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## 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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## **Abstract**

### **Background**

Knowledge on the association between heart failure (HF) etiologies, precipitant causes and clinical outcomes may help in ascertaining patients' 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 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 patients' outcome over the last decades, however those with worsening symptoms and/or signs of HF still have a poor prognosis<sup>1,2</sup>. Both the etiology of HF and the factors leading to its decompensation may influence outcomes and drug response<sup>3-7</sup>. Previous studies have shown that patients with HF of an ischemic etiology have a worse prognosis than those with non-ischemic etiology<sup>8,9</sup>, 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<sup>7,10,11</sup>. 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 are; 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<sup>12,13</sup>. 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<sup>14</sup>. 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<sup>14</sup> (**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 95<sup>th</sup> percentile and dynamic electrocardiographic alterations suggestive of acute myocardial ischemia<sup>15</sup>; AF, presence of AF on the electrocardiogram; hypertension, office 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  $\pm$  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  $\chi^2$  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 BIOSAT-CHF risk model <sup>16</sup>. The risk model for the composite outcome included age, HF hospitalization in the year before inclusion, presence of edema, N-terminal prohormone brain natriuretic peptide (NT-proBNP), SBP, hemoglobin, high-density lipoprotein levels, serum sodium concentration, and absence of beta-blocker. The risk model for all-cause mortality included age, higher blood urea nitrogen and NT-proBNP, lower hemoglobin and failure to prescribe a beta-blocker <sup>16</sup>. With regard to the precipitants, we performed multivariable analyses after adjusting for ischemic etiology 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's 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 worse 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 patients' characteristics according to the 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 variable associated with 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**). Moreover, 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),  $p=0.001$  (**Supplementary table 3**), and there was no interaction between ischemic HF and renal failure as a precipitant ( $p=0.30$ ). In contrast, 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 4**.

### **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 etiology and/or precipitant factors (all  $P\text{-value}>0.10$ ) (**Table 5 & Supplementary table 5**).

## **Discussion**

In ambulant and hospitalized patients with worsening heart failure, 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. HF treatment up-titration was not influenced by HF etiologies and precipitating factors. These findings suggest that both the HF etiology and the precipitating factors provide relevant and independent prognostic information, and that worse prognostic implications were not modified by treatment up-titration.

### **Heart Failure Etiologies**

Our results align with previous reports suggesting that the most common HF etiology was ischemia<sup>6, 17</sup>. Patients with ischemic HF were older, had more cardiovascular risk factors, comorbidities and were associated with worse prognosis<sup>8, 9, 18, 19</sup>.

Among patients with non-ischemic HF, valvular HF has also been associated with worse prognosis<sup>4</sup>, 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<sup>20, 21</sup>. 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<sup>22, 23</sup>. 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<sup>24-26</sup>.

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<sup>27</sup>.

### **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<sup>10, 28-31</sup>. Renal failure as a precipitant may be determined by clinical deterioration and by therapeutic approach such as diuresis and renin angiotensin aldosterone system inhibitors<sup>3</sup>. 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<sup>5, 11</sup>, whereas patients with hypertension had less comorbidities and less severe congestion<sup>5, 32</sup>. Both of the precipitants, non-adherence (used as referent variable in our

analyses) and hypertension, have been associated with more favorable outcomes<sup>5</sup>. 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<sup>5</sup>, prognostic implication of these precipitants may vary thus with term follow-up.

### **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<sup>32, 33</sup>. 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<sup>20, 21, 34, 35</sup>.

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 patients' 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 not on optimal guideline medical therapy. Although, this condition is frequent, results may not be generalizable to patients on optimal therapy. The HF etiologies and precipitants were ascertained by the treating physicians in their routine clinical practice, and 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, are frequently used as self-medications and therefore may be underreported. The number of each individual precipitant was small, potentially having limited power of the associations. However, our results were consistent with previous reports, reinforcing the external validation of our findings. After adjustment, the association between ischemic

HF etiology and all-cause mortality lost statistical significance (but not with the composite outcome of HF hospitalization or all-cause death), suggesting that the associations with all-cause death alone, might have been underpowered and/or diluted by death of non-cardiovascular causes. 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 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 patients' 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 precipitant.

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## **Disclosures**

MK and JPF have no conflicts of interest to disclose with regard to the present manuscript.

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**Table 1. Patient Characteristic according to the Heart Failure Etiologies**

Values are Mean  $\pm$  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  $\geq 50\%$  of Guideline-Recommended Target Doses**

HF, heart failure; HR, hazard ratio; CI, confidence interval; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker.

