Heart failure in the outpatient versus inpatient setting: findings from the BIOSTAT-CHF study

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Abstract

Introduction: Patients with symptomatic heart failure (HF) require additive therapies and have a poor prognosis. However, patient characteristics and clinical outcome between HF patients treated in the outpatient setting versus those who are hospitalized remain scarce.

Methods: The BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) included 2,516 patients with symptom and/or signs of HF: 1,694 as inpatients and 822 as outpatients.

Results: Compared to ambulatory HF patients, inpatients had higher heart rate, urea, NT-proBNP, lower blood pressure, lower eGFR, sodium, potassium, HDL-cholesterol, had more often peripheral edema, diabetes, anemia, and were less often treated with beta-blockers and ACEi. Outpatients had a more frequent history of HF hospitalization and received more frequently beta-blockers and/or ACEi/ARBs up-titrated to target doses ($p<0.001$). Inpatients had higher rates of the primary outcome of death or HF hospitalization: incidence-rate per 100 person-years=33.4 (31.1-35.9) for inpatients vs. 18.5 (16.4-21.0) for outpatients; adjusted HR (95%CI)=1.24 (1.07-1.43). Subdividing patients into low, intermediate and high-risk categories, the primary outcome event-rates were=14.3 (12.3-16.7), 36.6 (32.2-41.5), and 71.3 (64.4-79.0) for inpatients vs. 8.4 (6.6-10.6), 29.8 (24.5-36.2), and 43.3 (34.7-54.0) for outpatients, respectively. These findings were externally replicated.

Conclusions: Marked differences were observed between inpatients and outpatients with HF. Overall, inpatients were sicker and had higher event-rates. However, a substantial proportion of outpatients had similar or higher event-rates compared to inpatients. These findings suggest that HF outpatients also have poor prognosis and may be the focus of future trials.

Key-words: heart failure; trials; entry criteria; risk levels.

Introduction

Heart failure (HF) is one of the diseases with the greatest healthcare expenditure[1]. The most important reason for this huge healthcare burden is recurrent unplanned HF hospitalization[1, 2]. Therefore, outpatient visits are becoming more frequently used to treat HF symptoms and optimize medical treatment, including alteration of diuretic doses and initiation/up-titration of neurohormonal antagonists, with an effective impact in reducing HF hospitalizations[3].

Patients hospitalized for HF have poorer prognosis compared with lower-risk, ambulatory patients[4]. However, retrospective and post-hoc data derived from clinical trials suggest that patients managed for HF symptoms in the outpatient setting may have similarly adverse prognosis compared to those managed as inpatients[5, 6].

The BIOlogy Study to TAilored Treatment in Chronic Heart Failure (BIOSTAT-CHF) was a multicentre, multinational, European registry enrolling patients with HF and suboptimal medical treatment, either hospitalized or as outpatients[7]. It therefore allows the assessment of the clinical and prognostic differences of HF patients whether they have been hospitalized or not. Moreover, the identification of outpatients with a similar event risk as inpatients, would facilitate the selection of a wider population for future studies and randomized controlled trials (RCTs) without reducing the estimated event-rate and consequently not compromising the statistical power for assessing a potential treatment effect[8].

The aims of the present analysis are to: 1) compare the characteristics of patients enrolled as inpatients to those enrolled as outpatients; 2) to use the BIOSTAT-CHF risk score[9] to assess the event-risk of both inpatients and outpatients; and 3) to compare inpatients and outpatients according to the individual-patients` risk.

