



HAL
open science

Heart failure etiologies and clinical factors precipitating for worsening heart failure: Findings from BIOSTAT-CHF

Masatake Kobayashi, Adriaan A Voors, Nicolas Girerd, Maxime Billotte,
Stefan D Anker, John Cleland, Chim Lang, Leong Ng, Dirk J van Veldhuisen,
Kenneth Dickstein, et al.

► To cite this version:

Masatake Kobayashi, Adriaan A Voors, Nicolas Girerd, Maxime Billotte, Stefan D Anker, et al.. Heart failure etiologies and clinical factors precipitating for worsening heart failure: Findings from BIOSTAT-CHF. *European Journal of Internal Medicine*, 2020, 71, pp.62-69. 10.1016/j.ejim.2019.10.017. hal-02513245

HAL Id: hal-02513245

<https://hal.univ-lorraine.fr/hal-02513245>

Submitted on 13 May 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Heart Failure Etiologies and Clinical Factors precipitating for Worsening Heart

Failure: findings from BIOSTAT-CHF

Masatake Kobayashi ¹, Adriaan A. Voors ², Nicolas Girerd ¹, Maxime Billotte ¹, Stefan D. Anker ³, John G. Cleland ⁴, Chim C. Lang ⁵, Leong L. Ng ⁶, Dirk J. van Veldhuisen ², Kenneth Dickstein ^{7,8}, Macro Metra ⁹, Kevin Duarte ¹, Patrick Rossignol ¹, Faiez Zannad ¹, João Pedro Ferreira ¹

1. Université de Lorraine, INSERM, Centre d'Investigations Cliniques Plurithématique 1433, Inserm U1116, CHRU de Nancy and F-CRIN INI-CRCT, Nancy, France.
2. Department of Cardiology, University of Groningen, University Medical Center Groningen, Hanzeplein, Groningen, the Netherlands.
3. Innovative Clinical Trials, Department of Cardiology and Pneumology, University Medical Centre Göttingen (UMG), Göttingen, Germany.
4. National Heart & Lung Institute, Royal Brompton and Harefield Hospitals, Imperial College, London, UK.
5. Division of Molecular and Clinical Medicine, School of Medicine, University of Dundee, Ninewells Hospital & Medical School, Dundee, UK.
6. Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, and NIHR Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital, Leicester, LE3 9QP, UK.
7. University of Bergen, Bergen, Norway.
8. University of Stavanger, Stavanger, Norway.
9. Cardiology. University and Civil hospitals of Brescia. Italy.

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

Corresponding Author: João Pedro Ferreira

Centre d'Investigation Clinique 1433 module Plurithématique, CHRU Nancy - Hôpitaux de Brabois,
Institut Lorrain du Cœur et des Vaisseaux Louis Mathieu, Nancy, 54500, France

Email: j.ferreira@chru-nancy.fr

Total number of tables and figures: tables 5 figures 2

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^{1,2}. Both the etiology of HF and the factors leading to its decompensation may influence outcomes and drug response³⁻⁷. Previous studies have shown that patients with HF of an ischemic etiology have a 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 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^{12,13}. 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 guideline¹⁴. 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 guidelines¹⁴ (**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 ischemia¹⁵; 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 ± 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 BIOSAT-CHF risk model¹⁶. 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-blocker¹⁶. 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-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^{6, 17}. Patients with ischemic HF were older, had more cardiovascular risk factors, comorbidities and were associated with worse prognosis^{8, 9, 18, 19}.

Among patients with non-ischemic HF, valvular HF has also been associated with worse prognosis⁴, 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 etiologies²⁴⁻²⁶.

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 etiology²⁷.

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 inhibitors³. 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 outcomes⁵. 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 outcomes⁵, 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^{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 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.

Funding

This project was funded by a grant from the European Commission (FP7-242209-BIOSTAT-CHF; EudraCT 2010–020808–29). JPF, NG, PR and FZ are supported by a public grant overseen by the French National Research Agency (ANR) as part of the second “Investissements d’Avenir” program FIGHT-HF (reference: ANR-15-RHU-0004) and by the French PIA project “Lorraine Université d’Excellence”, reference ANR-15-IDEX-04-LUE. And by Contrat de Plan Etat-Lorraine and FEDER Lorraine.