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/m <sup>2</sup>	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
<b>Medical history</b>									
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
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
<b>Clinical profile</b>									
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
<b>Echocardiogram</b>									
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
<b>Medication at baseline</b>									
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
<b>Medication at 3 months</b>									
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

<b>% ACEi/ARB target dose</b>	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	<b>&lt;0.001</b>
<b>Beta-blocker ≥50% target dose</b>	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
<b>% beta-blocker target dose</b>	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
<b>Laboratory</b>									
<b>Hemoglobin, g/dl</b>	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	<b>0.002</b>	<b>&lt;0.001</b>
<b>Blood urea nitrogen, mg/dl</b>	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	<b>&lt;0.001</b>	<b>&lt;0.001</b>
<b>eGFR, mL/min/1.73m<sup>2</sup></b>	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	<b>&lt;0.001</b>	<b>&lt;0.001</b>
<b>Sodium, mmol/l</b>	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	<b>0.044</b>	<b>0.02</b>
<b>Potassium, mmol/l</b>	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	<b>0.02</b>	0.07
<b>NT-proBNP, pg/ml</b>	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**

	<b>Ischemic HF (N=1102)</b>	<b>Hypertensive HF (N=237)</b>	<b>Valvular HF (N=184)</b>	<b>Dilated Cardiomyopathy (N=563)</b>	<b>Other/Unknown (N=379)</b>	<b>P-value</b>
<b>Precipitating factor</b>						
<b>Acute coronary syndrome, N (%)</b>	94 (8.6 %)	4 (1.7 %)	2 (1.1 %)	5 (0.9 %)	16 (4.2 %)	<b>&lt;0.001</b>
<b>Atrial fibrillation, N (%)</b>	199 (18.1 %)	72 (30.5 %)	71 (38.8 %)	97 (17.3 %)	138 (36.5 %)	<b>&lt;0.001</b>
<b>Hypertension, N (%)</b>	43 (3.9 %)	51 (21.5 %)	9 (4.9 %)	12 (2.1 %)	19 (5.0 %)	<b>&lt;0.001</b>
<b>Renal failure, N (%)</b>	136 (12.4 %)	26 (11.0 %)	28 (15.2 %)	36 (6.4 %)	42 (11.1 %)	<b>0.001</b>
<b>Infection, N (%)</b>	59 (5.4 %)	13 (5.5 %)	10 (5.6 %)	20 (3.6 %)	26 (6.9 %)	0.25
<b>Non-adherence, N (%)</b>	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	
	HR (95% CI)	P-value	HR (95% CI)	P-value
<b>Dilated cardiomyopathy</b>	(reference)		(reference)	
<b>Ischemic HF</b>	1.76 (1.48 - 2.10)	<b>&lt;0.001</b>	1.34 (1.12 - 1.60)	<b>0.001</b>
<b>Hypertensive HF</b>	1.49 (1.16 - 1.91)	<b>0.002</b>	1.27 (0.99 - 1.62)	0.06
<b>Valvular HF</b>	1.85 (1.43 - 2.40)	<b>&lt;0.001</b>	1.21 (0.93 - 1.57)	0.16
<b>Other/Unknown</b>	1.32 (1.05 - 1.66)	<b>0.02</b>	1.17 (0.93 - 1.46)	0.19

All-cause death	Unadjusted		Adjusted for BIOSTAT-CHF risk model	
	HR (95% CI)	P-value	HR (95% CI)	P-value
<b>Dilated cardiomyopathy</b>	(reference)		(reference)	
<b>Ischemic HF</b>	1.72 (1.38 - 2.14)	<b>&lt;0.001</b>	1.05 (0.84 - 1.32)	0.66
<b>Hypertensive HF</b>	1.43 (1.04 - 1.95)	<b>0.03</b>	1.26 (0.92 - 1.73)	0.15
<b>Valvular HF</b>	1.58 (1.13 - 2.21)	<b>0.01</b>	1.12 (0.80 - 1.56)	0.52
<b>Other/Unknown</b>	1.34 (1.01 - 1.78)	<b>0.04</b>	1.15 (0.87 - 1.53)	0.32