Methods

Patient population and risk model development

BIOSTAT-CHF is a European project that enrolled 2,516 HF patients from 69 centres in 11 European countries to determine profiles of patients with HF that do not respond to recommended therapies, despite anticipated up-titration. The design and first results of the study and patients have been described elsewhere[7]. In brief, patients were aged ≥18 years with signs and symptoms of HF, confirmed either by a left ventricular ejection fraction (LVEF) of ≤40% or a BNP and/or NT-proBNP plasma levels >400 pg/mL and/or >2000 pg/mL, respectively. Patients needed to be treated with either oral or intravenous furosemide ≥40 mg/day or equivalent at the time of inclusion. Patients should not have been previously treated with evidence-based therapies (ACEi/ARBs and beta-blockers) or were receiving <50% of the target doses of at least one of these drugs at the time of inclusion[10, 11]. The first three months of treatment were considered to be the optimization phase after which a stabilization phase of 6 months was defined. During the optimization phase, initiation or up-titration of ACEi/ARB

and/or β-blocker was performed according to the routine clinical practice of the treating physicians, who were encouraged to follow the ESC guidelines at the time of treatment[10, 11]. Patients reaching at least 50% of the recommended dose of ACEi/ARB and/or β-blocker were considered successfully up-titrated.

The recruitment period was 24 months, starting from December 2010. The last patient was included on December 15, 2012.

The median follow-up was 21 months.

The primary outcome was a composite of HF hospitalization and all-cause death. The components of the primary outcome were also assessed separately as exploratory outcomes. The adjudication of HF hospitalization was performed by the treating physician. After the trial has ended all medical reports of the deadly event were read and adjudicated by an independent committee of cardiologists and cardiovascular death was also possible to ascertain.

Ethics Board approval was obtained and all participants signed written informed consent before entering the study.

The BIOSTAT-CHF risk models have been previously developed and validated[9].

Validation cohort

The findings presented herein were also externally validated. The BIOSTAT-CHF validation cohort was designed as a multicentre, prospective, observational study. The study population consisted of 1,738 patients from six centres in Scotland, UK. The recruitment period started in October 2010 and was completed in April 2014. Median follow-up was 21 months. Patients from the validation cohort were aged >18 years with a HF diagnosis based on echocardiographic evidence of left ventricular (LV) dysfunction or a previous documented admission with HF treated with furosemide ≥20 mg/day or equivalent, not previously treated or receiving ≤50% of target doses of ACE inhibitors/ARBs and/or beta-blockers according to the 2008 European Society of Cardiology guidelines. Patients could be enrolled as inpatients or from outpatient clinics[7].

Statistical analysis

Population description and comparison of outpatients vs. inpatients was performed using t-test, Mann-Whitney or chi-square test, as appropriate.

Cox proportional hazard regression models were used to model long-term event rate of the variables included in the previously published BIOSTAT-CHF risk models[9]. Proportional hazard assumption was verified graphically using "log-log" plots. Log-linearity was checked by testing the functional forms of the covariable by the Kolmogorov-type supremum test and by visual inspection by plotting the beta estimates versus the mean across quintiles. Missing predictor values were imputed using multichain Monte Carlo methods with Gibbs sampling[9]. We imputed missing data five times, performed the analysis over all five imputations and averaged results using Rubin's rules[12].

An integer-point risk score was created to assess each patients` individual risk and allow the comparison of outpatients to inpatients according to their probability of future events. In order to create a simple integer risk score, continuous variables included in the chosen model, were categorized into either two or three groups using a combination of established clinical cut-points and graphical examination of rates across quintiles. To simplify the risk score, integer points were assigned to each prognostic factor based upon the log-hazard ratio estimates. The total risk score for each patient was calculated by summing the points across all chosen prognostic variables. From the overall distribution of the risk score we formed three categories (tertiles) of risk, containing approximately equal number of events. Within each risk category we calculated the number of events, person-years at risk, and the overall event rate. Kaplan–Meier plots were drawn showing the cumulative incidence curves of outpatients vs. inpatients and risk category.

The covariates used for adjustment when comparing the hazard ratio of inpatients vs. outpatients were chosen from demographic (age and gender), clinical (previous HF hospitalization, use of beta-blockers and systolic blood pressure), and laboratory (NT-proBNP, blood urea nitrogen, hemoglobin, HDL-cholesterol, estimated glomerular filtration rate [eGFR] by the CKD-EPI formula[13, 14], and sodium). All these parameters were previously found to be independently associated with the outcomes in the BIOSTAT-CHF cohort and were the parameters used to build the risk models depicted herein (URL: https://biostat-chf.shinyapps.io/calc/)[9]. The BIOSTAT-CHF risk models were externally validated and showed good internal calibration and consistency across levels of risk and geographical regions[9].