Disclosures

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

PR received personal fees (consulting) from Novartis, Relypsa, AstraZeneca, Grünenthal, Stealth Peptides, Fresenius, Idorsia, Vifor Fresenius Medical Care Renal Pharma, Vifor and CTMA; lecture fees from Bayer and CVRx; cofounder of CardioRenal. AAV received consultancy fees and/or research grants from: Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, GSK,

Novartis, Roche Diagnostics, Servier. MM received consulting honoraria as member of trials' committees and advisory boards in the last 5 years from Bayer, Servier, Novartis.

Reference

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH and van der Meer P. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *European heart journal*. 2016;37:2129-200.
2. Mebazaa A, Yilmaz MB, Levy P, Ponikowski P, Peacock WF, Laribi S, Ristic AD, Lambrinou E, Masip J, Riley JP, McDonagh T, Mueller C, deFilippi C, Harjola VP, Thiele H, Piepoli MF, Metra M, Maggioni A, McMurray J, Dickstein K, Damman K, Seferovic PM, Ruschitzka F, Leite-Moreira AF, Bellou A, Anker SD and Filippatos G. Recommendations on pre-hospital & early hospital management of acute heart failure: a consensus paper from the Heart Failure Association of the European Society of Cardiology, the European Society of Emergency Medicine and the Society of Academic Emergency Medicine. *European journal of heart failure*. 2015;17:544-58.
3. Zannad F and Rossignol P. Cardiorenal Syndrome Revisited. *Circulation*. 2018;138:929-44.
4. Kajimoto K, Minami Y, Sato N and Kasanuki H. Etiology of Heart Failure and Outcomes in Patients Hospitalized for Acute Decompensated Heart Failure With Preserved or Reduced Ejection Fraction. *Am J Cardiol*. 2016;118:1881-1887.
5. Arrigo M, Gayat E, Parenica J, Ishihara S, Zhang J, Choi DJ, Park JJ, Alhabib KF, Sato N, Miro O, Maggioni AP, Zhang Y, Spinar J, Cohen-Solal A, Iwashyna TJ, Mebazaa A and Network G. Precipitating factors and 90-day outcome of acute heart failure: a report from the intercontinental GREAT registry. *European journal of heart failure*. 2017;19:201-208.
6. Shore S, Grau-Sepulveda MV, Bhatt DL, Heidenreich PA, Eapen ZJ, Hernandez AF, Yancy CW and Fonarow GC. Characteristics, Treatments, and Outcomes of Hospitalized Heart Failure Patients Stratified by Etiologies of Cardiomyopathy. *JACC Heart Fail*. 2015;3:906-16.
7. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghide M, Greenberg BH, O'Connor CM, Pieper K, Sun JL, Yancy CW and Young JB. Factors Identified as Precipitating Hospital Admissions for Heart Failure and Clinical Outcomes Findings From OPTIMIZE-HF. *Arch Intern Med*. 2008;168(8):847-854.
8. Bart BA, Shaw LK, McCants CB, Jr., Fortin DF, Lee KL, Califf RM and O'Connor CM. Clinical determinants of mortality in patients with angiographically diagnosed ischemic or nonischemic cardiomyopathy. *J Am Coll Cardiol*. 1997;30:1002-8.

9. Vedin O, Lam CSP, Koh AS, Benson L, Teng THK, Tay WT, Braun OO, Savarese G, Dahlstrom U and Lund LH. Significance of Ischemic Heart Disease in Patients With Heart Failure and Preserved, Midrange, and Reduced Ejection Fraction: A Nationwide Cohort Study. *Circ Heart Fail.* 2017;10.
10. Berkovitch A, Maor E, Sabbag A, Chernomordik F, Elis A, Arbel Y, Goldenberg I, Grossman E and Klempfner R. Precipitating Factors for Acute Heart Failure Hospitalization and Long-Term Survival. *Medicine (Baltimore).* 2015;94:e2330.
11. Ambardekar AV, Fonarow GC, Hernandez AF, Pan W, Yancy CW, Krantz MJ, Get With the Guidelines Steering C and Hospitals. Characteristics and in-hospital outcomes for nonadherent patients with heart failure: findings from Get With The Guidelines-Heart Failure (GWTG-HF). *Am Heart J.* 2009;158:644-52.
12. Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Hillege HL, Lang CC, Ter Maaten JM, Ng L, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zannad F, Zwinderman AH and Metra M. A systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure: rationale, design, and baseline characteristics of BIOSTAT-CHF. *European journal of heart failure.* 2016;18:716-26.
13. Ouwerkerk W, Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Hillege HL, Lang CC, Ter Maaten JM, Ng LL, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zannad F, Metra M and Zwinderman AH. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study. *European heart journal.* 2017;38:1883-1890.
14. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG and Swedberg K. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *European journal of heart failure.* 2008;10:933-89.
15. Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernandez-Aviles F, Fox KA, Hasdai D, Ohman EM, Wallentin L and Wijns W. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *European heart journal.* 2007;28:1598-660.
16. Voors AA, Ouwerkerk W, Zannad F, van Veldhuisen DJ, Samani NJ, Ponikowski P, Ng LL, Metra M, Ter Maaten JM, Lang CC, Hillege HL, van der Harst P, Filippatos G, Dickstein K, Cleland JG, Anker SD and Zwinderman AH. Development and validation of multivariable models to predict mortality and hospitalization in patients with heart failure. *European journal of heart failure.* 2017;19:627-634.