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	
<b>Non-adherence</b>	(reference)		(reference)		(reference)		
<b>Acute coronary syndrome</b>	1.08 (0.69 - 1.71)	0.74	1.18 (0.75 - 1.87)	0.48	1.10 (0.69 - 1.75)	0.68	0.95
<b>Atrial fibrillation</b>	1.10 (0.82 - 1.46)	0.54	1.01 (0.76 - 1.35)	0.95	1.04 (0.78 - 1.39)	0.78	
<b>Hypertension</b>	1.03 (0.66 - 1.61)	0.90	1.37 (0.88 - 2.15)	0.17	1.39 (0.89 - 2.18)	0.15	
<b>Renal failure</b>	2.61 (1.87 - 3.65)	<b>&lt;0.001</b>	1.48 (1.04 - 2.09)	<b>0.03</b>	1.49 (1.05 - 2.10)	<b>0.03</b>	
<b>Infection</b>	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	
<b>Non-adherence</b>	(reference)		(reference)		(reference)		
<b>Acute coronary syndrome</b>	1.18 (0.69 - 2.01)	0.54	1.22 (0.71 - 2.07)	0.47	1.24 (0.72 - 2.12)	0.44	0.67
<b>Atrial fibrillation</b>	1.06 (0.75 - 1.51)	0.73	1.04 (0.73 - 1.47)	0.85	1.03 (0.72 - 1.46)	0.89	
<b>Hypertension</b>	0.54 (0.27 - 1.07)	0.08	0.78 (0.39 - 1.55)	0.48	0.78 (0.39 - 1.55)	0.47	
<b>Renal failure</b>	2.83 (1.92 - 4.17)	<b>&lt;0.001</b>	1.44 (0.97 - 2.16)	0.07	1.44 (0.96 - 2.15)	0.08	
<b>Infection</b>	1.45 (0.88 - 2.40)	0.15	0.99 (0.59 - 1.64)	0.95	0.99 (0.59 - 1.64)	0.95	

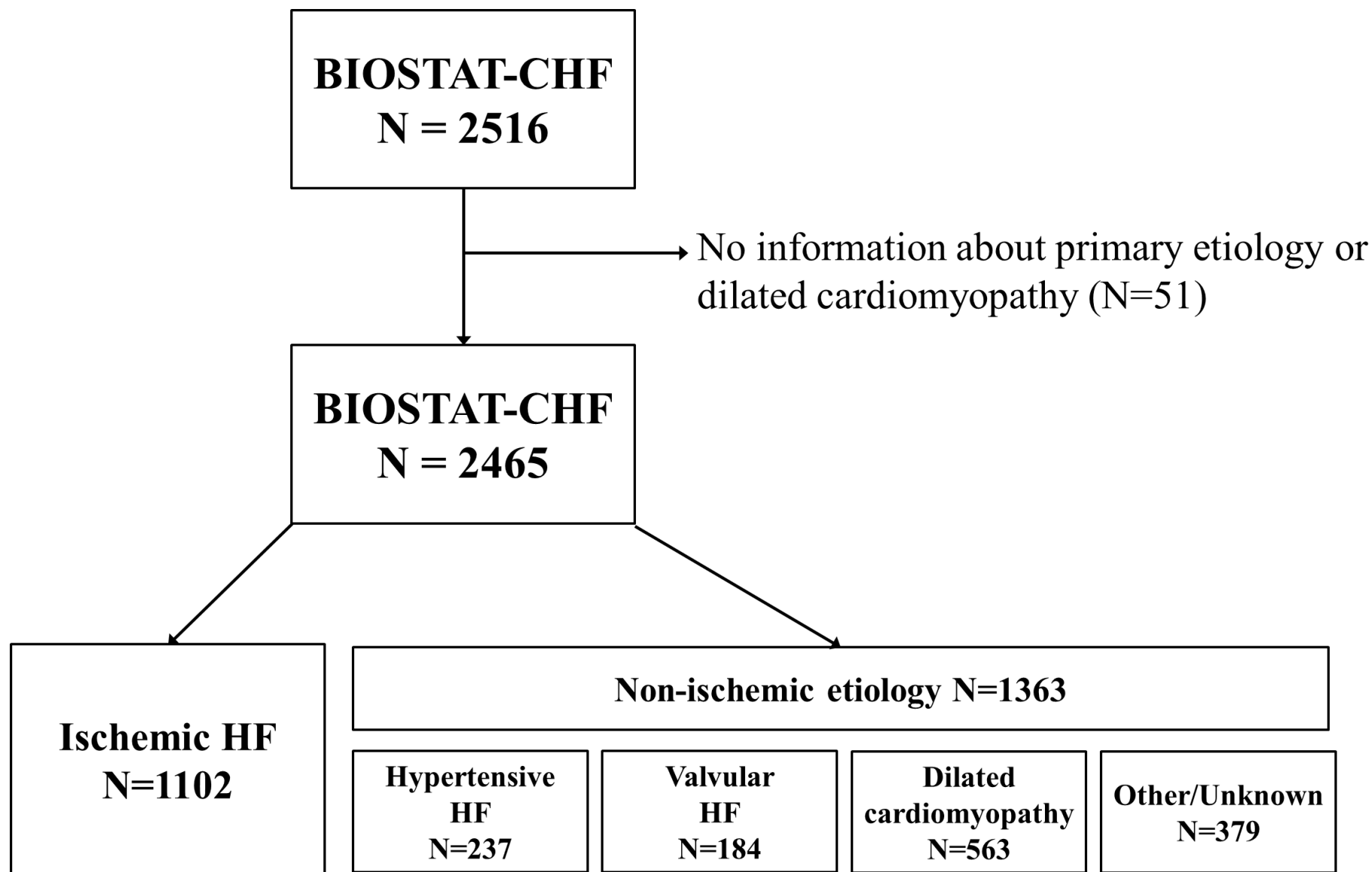
**Table 5. Cox Proportional Hazard Models for the Primary Outcome according to Successful Up-titration of  $\geq 50\%$  of Guideline-Recommended Target Doses**