Hospitalization for HF was analyzed using a competing risk model (accounting for death as competing risk), as described by Fine and Gray[15].

All the analyses were performed using STATA (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). A p-value <0.05 was considered as statistically significant.

Results

Characteristics of the study population

A total of 2,516 patients were analyzed, 822 as outpatients and 1,694 as inpatients. The mean age was ≈68 years and >70% were male. Compared to HF outpatients, in-hospital enrolled patients had higher heart rate, urea, NT-pro BNP, lower blood pressure, lower eGFR, sodium, potassium, HDL cholesterol, had more often peripheral edema, rales, orthopnea, elevated jugular venous pressure, NYHA class III or IV, new-onset HF admission, diabetes, anemia, and were less often treated with beta-blockers and ACE inhibitors (**Table 1**). Age and LVEF was similar between groups and outpatients had been more often hospitalized for HF in the previous year and had beta-blockers and/or ACEi/ARBs up-titrated more often (**Table 1**).

Outcome associations

Compared to HF outpatients, inpatients had higher rates of primary outcome events: adjusted HR (95%CI) =1.24 (1.07-1.43) and HF hospitalization events =1.38 (1.14-1.66), but not mortality =1.11 (0.92-1.34). **Table 2**. The Kaplan-Meier curves for the primary outcomes are shown in **Figure 1**.

Outpatients had 247 (30%) primary outcome events, 152 (18%) HF hospitalization events, and 155 (19%) deaths, with corresponding incidence rates per 100 person-years =18.5 (16.4-21.0), 11.4 (9.7-13.3), and 10.4 (9.0-12.3). Inpatients had 767 (45%) primary outcome events, 456 (27%) HF hospitalization events, and 502 (27%) deaths, with corresponding incidence rates per 100 person-years =33.4 (31.1-35.9), 19.8 (18.1-21.7), and 18.1 (16.6-19.8).

Risk model

The integer score derived from the BIOSTAT-CHF risk model provided a maximum of 15 points (**Table 3**). Dividing the risk score in tertiles we classified patients as: from 0 to 4 points =low risk (n=1,058); 5 to 7 points =intermediate risk (n=746); 8 to 15 points =high risk (n=712).

Incidence rates by risk categories

The primary outcome incidence rates per 100 person-years according to the risk categories were: low-risk =11.8 (10.4-13.4), intermediate risk =34.3 (30.8-38.1), and high risk =64.0 (58.3-70.2). **Table 4**.

The distribution of patients and events by categories of risk is depicted in **Table 4**. For outpatients, 437 (53%) were in the low risk, 233 (28%) in the intermediate risk, and 152 (19%) in the high-risk category. The corresponding n. (%) of primary outcome events by category of risk was 68 (16%), 100 (43%), and 79 (52%), respectively. For inpatients, 621 (37%) were in the low risk, 513 (30%) in the intermediate risk, and 560 (33%) in the high-risk category. The corresponding n. (%) of primary outcome events by category of risk was 162 (26%), 238 (46%), and 367 (66%), respectively.

Outpatients had primary outcome incidence rates of 8.4 (6.6-10.6), 29.8 (24.5-36.2), and 43.3 (34.7-54.0) for low, intermediate, and high-risk categories, respectively. Inpatients had primary outcome incidence rates of 14.3 (12.3-16.7), 36.6 (32.2-41.5), and 71.3 (64.4-79.0) for low, intermediate, and high-risk categories, respectively. **Table 4** & **Figure 2**. Incidence rates for the individual components of the primary outcome are depicted in **Table 4**. Outpatients in the intermediate and high-risk categories had similar event rates compared to inpatients overall. **Figure 3**.

External validation

Similar findings were found in the validation cohort. Outpatients in the intermediate and high-risk categories had similar primary outcome (HF hospitalization or death) event rates compared low-risk and intermediate-risk categories inpatients, respectively. **Supplemental Material Tables 1 to 3**.