17. Fox KF, Cowie MR, Wood DA, Coats AJ, Gibbs JS, Underwood SR, Turner RM, Poole-Wilson PA, Davies SW and Sutton GC. Coronary artery disease as the cause of incident heart failure in the population. *European heart journal*. 2001;22:228-36.
18. Lee DS, Gona P, Vasani RS, Larson MG, Benjamin EJ, Wang TJ, Tu JV and Levy D. Relation of disease pathogenesis and risk factors to heart failure with preserved or reduced ejection fraction: insights from the framingham heart study of the national heart, lung, and blood institute. *Circulation*. 2009;119:3070-7.
19. Frazier CG, Alexander KP, Newby LK, Anderson S, Iverson E, Packer M, Cohn J, Goldstein S and Douglas PS. Associations of gender and etiology with outcomes in heart failure with systolic dysfunction: a pooled analysis of 5 randomized control trials. *J Am Coll Cardiol*. 2007;49:1450-8.
20. Goliash G, Bartko PE, Pavo N, Neuhold S, Wurm R, Mascherbauer J, Lang IM, Strunk G and Hulsmann M. Refining the prognostic impact of functional mitral regurgitation in chronic heart failure. *European heart journal*. 2018;39:39-46.
21. Turina J, Hess O, Sepulcri F and Krayenbuehl HP. Spontaneous course of aortic valve disease. *European heart journal*. 1987;8:471-83.
22. Merlo M, Pivetta A, Pinamonti B, Stolfo D, Zecchin M, Barbati G, Di Lenarda A and Sinagra G. Long-term prognostic impact of therapeutic strategies in patients with idiopathic dilated cardiomyopathy: changing mortality over the last 30 years. *European journal of heart failure*. 2014;16:317-24.
23. Merlo M, Cannata A, Gobbo M, Stolfo D, Elliott PM and Sinagra G. Evolving concepts in dilated cardiomyopathy. *Eur J Heart Fail*. 2018;20:228-239.
24. Ferreira JP, Rossignol P, Machu JL, Sharma A, Girerd N, Anker SD, Cleland JG, Dickstein K, Filippatos G, Hillege HL, Lang CC, Ter Maaten JM, Metra M, Ng L, Ponikowski P, Samani NJ, van Veldhuisen DJ, Zwinderman AH, Voors A and Zannad F. Mineralocorticoid receptor antagonist pattern of use in heart failure with reduced ejection fraction: findings from BIOSTAT-CHF. *European journal of heart failure*. 2017;19:1284-1293.
25. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ and Pitt B. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med*. 2011;364:11-21.
26. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J and Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709-17.
27. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force M and Document R. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the

European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2016;18:891-975.

28. GC F and Gregg C. Fonarow MWTA, MD; Nancy M. Albert, RN, PhD; Wendy Gattis Stough, PharmD; Mihai Gheorghiade, MD; Barry H. Greenberg, MD; Christopher M. O'Connor, MD; Karen Pieper, MS; Jie Lena Sun, MS; Clyde W. Yancy, MD; James B. Young, MD. Factors Identified as Precipitating Hospital Admissions for Heart Failure and Clinical Outcomes; Findings From OPTIMIZE-HF. *Arch Intern Med*. 2008;168:847-854.

29. Kapoor JR, Kapoor R, Ju C, Heidenreich PA, Eapen ZJ, Hernandez AF, Butler J, Yancy CW and Fonarow GC. Precipitating Clinical Factors, Heart Failure Characterization, and Outcomes in Patients Hospitalized With Heart Failure With Reduced, Borderline, and Preserved Ejection Fraction. *JACC Heart Fail*. 2016;4:464-72.