		Ischemic vs Non-ischemic HF				Renal failure vs Other precipitants			
		N	Event	Adjusted HR (95% CI)	P-value for interaction	N	Event	Adjusted HR (95% CI)	P-value for interaction
<b>Overall</b>		933	345	1.19 (1.05 - 1.34)		193	103	1.44 (1.09 - 1.91)	
<b>ACEi/ARB <math>\geq 50\%</math> of target dose</b>	<b>Unsuccessful</b>	416	184	1.23 (1.05 - 1.45)	0.76	128	69	1.56 (1.11 - 2.18)	0.98
	<b>Successful</b>	517	161	1.12 (0.93 - 1.37)		65	34	1.13 (0.67 - 1.88)	
<b>BB <math>\geq 50\%</math> of target dose</b>	<b>Unsuccessful</b>	582	222	1.14 (0.98 - 1.33)	0.29	125	63	1.37 (0.98 - 1.93)	0.17
	<b>Successful</b>	351	123	1.28 (1.03 - 1.60)		68	40	1.88 (1.11 - 3.19)	
<b>ACEi/ARB or BB <math>\geq 50\%</math> of target dose</b>	<b>Unsuccessful</b>	294	129	1.29 (1.01 - 1.66)	0.97	88	43	0.99 (0.71 - 1.40)	0.37
	<b>Successful</b>	639	216	1.28 (1.05 - 1.55)		105	60	1.08 (0.80 - 1.46)	

