %)	73 (6.6 %)	103 (7.6 %)	4 (1.7 %)	69 (37.5 %)	16 (2.8 %)	14 (3.7 %)	0.42	<**0.001**
Prior HF admission, N (%)	780 (31.6 %)	383 (34.8 %)	397 (29.1 %)	71 (30.0 %)	56 (30.4 %)	181 (32.1 %)	89 (23.5 %)	**0.003**	**0.002**
Clinical profile									
NYHA class ≥III, N (%)	1491 (62.2 %)	680 (63.1 %)	811 (61.4 %)	145 (63.3 %)	127 (71.3 %)	321 (58.5 %)	218 (59.9 %)	0.41	**0.03**
Rales, N (%)	240 (19.0 %)	107 (18.8 %)	133 (19.1 %)	25 (18.4 %)	18 (16.2 %)	34 (13.4 %)	56 (28.9 %)	0.88	**0.001**
Juglar venous pressure, N (%)	544 (31.5 %)	249 (31.4 %)	295 (31.6 %)	43 (29.7 %)	54 (41.2 %)	112 (28.5 %)	86 (32.6 %)	0.92	0.10
Leg edema, N (%)	1230 (59.6 %)	511 (55.4 %)	719 (63.1 %)	136 (69.4 %)	120 (76.4 %)	254 (53.8 %)	209 (66.3 %)	**<0.001**	**<0.001**
Systolic blood pressure, mmHg	124.8 ± 21.9	124.2 ± 20.9	125.3 ± 22.6	140.6 ± 26.8	123.0 ± 21.2	121.0 ± 19.2	123.4 ± 21.3	0.39	**<0.001**
Heart rate, bpm	79.9 ± 19.5	75.9 ± 16.1	83.1 ± 21.3	84.2 ± 20.9	86.1 ± 22.1	81.3 ± 19.8	83.8 ± 23.0	**<0.001**	**<0.001**
Hospitalized patients, N (%)	1655 (67.1 %)	706 (64.0 %)	949 (69.6 %)	156 (65.8 %)	148 (80.4 %)	366 (65.0 %)	279 (73.6 %)	**0.003**	**<0.001**
Echocardiogram									
LVEF, %	31.0 ± 10.5	30.4 ± 9.0	31.4 ± 11.6	36.8 ± 11.6	37.3 ± 14.7	26.7 ± 7.8	32.5 ± 11.8	0.85	**<0.001**
LVEF ≤40%, N (%)	1973 (89.7 %)	915 (93.8 %)	1058 (86.4 %)	170 (77.3 %)	116 (69.0 %)	517 (98.3 %)	255 (82.3 %)	**<0.001**	**<0.001**
MR ≥moderate, N (%)	1103 (47.1 %)	483 (46.4 %)	620 (47.7 %)	98 (43.0 %)	96 (54.5 %)	272 (50.8 %)	154 (42.8 %)	0.51	**0.02**
Medication at baseline									
ACEi or ARB, N (%)	1783 (72.3 %)	773 (70.1 %)	1010 (74.1 %)	168 (70.9 %)	123 (66.8 %)	445 (79.0 %)	274 (72.3 %)	**0.03**	**0.001**
Beta-blocker, N (%)	2059 (83.5 %)	964 (87.5 %)	1095 (80.3 %)	177 (74.7 %)	136 (73.9 %)	477 (84.7 %)	305 (80.5 %)	**<0.001**	**<0.001**
MRA, N (%)	1312 (53.2 %)	601 (54.5 %)	711 (52.2 %)	98 (41.4 %)	79 (42.9 %)	346 (61.5 %)	188 (49.6 %)	0.24	**<0.001**
Loop diuretics, N (%)	2454 (99.6 %)	1101 (99.9 %)	1353 (99.3 %)	234 (98.7 %)	184 (100.0 %)	558 (99.1 %)	377 (99.5 %)	**0.04**	**0.04**
Digoxin, N (%)	481 (19.5 %)	150 (13.6 %)	331 (24.3 %)	46 (19.4 %)	48 (26.1 %)	145 (25.8 %)	92 (24.3 %)	**<0.001**	**<0.001**
Medication at 3 months									