Cardiovascular mortality

Cardiovascular mortality (CVM) represented 67% (441/657) of all deaths. The associations for CVM were similar to those above described for all-cause mortality. **Supplemental Tables 4 & 5**. The associations for the outcome of CVM or HF hospitalization were similar to those above described for the primary outcome (data not shown).

Discussion

The present study shows that HF inpatients were different from outpatients. Inpatients had more co-morbidities and higher overall event rates. However, outpatients classified as having intermediate and/or high risk had similar event-rates compared to inpatients overall population. Nevertheless, it should be noted that more than half (53%) of outpatients were classified as "low-risk" with corresponding low event rates that may not be suitable for a HF trial. In addition, the outcome difference between outpatients and inpatients was mainly observed due to differences in hospitalization rates. These data demonstrate that HF outpatients are patients at high risk of major events and should also be considered to be included in trials, as they may present similar risk to inpatients. Moreover, symptomatic HF in the outpatient setting could also be considered for incorporation in the composite primary outcome of contemporary trials, providing more detailed events (*e.g.*, IV diuretic administration and/or need for increasing oral diuretics) are available for adjudication. Moreover, the simple integer score generated in the present analysis provides a "ready-to-use" tool for enhancing patients` risk in future HF studies, particularly for outpatient selection – selecting intermediate to high-risk outpatients based on our risk score allows the selection of a HF population with similar event-rates compared to hospitalized patients. These findings were replicated externally. To the best of our knowledge this is the first study to compare outpatients vs. inpatients by levels of individual risk.

Many patients with symptomatic HF have a gradual evolution of congestive signs and symptoms, offering a potential window in which effective therapy may abort continued worsening and prevent the need for hospitalization[16]. Additionally, the so-called "home time" (i.e., time alive and out of a health care institution) is an important patient-centered outcome[17]. Hence, more focus should be provided to HF outpatients (e.g., in "IV diuretic clinics") as interventions in this setting may avoid downstream hospitalizations[16]. Outpatients may also be more suitable for medication up-titration as they may be less symptomatic and present less co-morbid conditions[16]. This assumption was corroborated in the present analysis in which HF outpatients had less co-morbidities and were more often up-titrated to target doses for both beta-blockers and ACEi/ARBs. Outpatients were admitted less frequently as "new-onset" HF. This is likely due to the fact that only patients with known HF history are referenced for HF clinics. It should be noted that patients with "new-onset" HF likely have improved survival compared to patients with chronic HF diagnoses[18], however the higher proportion of "new-onset" HF patients in the inpatient group did not reduce the overall risk of this population nor this variable was retained in the "best" risk model.

The event-rates observed in the BIOSTAT-CHF study (including the validation cohort) were superior to those observed in contemporary chronic HF RCTs but overlapped those observed in acute HF trials and registries[19-22]. For example, the event-rates per 100 person-years observed in the PARADIGM-HF (Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure) trial[19] for the primary outcome of HF hospitalization or cardiovascular death varied from 9 to 15 events per 100