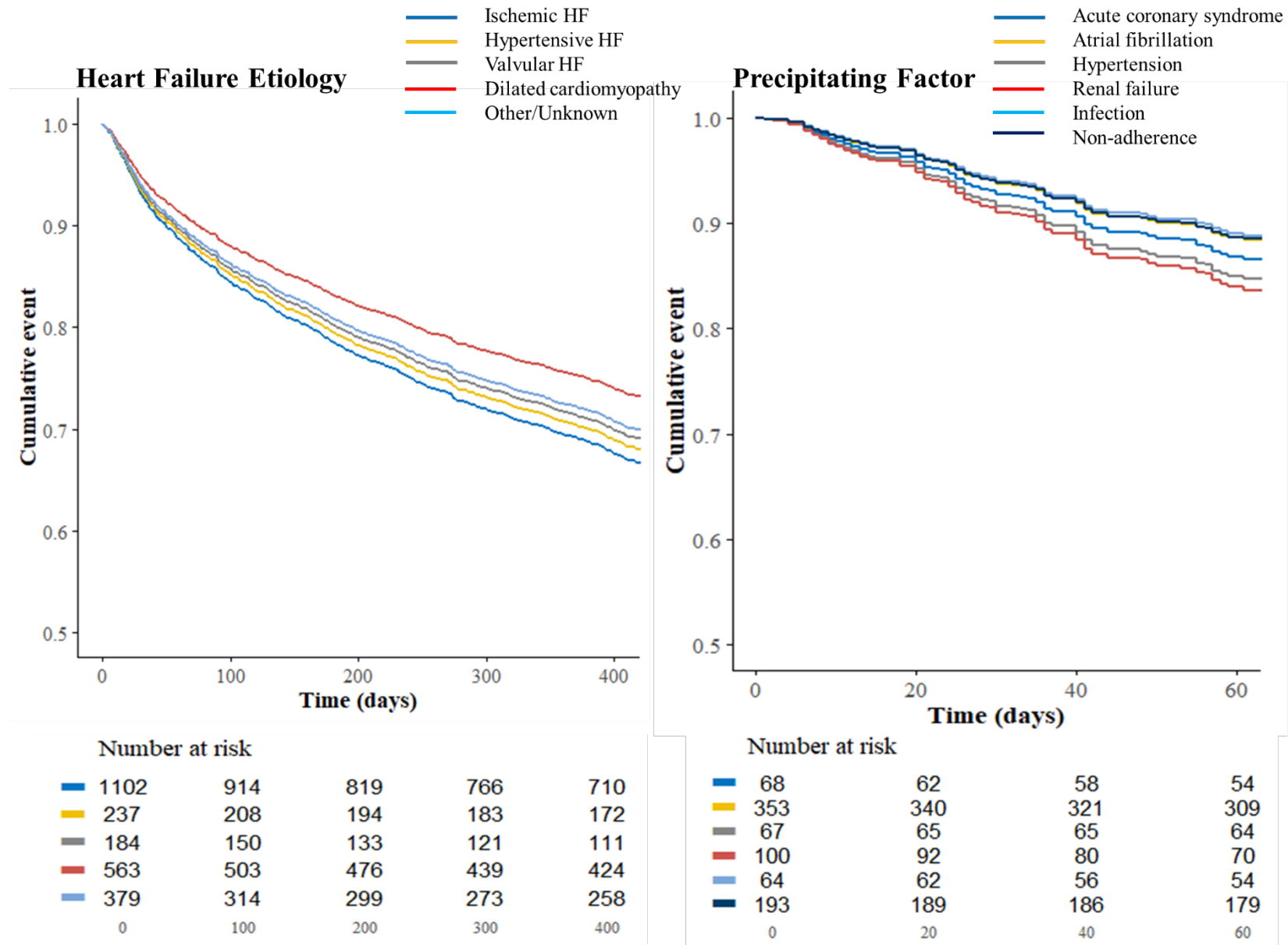
**Figure 1. Flowchart of Patients from the BIOSTAT-CHF**

**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  $\pm$  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 after Adjusting for BIOSTAT-CHF risk model and Renal Failure**

### **Supplementary table 4. 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 re-hospitalization was adjusted for BIOSTAT-CHF risk model.

### **Supplementary table 5. Interaction for the Primary Outcome between Heart Failure Treatment, Heart Failure Etiology and Precipitant**

HF, heart failure; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

### **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 <input type="checkbox"/> 0	Yes <input type="checkbox"/> 1
Ischemic heart disease	Primary <input type="checkbox"/> 1 Contributory <input type="checkbox"/> 2 Not Present <input type="checkbox"/> 3 Unknown <input type="checkbox"/> 4	
Hypertension	Primary <input type="checkbox"/> 1 Contributory <input type="checkbox"/> 2 Not Present <input type="checkbox"/> 3 Unknown <input type="checkbox"/> 4	
Cardiomyopathy	Primary <input type="checkbox"/> 1 Contributory <input type="checkbox"/> 2 Not Present <input type="checkbox"/> 3 Unknown <input type="checkbox"/> 4	
Valvular disease	Primary <input type="checkbox"/> 1 Contributory <input type="checkbox"/> 2 Not Present <input type="checkbox"/> 3 Unknown <input type="checkbox"/> 4	
Unknown etiology	Primary <input type="checkbox"/> 1 Contributory <input type="checkbox"/> 2 Not Present <input type="checkbox"/> 3 Unknown <input type="checkbox"/> 4	
Other	Primary <input type="checkbox"/> 1 Contributory <input type="checkbox"/> 2 Not Present <input type="checkbox"/> 3 Unknown <input type="checkbox"/> 4	

### 7 FAMILY HISTORY

7.7 Cause of the Heart Failure is a dilated cardiomyopathy?	No <input type="checkbox"/> 0 Yes <input type="checkbox"/> 1
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## 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

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CASE REPORT FORM A systems BIOlogy Study to TAIlored Treatment in Chronic Heart Failure (BIOSTAT-CHF)