ACEi/ARB ≥50% target dose	1286 (52.2 %)	572 (51.9 %)	714 (52.4 %)	154 (65.0 %)	70 (38.0 %)	297 (52.8 %)	193 (50.9 %)	0.81	**<0.001**
% ACEi/ARB target dose	50.0 (25.0 - 66.7)	50.0 (16.7 - 62.5)	50.0 (25.0 – 75.0)	50.0 (25.0 - 100.0)	25.0 (12.5 - 50.0)	50.0 (25.0 - 75.0)	50.0 (25.0 - 62.5)	0.08	**<0.001**
Beta-blocker ≥50% target dose	879 (35.7 %)	404 (36.7 %)	475 (34.8 %)	89 (37.6 %)	64 (34.8 %)	185 (32.9 %)	137 (36.1 %)	0.35	0.58
% beta-blocker target dose	25.0 (12.5 - 50.0)	25.0 (12.5 - 50.0)	25.0 (12.5 – 50.0)	25.0 (12.5 - 50.0)	25.0 (8.3 - 50.0)	25.0 (12.5 - 50.0)	25.0 (12.5 - 50.0)	0.62	0.36
Laboratory									
Hemoglobin, g/dl	13.2 ± 1.9	13.0 ± 1.9	13.3 ± 1.9	13.0 ± 1.8	12.8 ± 1.9	13.6 ± 1.8	13.4 ± 1.9	**0.002**	**<0.001**
Blood urea nitrogen, mg/dl	41.8 ± 32.6	44.8 ± 34.7	39.3 ± 30.6	37.1 ± 26.3	43.6 ± 36.4	40.1 ± 30.5	37.4 ± 29.7	**<0.001**	**<0.001**
eGFR, mL/min/1.73m²	62.0 ± 24.3	58.9 ± 23.2	64.5 ± 24.8	61.2 ± 24.1	58.6 ± 22.8	68.5 ± 25.7	63.9 ± 23.9	**<0.001**	**<0.001**
Sodium, mmol/l	139.1 ± 4.0	139.0 ± 3.9	139.3 ± 4.0	139.8 ± 4.3	139.0 ± 3.7	139.1 ± 4.0	139.3 ± 4.1	**0.044**	**0.02**
Potassium, mmol/l	4.3 ± 0.6	4.3 ± 0.6	4.2 ± 0.6	4.2 ± 0.6	4.2 ± 0.6	4.3 ± 0.6	4.2 ± 0.5	**0.02**	0.07
NT-proBNP, pg/ml	4280 (2359-8475)	3988 (2288-8220)	4341 (2400-8576)	3808 (2366-7539)	4883 (2621-8282)	4339 (1938-9019)	4443 (2604-8538)	0.61	0.51

Table 2. Prevalence of Precipitating Factors according to the Heart Failure Etiologies

	Ischemic HF (N=1102)	Hypertensive HF (N=237)	Valvular HF (N=184)	Dilated Cardiomyopathy (N=563)	Other/Unknown (N=379)	P-value
Precipitating factor						
Acute coronary syndrome, N (%)	94 (8.6 %)	4 (1.7 %)	2 (1.1 %)	5 (0.9 %)	16 (4.2 %)	**<0.001**
Atrial fibrillation, N (%)	199 (18.1 %)	72 (30.5 %)	71 (38.8 %)	97 (17.3 %)	138 (36.5 %)	**<0.001**
Hypertension, N (%)	43 (3.9 %)	51 (21.5 %)	9 (4.9 %)	12 (2.1 %)	19 (5.0 %)	**<0.001**
Renal failure, N (%)	136 (12.4 %)	26 (11.0 %)	28 (15.2 %)	36 (6.4 %)	42 (11.1 %)	**0.001**
Infection, N (%)	59 (5.4 %)	13 (5.5 %)	10 (5.6 %)	20 (3.6 %)	26 (6.9 %)	0.25
Non-adherence, N (%)	160 (14.5 %)	25 (10.5 %)	20 (10.9 %)	86 (15.3 %)	49 (12.9 %)	0.27

Table 3. Cox Proportional Hazard Models of the Heart Failure Etiologies for the Clinical Outcomes

Composite outcome	Unadjusted		Adjusted for BIOSTAT-CHF risk model		Adjusted for BIOSTAT-CHF risk model plus renal failure		P-value for interaction with renal failure
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	
Dilated cardiomyopathy	(reference)		(reference)		(reference)		
Ischemic HF	1.76 (1.48 - 2.10)	**<0.001**	1.34 (1.12 - 1.60)	**0.001**	1.34 (1.12 – 1.60)	**0.001**	
Hypertensive HF	1.49 (1.16 - 1.91)	**0.002**	1.27 (0.99 - 1.62)	0.06	1.26 (0.98 – 1.62)	0.07	0.30
Valvular HF	1.85 (1.43 - 2.40)	**<0.001**	1.21 (0.93 - 1.57)	0.16	1.21 (0.93 – 1.57)	0.16	
Other/Unknown	1.32 (1.05 - 1.66)	**0.02**	1.17 (0.93 - 1.46)	0.19	1.16 (0.92 – 1.46)	0.21	
All-cause death	**Unadjusted**		**Adjusted for BIOSTAT-CHF risk model**		**Adjusted for BIOSTAT-CHF risk model plus renal failure**		**P-value for interaction with renal failure**
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	
Dilated cardiomyopathy	(reference)		(reference)		(reference)		
Ischemic HF	1.72 (1.38 - 2.14)	**<0.001**	1.05 (0.84 - 1.32)	0.66	1.06 (0.85 – 1.33)	0.62	
Hypertensive HF	1.43 (1.04 - 1.95)	**0.03**	1.26 (0.92 - 1.73)	0.15	1.26 (0.92 – 1.73)	0.14	0.46
Valvular HF	1.58 (1.13 - 2.21)	**0.01**	1.12 (0.80 - 1.56)	0.52	1.12 (0.80 – 1.56)	0.54	
Other/Unknown	1.34 (1.01 - 1.78)	**0.04**	1.15 (0.87 - 1.53)	0.32	1.15 (0.87 – 1.52)	0.33	
Cardiovascular death	**Unadjusted**		**Adjusted for BIOSTAT-CHF risk model**		**Adjusted for BIOSTAT-CHF risk model plus renal failure**		**P-value for interaction with renal failure**
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	
Dilated cardiomyopathy	(reference)		(reference)		(reference)		
Ischemic HF	1.76 (1.35 – 2.29)	**<0.001**	1.27 (0.97 – 1.66)	0.08	1.27 (0.97 – 1.65)	0.08	
Hypertensive HF	1.29 (0.87 – 1.91)	0.21	1.08 (0.73 – 1.61)	0.69	1.08 (0.73 – 1.60)	0.70	0.55
Valvular HF	1.47 (0.97 – 2.22)	0.07	0.92 (0.60 – 1.39)	0.68	0.91 (0.60 – 1.39)	0.67	
Other/Unknown	1.24 (0.87 – 1.75)	0.23	1.06 (0.75 – 1.50)	0.74	1.05 (0.74 – 1.49)	0.77	