person-years (depending on the geographic region[23]) which were lower than those that we observed in BIOSTAT-HF for outpatients (16 to 21 events per 100 person-years) and nearly half of the event-rates observed for inpatients (31 to 36 events per 100 person-years). However, we must consider the different inclusion criteria of the two studies, chronic stable HF in PARADIGM-HF versus symptomatic and under-treated HF in BIOSTAT-CHF, and that cardiovascular, rather than all-cause, mortality was assessed as a component of the primary endpoint in PARADIGM-HF. Comparable event-rates were only observed in the lower risk category of the BIOSTAT-CHF (10 to 13 events per 100 person-years). The event rates observed in the Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms (EMPHASIS-HF) trial[24] were also much lower compared to those observed in the BIOSTAT-CHF, with only the high-risk patients in the placebo group in the EMPHASIS-HF having similar event rates (for the primary outcome of cardiovascular death or HF hospitalization) to those observed in inpatients from BIOSTAT (~39 per 100 person-years)[25]. These findings suggest that patients with HF enrolled in the BIOSTAT-CHF were more severe than those enrolled in contemporary chronic HF trials. However, HF symptoms were not needed at the time of enrolment in these trials, and patients were younger, less symptomatic and with less co-morbidities than those enrolled in the BIOSTAT-CHF[19, 24]. The proportion of events observed in the EVEREST (Effects of Oral Tolvaptan in Patients Hospitalized for Worsening Heart Failure) trial in a median follow-up of 10 months, overlapped that observed in BIOSTAT-CHF. The EVEREST trial (tolvaptan vs. placebo) was "neutral", and 41% of patients experienced cardiovascular death or HF hospitalization and 26% died from any cause[21]. This proportion of events is similar to that observed in the intermediate risk of the BIOSTAT-CHF population, both for inpatients and outpatients. In the ASTRONAUT (Effect of Aliskiren on Postdischarge Mortality and Heart Failure Readmissions Among Patients Hospitalized for Heart Failure) trial, during a median follow-up of 11 months there were no statistically significant differences between aliskiren and placebo in events, and 25% of patients died from cardiovascular causes or were hospitalized for HF and 18% died from any cause[22]. The proportion of events in the ASTRONAUT trial are more similar to those observed in the low risk category for inpatients and intermediate risk for outpatients. Regarding "acute" HF registries, the event-rates observed in patients with decompensated HF in the ESC-HF-LT (European Society of Cardiology Heart Failure Long-Term Registry) overlapped those observed herein. These findings suggest that the BIOSTAT-CHF population resembles much more an "acute" rather than "chronic" HF population[20]. These findings suggest that outpatients with HF signs and symptoms plus elevated NPs are also a "high-risk" population[6].

As stated in the protocol, dose up-titration to target doses of evidence-based therapies was always recommended. However, only 53% and 40% of the patients reached ≥50% of the target doses of ACEi/ARB and BB, respectively. Not reaching ≥50% of the target dose of ACEi/ARB or BB was associated with worse outcomes (compared with patients who reached >50% of the target dose)[26]. MRAs remained extensively underused throughout the study[27].

In the present analysis we also found that the higher event-rates observed in inpatients was mostly due to the burden of HF hospitalization (with similar rates for outpatients in intermediate/high risk categories). Hence, reducing HF symptoms and the burden of hospitalizations is an important target of any HF intervention or therapy[19, 24, 28]. However, this also shows that HF hospitalization and mortality may be dissociated in the clinical course of the HF patients and that the variables related with HF hospitalization may differ from those related with mortality[29]. In the present study cardiovascular mortality represented 67% of all deaths, and the associations described for all-cause death are similar to those observed for cardiovascular mortality.

Risk enhancement strategies are used in HF trials and registries in order to increase the specificity for the presence of HF and the odds of subsequent events necessary to ascertain prognostic associations and/or treatment effect with adequate power and precision. Hence, many studies include only patients hospitalized for HF as these have higher risk for subsequent events[19, 30]. Moreover, NP thresholds are increasingly used with both purposes of increasing HF specificity and risk[19, 28, 29]. In the present study we demonstrate that a high proportion of outpatients have similar risk as inpatients. Due to the high event rate in these outpatients with HF, they might also be a target for better future therapies. In this regard, the present study provides a useful tool for "risk-enhancement" in futures HF studies and trials.

Limitations

Several limitations should be acknowledged in this analysis. First, this is a post-hoc analysis of a prospective non-randomized observational study, therefore all limitations inherent to such analysis are applied herein, including the inability to infer causality. Second, the data from the BIOSTAT-CHF come from European centres only and may not be representative of HF patients in other world regions. Third, all patients enrolled in the BIOSTAT-CHF had severe symptoms and high NP levels, hence these findings cannot be generalized to less symptomatic HF patients. Fourth, the proportion of patients (especially outpatients) with LVEF >40% was very low (4 to 12 %) and these results cannot be generalised to patients with "mid-range or preserved" ejection fraction. Lastly, IV diuretic use was not registered in the outpatient setting, hence we cannot ascertain how many of these patients could be considered as "true" worsening HF.