Protocol version 2.6 Amended, dated 25 April 2012

CRF version 2.0.0, dated: 21 December 2012

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
<b>Age, yrs</b>	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	<b>&lt;0.001</b>
<b>Male, N (%)</b>	595 (70.4 %)	46 (67.6 %)	250 (70.8 %)	40 (59.7 %)	73 (73.0 %)	39 (60.9 %)	147 (76.2 %)	0.07
<b>Body mass index, kg/m<sup>2</sup></b>	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
<b>Medical history</b>								
<b>Hypertension, N (%)</b>	519 (61.4 %)	40 (58.8 %)	204 (57.8 %)	64 (95.5 %)	64 (64.0 %)	35 (54.7 %)	112 (58.0 %)	<b>&lt;0.001</b>
<b>Diabetes mellitus, N (%)</b>	288 (34.1 %)	27 (39.7 %)	100 (28.3 %)	23 (34.3 %)	44 (44.0 %)	22 (34.4 %)	72 (37.3 %)	<b>0.04</b>
<b>Myocardial infarction, N (%)</b>	293 (34.7 %)	53 (77.9 %)	85 (24.1 %)	16 (23.9 %)	46 (46.0 %)	26 (40.6 %)	67 (34.7 %)	<b>&lt;0.001</b>
<b>Stroke, N (%)</b>	94 (11.1 %)	5 (7.4 %)	46 (13.0 %)	2 (3.0 %)	12 (12.0 %)	12 (18.8 %)	17 (8.8 %)	<b>0.04</b>
<b>PAD, N (%)</b>	105 (12.4 %)	7 (10.3 %)	35 (9.9 %)	11 (16.4 %)	18 (18.0 %)	9 (14.1 %)	25 (13.0 %)	0.27
<b>COPD, N (%)</b>	144 (17.0 %)	10 (14.7 %)	54 (15.3 %)	9 (13.4 %)	18 (18.0 %)	24 (37.5 %)	29 (15.0 %)	<b>&lt;0.001</b>
<b>Prior HF admission, N (%)</b>	258 (30.5 %)	8 (11.8 %)	104 (29.5 %)	14 (20.9 %)	46 (46.0 %)	18 (28.1 %)	68 (35.2 %)	<b>&lt;0.001</b>
<b>Clinical profile</b>								
<b>NYHA class ≥III, N (%)</b>	551 (67.4 %)	32 (50.0 %)	234 (67.8 %)	36 (57.1 %)	75 (78.9 %)	51 (83.6 %)	123 (64.7 %)	<b>&lt;0.001</b>
<b>Rales, N (%)</b>	101 (20.4 %)	9 (20.5 %)	44 (21.9 %)	6 (13.0 %)	14 (25.9 %)	14 (26.9 %)	14 (14.1 %)	0.25
<b>Juglar venous pressure, N (%)</b>	183 (31.2 %)	9 (20.0 %)	78 (32.5 %)	10 (21.7 %)	29 (35.8 %)	21 (48.8 %)	36 (27.5 %)	<b>0.03</b>
<b>Leg edema, N (%)</b>	470 (66.0 %)	23 (46.0 %)	223 (73.1 %)	33 (60.0 %)	62 (68.9 %)	41 (71.9 %)	88 (56.8 %)	<b>&lt;0.001</b>
<b>Systolic blood pressure, mmHg</b>	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	<b>&lt;0.001</b>
<b>Heart rate, bpm</b>	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	<b>&lt;0.001</b>
<b>Hospitalized patients, N (%)</b>	682 (80.7 %)	65 (95.6 %)	283 (80.2 %)	56 (83.6 %)	86 (86.0 %)	63 (98.4 %)	129 (66.8 %)	<b>&lt;0.001</b>
<b>Echocardiogram</b>								
<b>LVEF, %</b>	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	<b>&lt;0.001</b>
<b>MR ≥moderate, N (%)</b>	378 (46.8 %)	18 (27.7 %)	178 (52.0 %)	20 (30.3 %)	46 (50.0 %)	26 (43.3 %)	90 (49.2 %)	<b>&lt;0.001</b>
<b>Medication at baseline</b>								
<b>ACEi or ARB, N (%)</b>	609 (72.1 %)	55 (80.9 %)	252 (71.4 %)	49 (73.1 %)	58 (58.0 %)	42 (65.6 %)	153 (79.3 %)	<b>0.002</b>
<b>%ACEi or ARB target dose</b>	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)	<b>0.03</b>
<b>Beta-blocker, N (%)</b>	697 (82.5 %)	60 (88.2 %)	290 (82.2 %)	52 (77.6 %)	79 (79.0 %)	46 (71.9 %)	170 (88.1 %)	<b>0.03</b>
<b>%beta-blocker target dose</b>	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
<b>MRA, N (%)</b>	441 (52.2 %)	29 (42.6 %)	185 (52.4 %)	27 (40.3 %)	39 (39.0 %)	35 (54.7 %)	126 (65.3 %)	<b>&lt;0.001</b>