Table 4. Cox Proportional Hazard Models of Precipitating Factors for the Clinical Outcomes

Composite outcome	Unadjusted		Adjusted for BIOSTAT-CHF risk model		Adjusted for BIOSTAT-CHF risk model plus Ischemic etiology		P-value for interaction with HF etiologies
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	
Non-adherence	(reference)		(reference)		(reference)		
Acute coronary syndrome	1.08 (0.69 - 1.71)	0.74	1.18 (0.75 - 1.87)	0.48	1.10 (0.69 - 1.75)	0.68	
Atrial fibrillation	1.10 (0.82 - 1.46)	0.54	1.01 (0.76 - 1.35)	0.95	1.04 (0.78 - 1.39)	0.78	0.95
Hypertension	1.03 (0.66 - 1.61)	0.90	1.37 (0.88 - 2.15)	0.17	1.39 (0.89 - 2.18)	0.15	
Renal failure	2.61 (1.87 - 3.65)	**<0.001**	1.48 (1.04 - 2.09)	**0.03**	1.49 (1.05 - 2.10)	**0.03**	
Infection	1.31 (0.85 - 2.01)	0.23	0.97 (0.62 - 1.49)	0.87	0.97 (0.63 - 1.50)	0.88	
All-cause death	**Unadjusted**		**Adjusted for BIOSTAT-CHF risk model**		**Adjusted for BIOSTAT-CHF risk model plus Ischemic etiology**		**P-value for interaction with HF etiologies**
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	
Non-adherence	(reference)		(reference)		(reference)		
Acute coronary syndrome	1.18 (0.69 - 2.01)	0.54	1.22 (0.71 - 2.07)	0.47	1.24 (0.72 - 2.12)	0.44	
Atrial fibrillation	1.06 (0.75 - 1.51)	0.73	1.04 (0.73 - 1.47)	0.85	1.03 (0.72 - 1.46)	0.89	0.67
Hypertension	0.54 (0.27 - 1.07)	0.08	0.78 (0.39 - 1.55)	0.48	0.78 (0.39 - 1.55)	0.47	
Renal failure	2.83 (1.92 - 4.17)	**<0.001**	1.44 (0.97 - 2.16)	0.07	1.44 (0.96 - 2.15)	0.08	
Infection	1.45 (0.88 - 2.40)	0.15	0.99 (0.59 - 1.64)	0.95	0.99 (0.59 - 1.64)	0.95	
Cardiovascular death	**Unadjusted**		**Adjusted for BIOSTAT-CHF risk model**		**Adjusted for BIOSTAT-CHF risk model plus Ischemic etiology**		**P-value for interaction with HF etiologies**
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	
Non-adherence	(reference)		(reference)		(reference)		
Acute coronary syndrome	1.40 (0.76 – 2.58)	0.29	1.57 (0.85 – 2.91)	0.15	1.48 (0.79 – 2.77)	0.22	
Atrial fibrillation	1.17 (0.77 – 1.78)	0.47	1.04 (0.68 – 1.58)	0.86	1.07 (0.70 – 1.63)	0.76	0.73
Hypertension	0.48 (0.20 – 1.16)	0.10	0.71 (0.30 – 1.72)	0.45	0.72 (0.30 – 1.74)	0.47	
Renal failure	2.95 (1.84 – 4.72)	**<0.001**	1.47 (0.90 – 2.40)	0.12	1.49 (0.92 – 2.43)	0.11	
Infection	1.38 (0.74 – 2.59)	0.31	0.97 (0.51 – 1.82)	0.92	0.97 (0.52 – 1.82)	0.92	

Table 5. Cox Proportional Hazard Models for the Primary Outcome according to Successful Up-titration of ≥50% of Guideline-Recommended Target Doses

		Ischemic vs Non-ischemic HF		Renal failure vs Other precipitants	
		Adjusted HR (95% CI)	**P-value for interaction**	**Adjusted HR (95% CI)**	**P-value for interaction**
Overall		1.19 (1.05 - 1.34)		1.36 (0.98 - 1.89)	
ACEi/ARB ≥50% of target dose	**Unsuccessful**	1.30 (1.09 - 1.56)	0.59	1.51 (1.01 - 2.24)	0.62
	Successful	1.16 (0.94 - 1.42)		1.05 (0.58 - 1.88)	
BB ≥50% of target dose	**Unsuccessful**	1.22 (1.03 - 1.44)	0.69	1.19 (0.79 - 1.81)	0.19
	Successful	1.27 (1.01 - 1.61)		1.94 (1.09 - 3.44)	
ACEi/ARB or BB ≥50% of target dose	**Unsuccessful**	1.30 (1.05 - 1.61)	0.72	1.23 (0.75 - 2.02)	0.47
	Successful	1.20 (1.01 - 1.43)		1.46 (0.93 - 2.29)	