Conclusions

Marked differences were observed between inpatients and outpatients with HF. Overall, inpatients were sicker and had higher event-rates. However, a substantial proportion of outpatients had similar or higher event-rates compared to inpatients. These findings suggest that HF outpatients, usually not enrolled in HF trials nor considered as endpoints, also have poor prognosis and may be the focus of future trials.

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Disclosures

None.

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Table 1. Baseline characteristics of the study population

Patients` characteristics	Outpatient	Inpatient	P-value
n=2,516	n=822	n=1,694	
Age, yr	68.1 ± 11.3	68.5 ± 12.3	0.45
Male, n (%)	629 (77 %)	1217 (72 %)	0.013
BMI, Kg/m^2	27.8 ± 5.1	27.9 ± 5.7	0.62
Heart rate, bpm	75.3 ± 16.0	85.7 ± 22.8	<0.001
SBP, mmHg	127.3 ± 19.9	123.5 ± 22.7	<0.001
Ischemic HF, n (%)	397 (48 %)	706 (42 %)	0.002
HFH in the last year, n (%)	332 (40 %)	462 (27 %)	<0.001
Peripheral edema, n (%)	298 (36 %)	958 (57 %)	<0.001
Pulmonary congestion/Rales, n (%)	208 (26 %)	1,083 (65%)	<0.001
Elevated JVP, n (%)	119 (22 %)	435 (36 %)	<0.001
Orthopnea, n (%)	134 (16 %)	745 (44 %)	<0.001
NYHA class III or IV, n (%)	378 (46 %)	1,144 (70 %)	<0.001
LVEF, %	30.5 ± 8.6	31.3 ± 11.5	0.063
LVEF >40%, n (%)	33 (4 %)	202 (12 %)	<0.001
Worsening HF admission, n (%)	422 (51 %)	950 (56 %)	
New-onset HF admission, n (%)	78 (10 %)	624 (37 %)	<0.001
Non-documented/Other, n (%)	322 (39 %)	120 (7 %)	
Atrial fibrillation, n (%)	359 (44 %)	784 (46 %)	0.22
Diabetes, n (%)	236 (29 %)	583 (34 %)	0.004
COPD, n (%)	132 (16 %)	304 (18 %)	0.24
Anemia, n (%)	182 (22 %)	681 (40 %)	<0.001
Urea, mmol/L	13.0 ± 6.2	15.8 ± 12.2	<0.001
eGFR, $ml/min/1.73m^2$	67.5 ± 22.8	59.9 ± 23.0	<0.001
Sodium, mmol/L	139.7 ± 3.1	138.8 ± 4.1	<0.001
Potassium, mmol/L	4.4 ± 0.5	4.2 ± 0.6	<0.001
HDL, mmol/L	1.2 ± 0.4	1.1 ± 0.4	<0.001
NT-pro BNP, pg/mL	2,904 (1,490-5,078)	5,000 (2,689-9,577)	<0.001
No beta-blocker, n (%)	85 (10 %)	338 (20 %)	<0.001
No ACEi/ARB	172 (21 %)	524 (31 %)	<0.001
No MRA, n (%)	396 (48 %)	781 (46 %)	0.33
Up-titration* (n=2139)	n=769	n=1370	
ACEi/ARB, n (%)	488 (63%)	682 (50%)	<0.001
Beta-blocker, n (%)	337 (44 %)	440 (32 %)	<0.001
ACEi/ARB or beta-blocker, n (%)	586 (76 %)	859 (63%)	<0.001

Legend: BMI, body mass index; SBP, systolic blood pressure; JVP, jugular venous pressure; HFH, heart failure hospitalization; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; HDH, high-density lipoprotein cholesterol; NT-pro BNP, N-terminal pro brain natriuretic peptide; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist.

*Up-titration period occurred during the first 3 months after inclusion in the study, hence patients who died or that were lost to follow-up were excluded from the up-titration analysis (see methods section).