<b>Loop diuretics dose, mg</b>	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)	<b>0.02</b>
<b>Medication at 3 months</b>								
<b>ACEi/ARB ≥50% target dose</b>	419 (49.6 %)	36 (52.9 %)	172 (48.7 %)	45 (67.2 %)	31 (31.0 %)	33 (51.6 %)	102 (52.8 %)	<b>&lt;0.001</b>
<b>%ACEi/ARB target dose</b>	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)	<b>&lt;0.001</b>
<b>Beta-blocker ≥50% target dose</b>	280 (33.1 %)	16 (23.5 %)	134 (38.0 %)	26 (38.8 %)	36 (36.0 %)	19 (29.7 %)	49 (25.4 %)	<b>0.02</b>
<b>%beta-blocker target dose</b>	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
<b>Laboratory</b>								
<b>Hemoglobin, g/dl</b>	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	<b>&lt;0.001</b>
<b>Blood urea nitrogen, mg/dl</b>	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	<b>&lt;0.001</b>
<b>eGFR, mL/min/1.73m<sup>2</sup></b>	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	<b>&lt;0.001</b>
<b>Sodium, mmol/l</b>	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	<b>&lt;0.001</b>
<b>Potassium, mmol/l</b>	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	<b>&lt;0.001</b>
<b>NT-proBNP, pg/ml</b>	4770 (585 - 8797)	3408 (1941 - 7764)	3899 (2559 - 7419)	4988 (3183 - 7921)	7500 (3723 - 15805)	7255 (3290 - 14111)	5000 (2090 - 8105)	<b>&lt;0.001</b>

**Supplementary table 3. Cox Proportional Hazard Models of the Heart Failure Etiologies after Adjustment for BIOSTAT-CHF risk model and Renal Failure**

Composite outcome	Adjusted for BIOSTAT-CHF risk model and renal failure		P-value for interaction with renal failure
	HR (95% CI)	P-value	
<b>Dilated cardiomyopathy</b>	(reference)		
<b>Ischemic HF</b>	1.34 (1.12 – 1.60)	<b>0.001</b>	0.30
<b>Hypertensive HF</b>	1.26 (0.98 – 1.62)	0.07	
<b>Valvular HF</b>	1.21 (0.93 – 1.57)	0.16	
<b>Other/Unknown</b>	1.16 (0.92 – 1.46)	0.21	
All-cause death	Adjusted for BIOSTAT-CHF risk model and renal failure		P-value for interaction with renal failure
	HR (95% CI)	P-value	
<b>Dilated cardiomyopathy</b>	(reference)		
<b>Ischemic HF</b>	1.06 (0.85 – 1.33)	0.62	0.46
<b>Hypertensive HF</b>	1.26 (0.92 – 1.73)	0.14	
<b>Valvular HF</b>	1.12 (0.80 – 1.56)	0.54	
<b>Other/Unknown</b>	1.15 (0.87 – 1.52)	0.33	