Figure 1. Flowchart of Patients from the BIOSTAT-CHF

Figure 2. BIOSTAT-CHF risk model-adjusted Survival Curves for the Primary Outcome according to the Heart Failure Etiologies and Precipitating Factors

Figure 1. Flowchart of Patients from the BIOSTAT-CHF

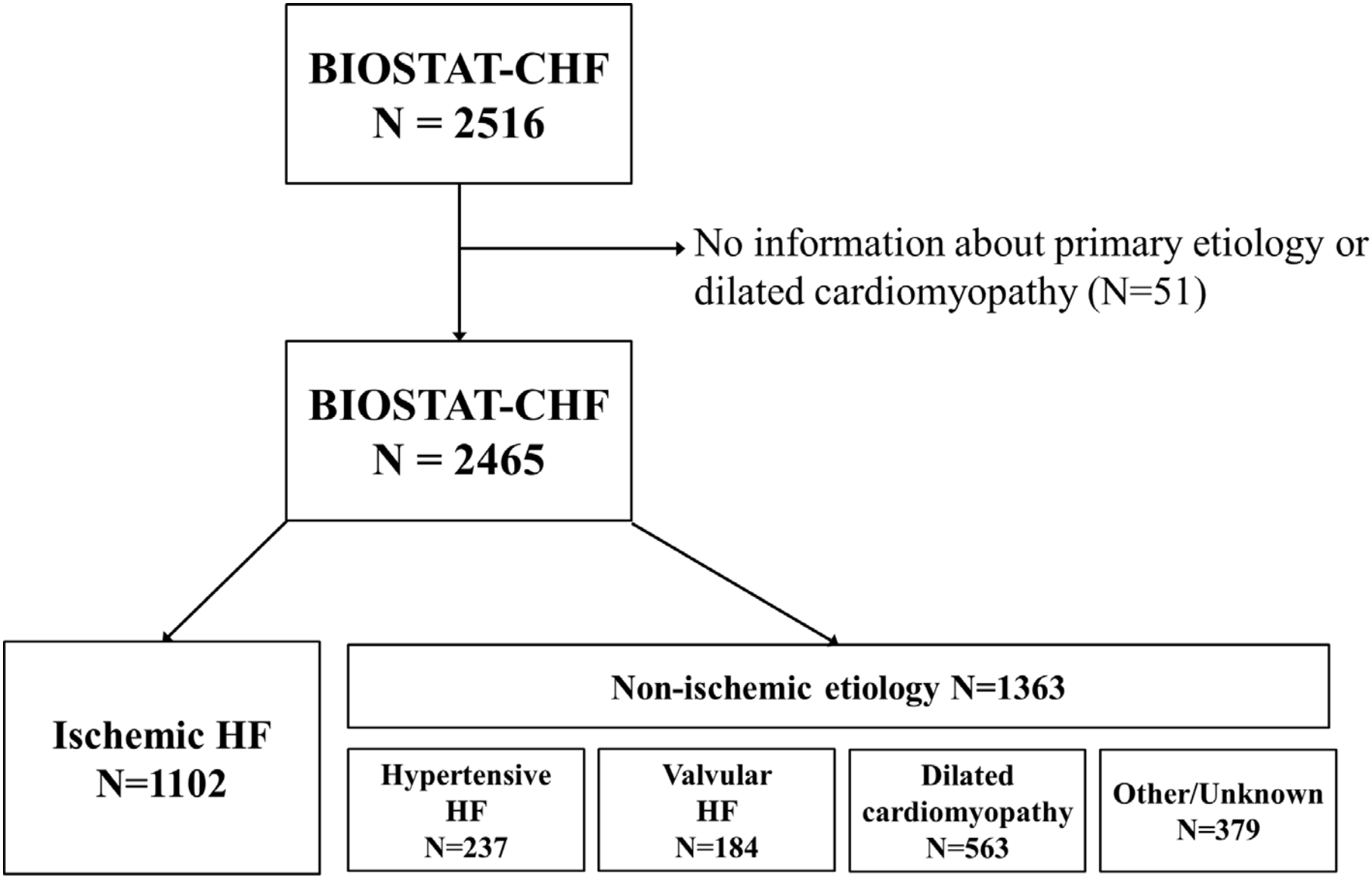
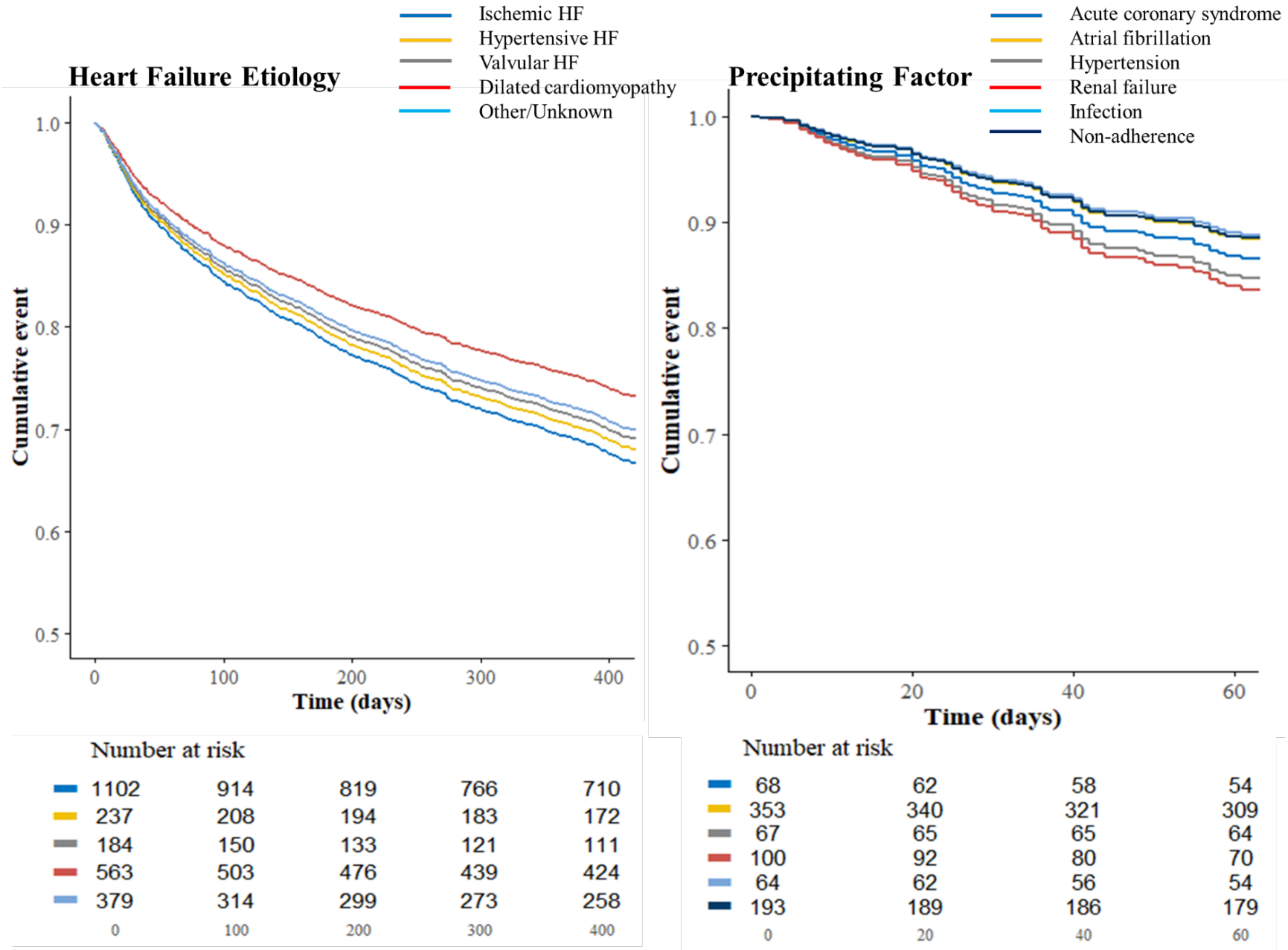