30. Cioffi G, Mortara A, Di Lenarda A, Oliva F, Lucci D, Senni M, Cacciatore G, Chinaglia A, Tarantini L, Metra M, Maggioni AP and Tavazzi L. Clinical features, and in-hospital and 1-year mortalities of patients with acute heart failure and severe renal dysfunction. Data from the Italian Registry IN-HF Outcome. *Int J Cardiol*. 2013;168:3691-7.

31. Kang J, Park JJ, Cho YJ, Oh IY, Park HA, Lee SE, Kim MS, Cho HJ, Lee HY, Choi JO, Hwang KK, Kim KH, Yoo BS, Kang SM, Baek SH, Jeon ES, Kim JJ, Cho MC, Chae SC, Oh BH and Choi DJ. Predictors and Prognostic Value of Worsening Renal Function During Admission in HFpEF Versus HFrEF: Data From the KorAHF (Korean Acute Heart Failure) Registry. *J Am Heart Assoc*. 2018;7.

32. Chioncel O, Mebazaa A, Harjola VP, Coats AJ, Piepoli MF, Crespo-Leiro MG, Laroche C, Seferovic PM, Anker SD, Ferrari R, Ruschitzka F, Lopez-Fernandez S, Miani D, Filippatos G and Maggioni AP. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. *European journal of heart failure*. 2017;19:1242-1254.

33. Shoaib A, Farag M, Nolan J, Rigby A, Patwala A, Rashid M, Kwok CS, Perveen R, Clark AL, Komajda M and Cleland JGF. Mode of presentation and mortality amongst patients hospitalized with heart failure? A report from the First Euro Heart Failure Survey. *Clin Res Cardiol*. 2018.

34. Grigioni F, Avierinos JF, Ling LH, Scott CG, Bailey KR, Tajik AJ, Frye RL and Enriquez-Sarano M. Atrial fibrillation complicating the course of degenerative mitral regurgitation: determinants and long-term outcome. *J Am Coll Cardiol*. 2002;40:84-92.

35. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, Young JB and Tang WH. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol*. 2009;53:589-96.

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 ²	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
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	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Dilated cardiomyopathy	(reference)		(reference)	
Ischemic HF	1.76 (1.48 - 2.10)	<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
Valvular HF	1.85 (1.43 - 2.40)	<0.001	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

All-cause death	Unadjusted		Adjusted for BIOSTAT-CHF risk model	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Dilated cardiomyopathy	(reference)		(reference)	
Ischemic HF	1.72 (1.38 - 2.14)	<0.001	1.05 (0.84 - 1.32)	0.66
Hypertensive HF	1.43 (1.04 - 1.95)	0.03	1.26 (0.92 - 1.73)	0.15
Valvular HF	1.58 (1.13 - 2.21)	0.01	1.12 (0.80 - 1.56)	0.52
Other/Unknown	1.34 (1.01 - 1.78)	0.04	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	
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	0.95
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	
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	
	Unadjusted		Adjusted for BIOSTAT-CHF risk model		Adjusted for BIOSTAT-CHF risk model plus Ischemic etiology		P-value for interaction with HF etiologies
All-cause death	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	0.67
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	
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	

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	
Overall	933	345	1.19 (1.05 - 1.34)		193	103	1.44 (1.09 - 1.91)		
ACEi/ARB $\geq 50\%$ of target dose	Unsuccessful	416	184	1.23 (1.05 - 1.45)	0.76	128	69	1.56 (1.11 - 2.18)	0.98
	Successful	517	161	1.12 (0.93 - 1.37)		65	34	1.13 (0.67 - 1.88)	
BB $\geq 50\%$ of target dose	Unsuccessful	582	222	1.14 (0.98 - 1.33)	0.29	125	63	1.37 (0.98 - 1.93)	0.17
	Successful	351	123	1.28 (1.03 - 1.60)		68	40	1.88 (1.11 - 3.19)	
ACEi/ARB or BB $\geq 50\%$ of target dose	Unsuccessful	294	129	1.29 (1.01 - 1.66)	0.97	88	43	0.99 (0.71 - 1.40)	0.37
	Successful	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