Table 2. Hazard ratios, incidence rates and respective 95% confidence intervals for the study outcomes

Inpatient vs. Outpatient	Crude HR (95%CI)	P-value	Adjusted HR (95%CI)*	P-value
HFH or death	1.74 (1.51-2.01)	<0.001	1.24 (1.07-1.43)	0.005
Death	1.72 (1.43-2.06)	<0.001	1.11 (0.92-1.34)	0.26
HFH	1.67 (1.39-2.01)	<0.001	1.38 (1.14-1.66)	0.001

*Adjusted on the BIOSTAT-CHF risk model including age, heart failure hospitalization in the previous year, peripheral edema, systolic blood pressure, estimated glomerular filtration rate, urea, NT-pro BNP, hemoglobin, HDL cholesterol, sodium, and beta-blocker use.

Table 3. Multivariate risk model

Final model	**HR (95%CI)**	**Coef.**	**P-value**	**Integer**
Age ≤65 yr	Reference	-	-	-
Age 65 to 75	1.09 (0.91-1.30)	0.09	0.35	-
Age >75	1.34 (1.12-1.60)	0.29	0.002	+1
HFH in the last year	1.44 (1.25-1.65)	0.36	<0.001	+1
Peripheral edema	1.31 (1.11-1.53)	0.26	0.001	+1
SBP ≤110 mmHg	1.28 (1.11-1.47)	0.25	0.001	+1
eGFR >60 ml/min/1.73m^2	Reference	-	-	-
eGFR 45 to 60	1.19 (0.99-1.42)	0.17	0.058	-
eGFR <45	1.37 (1.14-1.65)	0.32	0.001	+1
Urea <8 mmol/L	Reference	-	-	-
Urea 8 to 16	1.26 (1.04-1.54)	0.23	0.019	+1
Urea >16	1.50 (1.20-1.86)	0.40	<0.001	+1
NT-pro BNP 2000-3000 pg/mL	Reference	-	-	-
NT-pro BNP 3000-7000	2.04 (1.65-2.54)	0.71	<0.001	+2
NT-pro BNP >7000	2.86 (2.26-3.62)	1.05	<0.001	+3
Anemia	1.32 (1.15-1.52)	0.28	<0.001	+1
HDL <1 mmol/L	1.20 (1.03-1.40)	0.19	0.017	+1
Sodium <135 mmol/L	1.16 (0.97-1.38)	0.15	0.10	-
No beta-blocker at baseline	1.37 (1.16-1.61)	0.31	<0.001	+1

The presented model was built for the primary outcome of heart failure hospitalization or death*.
C-index=0.70

Legend: HFH, hospitalization for heart failure; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; NT-pro BNP, N-terminal pro brain natriuretic peptide; HDL, high-density cholesterol.

*The best risk model incorporates the same variables for all the studied outcomes (URL: https://biostat-chf.shinyapps.io/calc/).

Table 4. Event proportion and incidence rates per 100-person years of outpatients and inpatients by categories of the risk score and study outcomes