Figure 2. BIOSTAT-CHF risk model-adjusted Survival Curves for the Primary Outcome according to the Heart Failure Etiologies and Precipitating Factors



Supplementary table 1. Heart Failure Etiologies and Precipitating Factors in the Protocol of BIOSTAT-CHF

Supplementary table 2. Patients Characteristics according to Precipitating Factors

Values are Mean ± SD, n (%) or median (25th to 75th percentile)

ACS, acute coronary syndrome; PAD, peripheral artery disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal prohormone brain natriuretic peptide.

Supplementary table 3. Cox Proportional Hazard Models of the Heart Failure Etiologies for the Primary Outcome in Ambulant and Hospitalized Patients

HR, hazard ratio; CI, confidence interval; HF, heart failure.

Cox hazard model for the composite of all-cause mortality or HF hospitalization was adjusted for BIOSTAT-CHF risk model.

Supplementary table 4. Cox Proportional Hazard Models of the Heart Failure Etiologies for the Primary Outcome in Patients with Reduced Ejection Fraction

HR, hazard ratio; CI, confidence interval; HF, heart failure.

Cox hazard model for the composite of all-cause mortality or HF hospitalization was adjusted for BIOSTAT-CHF risk model.

Supplementary figure 1. Unadjusted Survival Curves for the Primary Outcome according to the Heart Failure Etiologies and Precipitating Factors (Overall Term Follow-up)

Supplementary figure 2. Unadjusted Survival Curves for the Primary Outcome according to the Heart Failure Etiologies and Precipitating Factors

Supplementary table 1. Heart Failure Etiologies and Precipitating Factors in the Protocol of BIOSTAT-CHF

5 MEDICAL HISTORY: HEART FAILURE

Etiology assessed	No □0 Yes □1
Ischemic heart disease	Primary □1 Contributory □2 Not Present □3 Unknown □4
Hypertension	Primary □1 Contributory □2 Not Present □3 Unknown □4
Cardiomyopathy	Primary □1 Contributory □2 Not Present □3 Unknown □4
Valvular disease	Primary □1 Contributory □2 Not Present □3 Unknown □4
Unknown etiology	Primary □1 Contributory □2 Not Present □3 Unknown □4
Other	Primary □1 Contributory □2 Not Present □3 Unknown □4