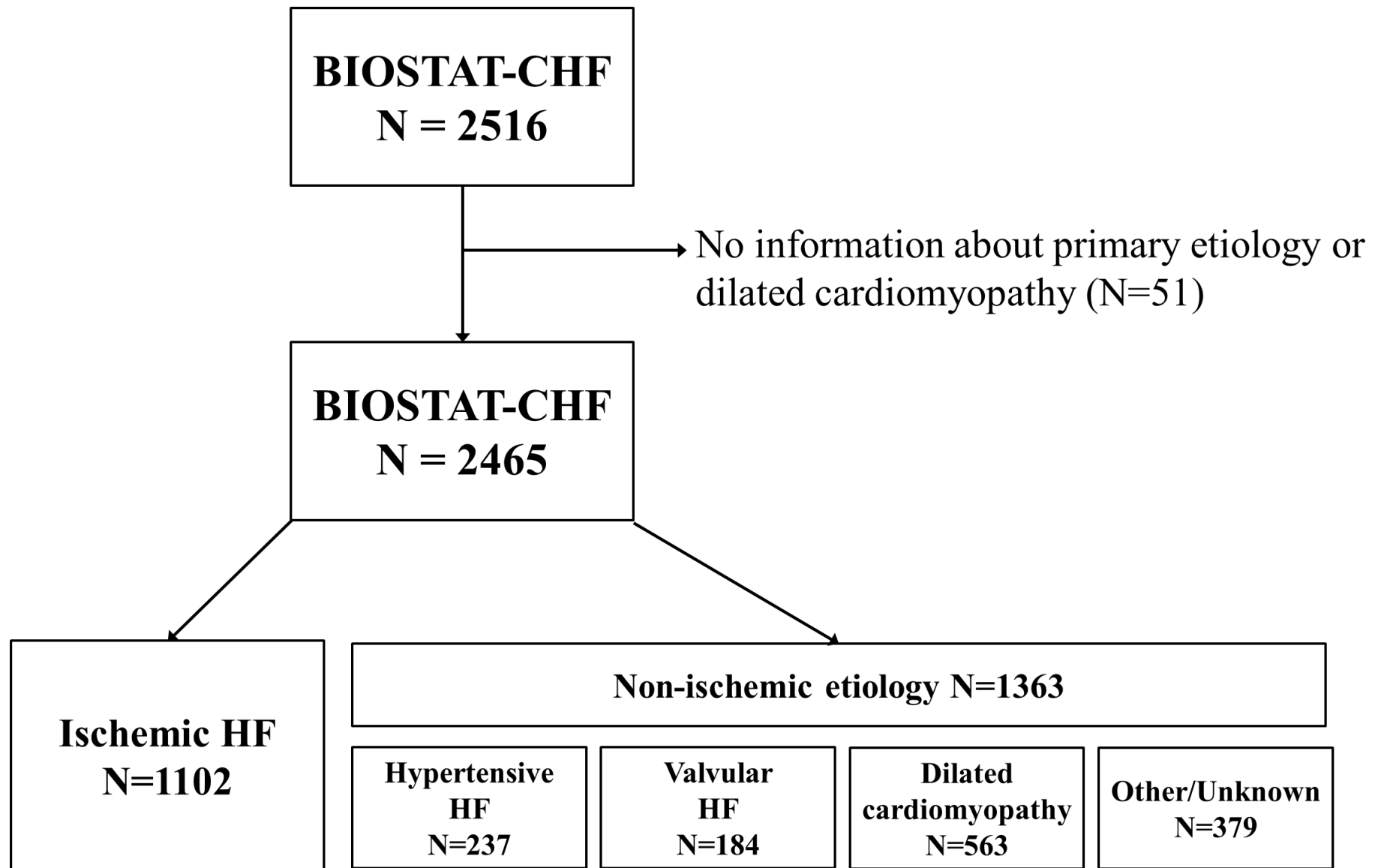