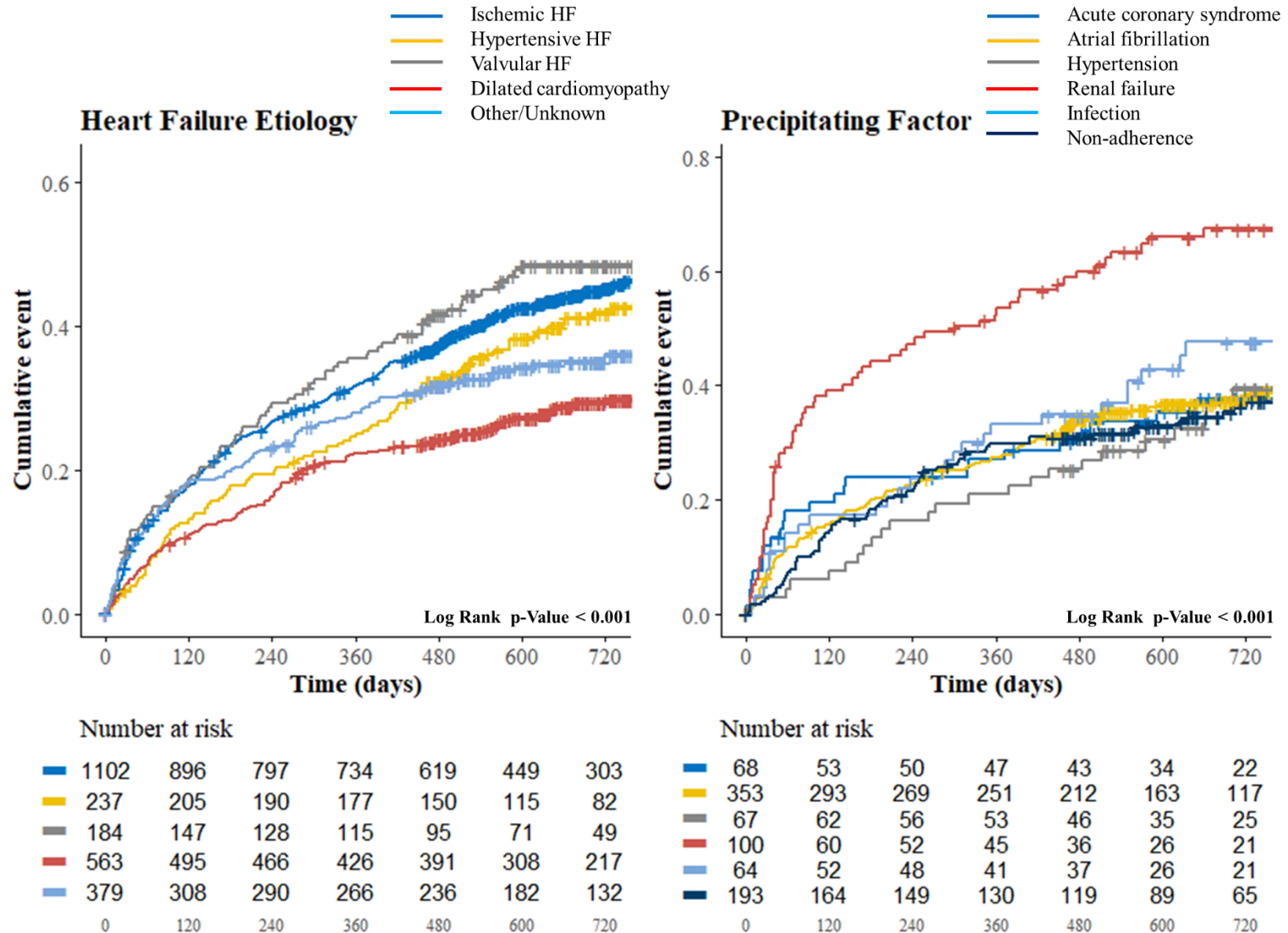
**Supplementary table 4. Cox Proportional Hazard Models of the Heart Failure Etiologies for the Primary Outcome in Ambulant and Hospitalized Patients**

	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	
<b>Etiologies</b>									
<b>Dilated cardiomyopathy</b>	197	17.3	(reference)		366	35.8	(reference)		
<b>Ischemic HF</b>	397	34.3	1.46 (0.99 - 2.14)	0.056	705	52.1	1.32 (1.08 - 1.61)	<b>0.007</b>	
<b>Hypertensive HF</b>	81	40.7	1.50 (0.92 - 2.44)	0.11	156	42.9	1.17 (0.87 - 1.57)	0.31	0.51
<b>Valvular HF</b>	36	41.7	1.48 (0.80 - 2.74)	0.21	148	48	1.14 (0.85 - 1.52)	0.39	
<b>Other/Unknown</b>	100	26	1.26 (0.75 - 2.10)	0.38	279	39.4	1.11 (0.86 - 1.43)	0.42	

**Supplementary table 5. Interaction for the Primary Outcome between Heart Failure Treatment, Heart Failure Etiology and Precipitant**

	P-value for interaction	
	with HF etiology	with precipitant
<b>ACEi/ARB <math>\geq 50\%</math> of target dose</b>	0.79	0.29
<b>Beta-blocker <math>\geq 50\%</math> of target dose</b>	0.55	0.41
<b>ACEi/ARB or beta-blocker <math>\geq 50\%</math> of target dose</b>	0.93	0.93

**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