7 FAMILY HISTORY

7.7 Cause of the Heart Failure is a dilated cardiomyopathy?	No □0 Yes □1

10 INPATIENT HOSPITALIZATION / OUTPATIENT CLINIC

10.4 Precipitating factors for this hospitalization / outpatient clinic visit?	No □0 Yes □1
If Yes, specify:	□□□□□□□□□□□□□□□
10.4.1 Acute coronary syndrome	Present □1 Absent □2 Not certain □3
10.4.2 Non-Compliance (behavior, drugs)	Present □1 Absent □2 Not certain □3
10.4.3 Atrial Fibrillation	Present □1 Absent □2 Not certain □3
10.4.4 Ventricular Arrhythmia	Present □1 Absent □2 Not certain □3
10.4.5 Infection	Present □1 Absent □2 Not certain □3
10.4.6 Uncontrolled hypertension	Present □1 Absent □2 Not certain □3
10.4.7 Brady arrhythmias	Present □1 Absent □2 Not certain □3
10.4.8 Renal dysfunction	Present □1 Absent □2 Not certain □3
10.4.9 Iatrogenic	Present □1 Absent □2 Not certain □3
10.4.10 Other?	Present □1 Absent □2 Not certain □3
If Yes, specify	□□□□□□□□□□□□□□□

Supplementary table 2. Patients Characteristics according to Precipitating Factors

	Global (N=845)	ACS (N=68)	Atrial fibrillation (N=353)	Hypertension (N=67)	Renal failure (N=100)	Infection (N=64)	Non-adherence (N=193)	p-value
Age, yrs	68.8 ± 12.0	69.1 ± 12.0	71.2 ± 10.6	68.5 ± 12.3	71.4 ± 13.0	68.7 ± 11.2	63.2 ± 12.5	**<0.001**
Male, N (%)	595 (70.4 %)	46 (67.6 %)	250 (70.8 %)	40 (59.7 %)	73 (73.0 %)	39 (60.9 %)	147 (76.2 %)	0.07
Body mass index, kg/m²	28.1 ± 5.3	27.5 ± 5.0	28.5 ± 5.5	28.0 ± 5.0	27.5 ± 4.9	26.8 ± 4.6	28.3 ± 5.6	0.21
Medical history								
Hypertension, N (%)	519 (61.4 %)	40 (58.8 %)	204 (57.8 %)	64 (95.5 %)	64 (64.0 %)	35 (54.7 %)	112 (58.0 %)	**<0.001**
Diabetes mellitus, N (%)	288 (34.1 %)	27 (39.7 %)	100 (28.3 %)	23 (34.3 %)	44 (44.0 %)	22 (34.4 %)	72 (37.3 %)	**0.04**
Myocardial infarction, N (%)	293 (34.7 %)	53 (77.9 %)	85 (24.1 %)	16 (23.9 %)	46 (46.0 %)	26 (40.6 %)	67 (34.7 %)	**<0.001**
Stroke, N (%)	94 (11.1 %)	5 (7.4 %)	46 (13.0 %)	2 (3.0 %)	12 (12.0 %)	12 (18.8 %)	17 (8.8 %)	**0.04**
PAD, N (%)	105 (12.4 %)	7 (10.3 %)	35 (9.9 %)	11 (16.4 %)	18 (18.0 %)	9 (14.1 %)	25 (13.0 %)	0.27
COPD, N (%)	144 (17.0 %)	10 (14.7 %)	54 (15.3 %)	9 (13.4 %)	18 (18.0 %)	24 (37.5 %)	29 (15.0 %)	**<0.001**
Prior HF admission, N (%)	258 (30.5 %)	8 (11.8 %)	104 (29.5 %)	14 (20.9 %)	46 (46.0 %)	18 (28.1 %)	68 (35.2 %)	**<0.001**
Clinical profile								
NYHA class ≥III, N (%)	551 (67.4 %)	32 (50.0 %)	234 (67.8 %)	36 (57.1 %)	75 (78.9 %)	51 (83.6 %)	123 (64.7 %)	**<0.001**
Rales, N (%)	101 (20.4 %)	9 (20.5 %)	44 (21.9 %)	6 (13.0 %)	14 (25.9 %)	14 (26.9 %)	14 (14.1 %)	0.25
Juglar venous pressure, N (%)	183 (31.2 %)	9 (20.0 %)	78 (32.5 %)	10 (21.7 %)	29 (35.8 %)	21 (48.8 %)	36 (27.5 %)	**0.03**
Leg edema, N (%)	470 (66.0 %)	23 (46.0 %)	223 (73.1 %)	33 (60.0 %)	62 (68.9 %)	41 (71.9 %)	88 (56.8 %)	**<0.001**
Systolic blood pressure, mmHg	125.8 ± 24.1	119.3 ± 22.3	123.7 ± 19.4	169.9 ± 25.8	118.9 ± 20.6	122.0 ± 22.8	121.4 ± 18.0	**<0.001**
Heart rate, bpm	82.6 ± 21.4	75.3 ± 15.5	89.0 ± 24.6	84.0 ± 21.3	73.9 ± 11.9	84.7 ± 22.0	76.7 ± 16.1	**<0.001**
Hospitalized patients, N (%)	682 (80.7 %)	65 (95.6 %)	283 (80.2 %)	56 (83.6 %)	86 (86.0 %)	63 (98.4 %)	129 (66.8 %)	**<0.001**
Echocardiogram								
LVEF, %	32.1 ± 11.2	31.8 ± 7.9	33.9 ± 12.1	34.9 ± 10.2	31.8 ± 11.0	31.3 ± 15.2	28.5 ± 8.3	**<0.001**
MR ≥moderate, N (%)	378 (46.8 %)	18 (27.7 %)	178 (52.0 %)	20 (30.3 %)	46 (50.0 %)	26 (43.3 %)	90 (49.2 %)	**<0.001**
Medication at baseline								
ACEi or ARB, N (%)	609 (72.1 %)	55 (80.9 %)	252 (71.4 %)	49 (73.1 %)	58 (58.0 %)	42 (65.6 %)	153 (79.3 %)	**0.002**
%ACEi or ARB target dose	25.0 (0.0 - 50.0)	25.0 (12.5 - 50.0)	25.0 (0 - 50.0)	50.0 (0 - 100.0)	15.5 (0 - 50.0)	25.0 (0 - 50.0)	25.0 (12.5 - 50.0)	**0.03**
Beta-blocker, N (%)	697 (82.5 %)	60 (88.2 %)	290 (82.2 %)	52 (77.6 %)	79 (79.0 %)	46 (71.9 %)	170 (88.1 %)	**0.03**
%beta-blocker target dose	23.8 (6.2 - 37.5)	25.0 (12.5 - 37.5)	25.0 (6.2 - 50.0)	15.6 (4.2 - 50.0)	12.5 (4.2 - 50.0)	12.5 (0 - 48.8)	12.5 (6.2 - 25.0)	0.22
MRA, N (%)	441 (52.2 %)	29 (42.6 %)	185 (52.4 %)	27 (40.3 %)	39 (39.0 %)	35 (54.7 %)	126 (65.3 %)	**<0.001**