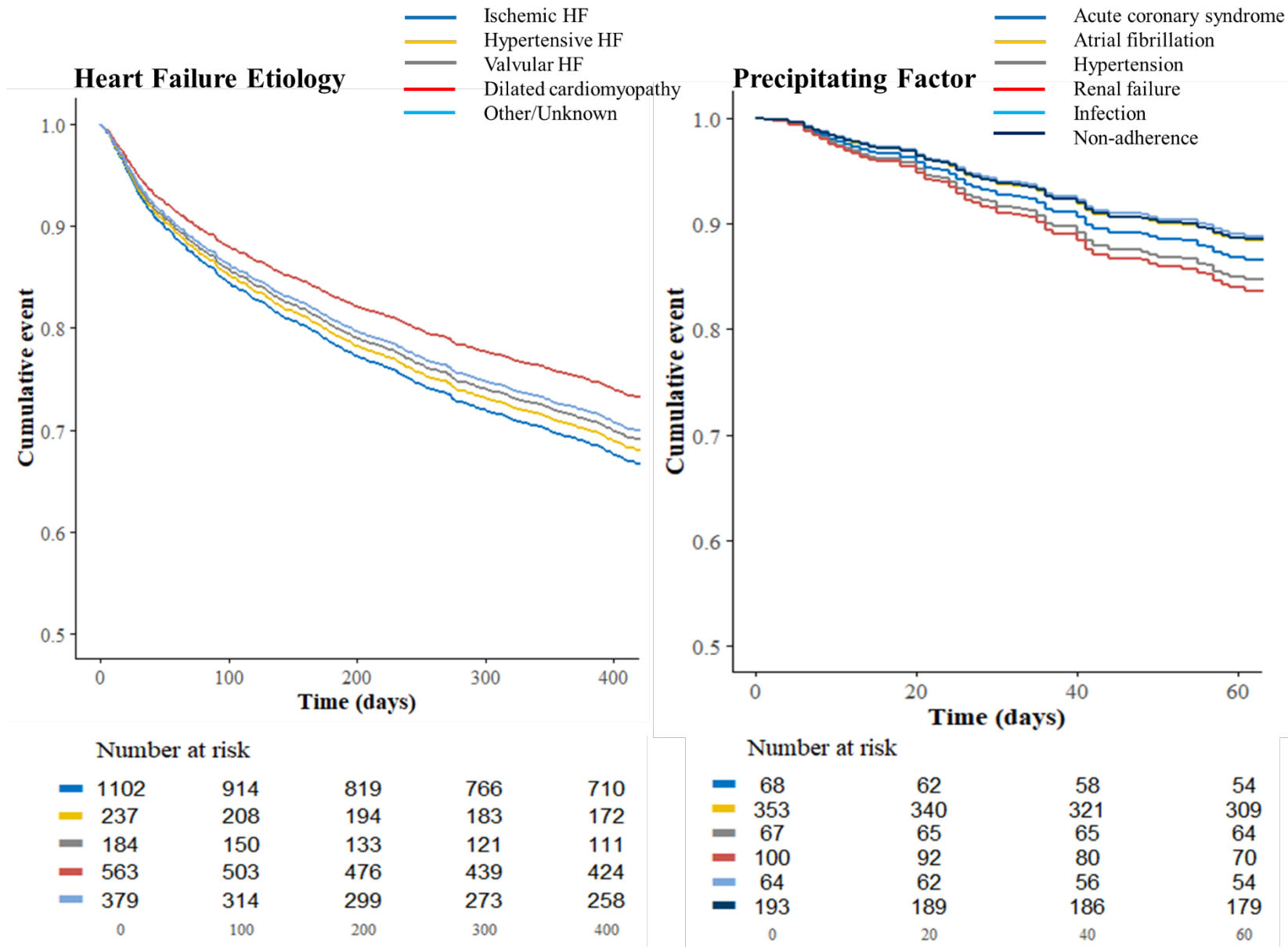