Loop diuretics dose, mg	40.0 (20.0 - 80.0)	40.0 (25.0 - 80.0)	40.0 (8.0 - 80.0)	40.0 (20.0 - 80.0)	40.0 (20.0 - 100.0)	40.0 (25.0 - 80.0)	40.0 (40.0 - 75.0)	**0.02**
Medication at 3 months								
ACEi/ARB ≥50% target dose	419 (49.6 %)	36 (52.9 %)	172 (48.7 %)	45 (67.2 %)	31 (31.0 %)	33 (51.6 %)	102 (52.8 %)	**<0.001**
%ACEi/ARB target dose	37.5 (25.0 - 62.5)	50.0 (20.8 - 50.0)	37.5 (25.0 - 50.0)	50.0 (25.0 - 100.0)	20.8 (0 - 50.0)	50.0 (25.0 - 75.0)	50.0 (25.0 - 62.5)	**<0.001**
Beta-blocker ≥50% target dose	280 (33.1 %)	16 (23.5 %)	134 (38.0 %)	26 (38.8 %)	36 (36.0 %)	19 (29.7 %)	49 (25.4 %)	**0.02**
%beta-blocker target dose	25.0 (12.5 - 50.0)	25.0 (14.6 - 47.5)	25.0 (12.5 - 50.0)	25.0 (12.5 - 50.0)	25.0 (8.3 - 50.0)	25.0 (6.2 - 50.0)	25.0 (12.5 - 50.0)	0.06
Laboratory								
Hemoglobin, g/dl	13.2 ± 1.9	12.7 ± 1.8	13.5 ± 1.9	13.6 ± 1.5	11.9 ± 2.1	12.4 ± 1.7	13.5 ± 1.9	**<0.001**
Blood urea nitrogen, mg/dl	39.7 ± 30.6	34.2 ± 33.1	36.2 ± 28.2	31.7 ± 26.5	61.5 ± 38.6	30.7 ± 19.7	41.8 ± 27.7	**<0.001**
eGFR, mL/min/1.73m²	62.5 ± 24.9	68.6 ± 20.0	65.8 ± 21.2	68.1 ± 26.5	30.5 ± 8.9	68.3 ± 36.0	67.7 ± 20.9	**<0.001**
Sodium, mmol/l	139.1 ± 3.9	138.8 ± 3.4	139.4 ± 3.8	140.3 ± 3.4	138.2 ± 4.3	137.2 ± 4.6	139.3 ± 3.9	**<0.001**
Potassium, mmol/l	4.3 ± 0.6	4.2 ± 0.5	4.2 ± 0.5	4.2 ± 0.6	4.4 ± 0.7	4.0 ± 0.6	4.4 ± 0.7	**<0.001**
NT-proBNP, pg/ml	4770 (585 - 8797)	3408 (1941 - 7764)	3899 (2559 - 7419)	4988 (3183 - 7921)	7500 (3723 - 15805)	7255 (3290 - 14111)	5000 (2090 - 8105)	**<0.001**

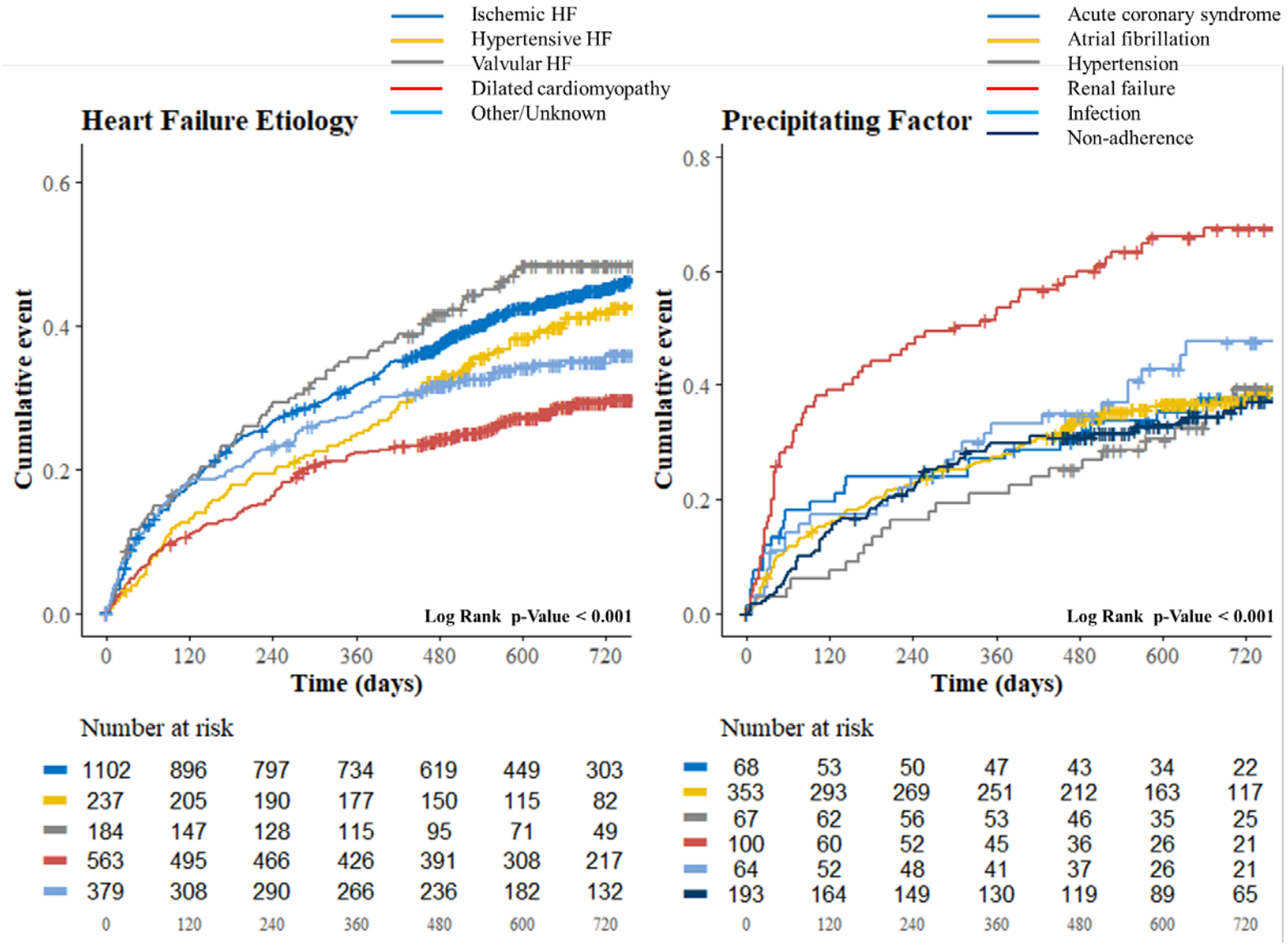
Supplementary table 3. Cox Proportional Hazard Models of the Heart Failure Etiologies for the Primary Outcome in Ambulant and Hospitalized Patients

	Ambulant Patients				Hospitalized Patients				P-value for interaction with ambulatory/ hospitalization
	N	Event (%)	HR (95% CI)	P-value	N	Event (%)	HR (95% CI)	P-value	
Etiologies									
Dilated cardiomyopathy	197	17.3	(reference)		366	35.8	(reference)		
Ischemic HF	397	34.3	1.46 (0.99 - 2.14)	0.056	705	52.1	1.32 (1.08 - 1.61)	**0.007**	
Hypertensive HF	81	40.7	1.50 (0.92 - 2.44)	0.11	156	42.9	1.17 (0.87 - 1.57)	0.31	0.51
Valvular HF	36	41.7	1.48 (0.80 - 2.74)	0.21	148	48	1.14 (0.85 - 1.52)	0.39	
Other/Unknown	100	26	1.26 (0.75 - 2.10)	0.38	279	39.4	1.11 (0.86 - 1.43)	0.42	

Supplementary table 4. Cox Proportional Hazard Models of the Heart Failure Etiologies for the Primary Outcome in Patients with Reduced Ejection Fraction

	N	Event (%)	HR (95% CI)	P-value
Etiologies				
Dilated cardiomyopathy	517	28.8	(reference)	
Ischemic HF	915	43.6	1.36 (1.13 - 1.65)	**0.001**
Hypertensive HF	170	40.0	1.24 (0.93 - 1.66)	0.14
Valvular HF	116	37.9	0.99 (0.70 - 1.38)	0.94
Other/Unknown	255	32.5	1.19 (0.91 - 1.56)	0.20

Supplementary figure 1. Unadjusted Survival Curves for the Primary Outcome according to the Heart Failure Etiologies and Precipitating Factors (Overall Term Follow-up)



Supplementary figure 2. Unadjusted Survival Curves for the Primary Outcome according to the Heart Failure Etiologies and Precipitating Factors