Figure 2. BIOSTAT-CHF risk model-adjusted Survival Curves for the Primary Outcome according to the Heart Failure Etiologies and Precipitating Factors



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
---	-------------------------------	--------------------------------

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/m ²	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 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	
Dilated cardiomyopathy	(reference)		
Ischemic HF	1.34 (1.12 – 1.60)	0.001	
Hypertensive HF	1.26 (0.98 – 1.62)	0.07	0.30
Valvular HF	1.21 (0.93 – 1.57)	0.16	
Other/Unknown	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	
Dilated cardiomyopathy	(reference)		
Ischemic HF	1.06 (0.85 – 1.33)	0.62	
Hypertensive HF	1.26 (0.92 – 1.73)	0.14	0.46
Valvular HF	1.12 (0.80 – 1.56)	0.54	
Other/Unknown	1.15 (0.87 – 1.52)	0.33	

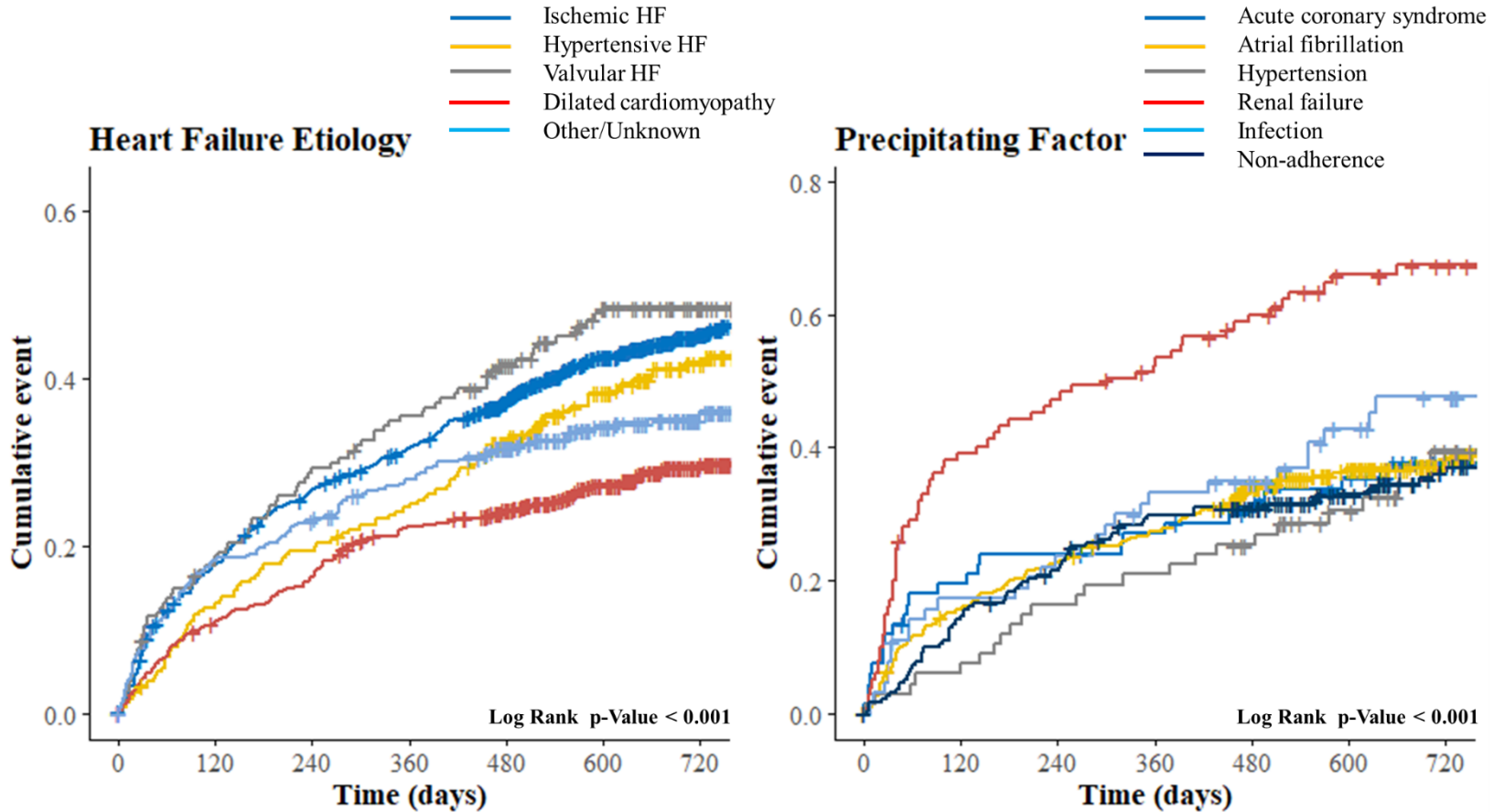
Supplementary table 4. Cox Proportional Hazard Models of the Heart Failure Etiologies for the Primary Outcome in Ambulant and Hospitalized Patients

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

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



Number at risk

■	1102	896	797	734	619	449	303
■	237	205	190	177	150	115	82
■	184	147	128	115	95	71	49
■	563	495	466	426	391	308	217
■	379	308	290	266	236	182	132
	0	120	240	360	480	600	720

Number at risk

■	68	53	50	47	43	34	22
■	353	293	269	251	212	163	117
■	67	62	56	53	46	35	25
■	100	60	52	45	36	26	21
■	64	52	48	41	37	26	21
■	193	164	149	130	119	89	65
	0	120	240	360	480	600	720

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