HFH or death	Total		Outpatients		Inpatients	
Risk category	n. pts/events (%)	Incidence-rate	n. pts/events (%)	Incidence-rate	n. pts/events (%)	Incidence-rate
Low (0-4)	1,058/230 (22 %)	11.8 (10.4-13.4)	437/68 (16 %)	8.4 (6.6-10.6)	621/162 (26 %)	14.3 (12.3-16.7)
Intermediate (5-6)	746/338 (45 %)	34.3 (30.8-38.1)	233/100 (43 %)	29.8 (24.5-36.2)	513/238 (46 %)	36.6 (32.2-41.5)
High (7-15)	712/446 (63 %)	64.0 (58.3-70.2)	152/79 (52 %)	43.3 (34.7-54.0)	560/367 (66 %)	71.3 (64.4-79.0)
Death	Total		Outpatients		Inpatients	
Risk category	n. pts/events (%)	Incidence-rate	n. pts/events (%)	Incidence-rate	n. pts/events (%)	Incidence-rate
Low (0-4)	1,058/131 (12 %)	6.3 (5.3-7.4)	437/44 (10 %)	5.2 (3.8-7.0)	621/87 (14 %)	7.0 (5.7-8.6)
Intermediate (5-6)	746/200 (27 %)	16.3 (14.2-18.7)	233/59 (25 %)	14.6 (11.3-18.9)	513/141 (27 %)	17.2 (14.5-20.2)
High (7-15)	712/326 (46 %)	35.1 (31.5-39.1)	152/52 (34 %)	23.2 (17.7-30.4)	560/274 (49 %)	38.9 (34.5-43.7)
HFH	Total		Outpatients		Inpatients	
Risk category	n. pts/events (%)	Incidence-rate	n. pts/events (%)	Incidence-rate	n. pts/events (%)	Incidence-rate
Low (0-4)	1,058/142 (13 %)	7.3 (6.2-8.6)	437/39 (9 %)	4.8 (3.5-6.6)	621/103 (17 %)	9.1 (7.5-11.1)
Intermediate (5-6)	746/213 (29 %)	21.5 (18.8-24.6)	233/63 (27 %)	18.7 (14.6-23.9)	513/150 (29 %)	23.0 (19.6-27.0)
High (7-15)	712/253 (36 %)	36.1 (31.9-40.8)	152/50 (33 %)	27.2 (20.6-35.9)	560/203 (36 %)	39.2 (34.1-45.0)

Legend: HFH, hospitalization for heart failure; n., number; pts, patients.

Figure 1. Kaplan-Meier failure estimates for the primary outcome of heart failure hospitalization or death

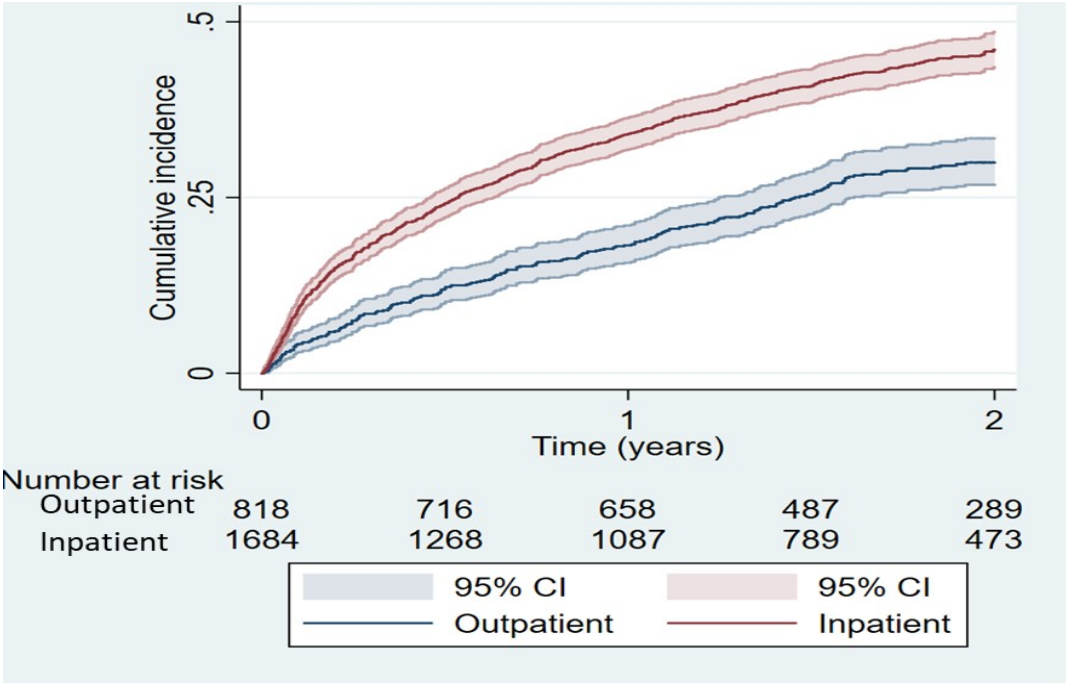


Figure 2. Incidence rates per 100 person-years for the primary outcome of heart failure hospitalization or death by tertiles of risk score

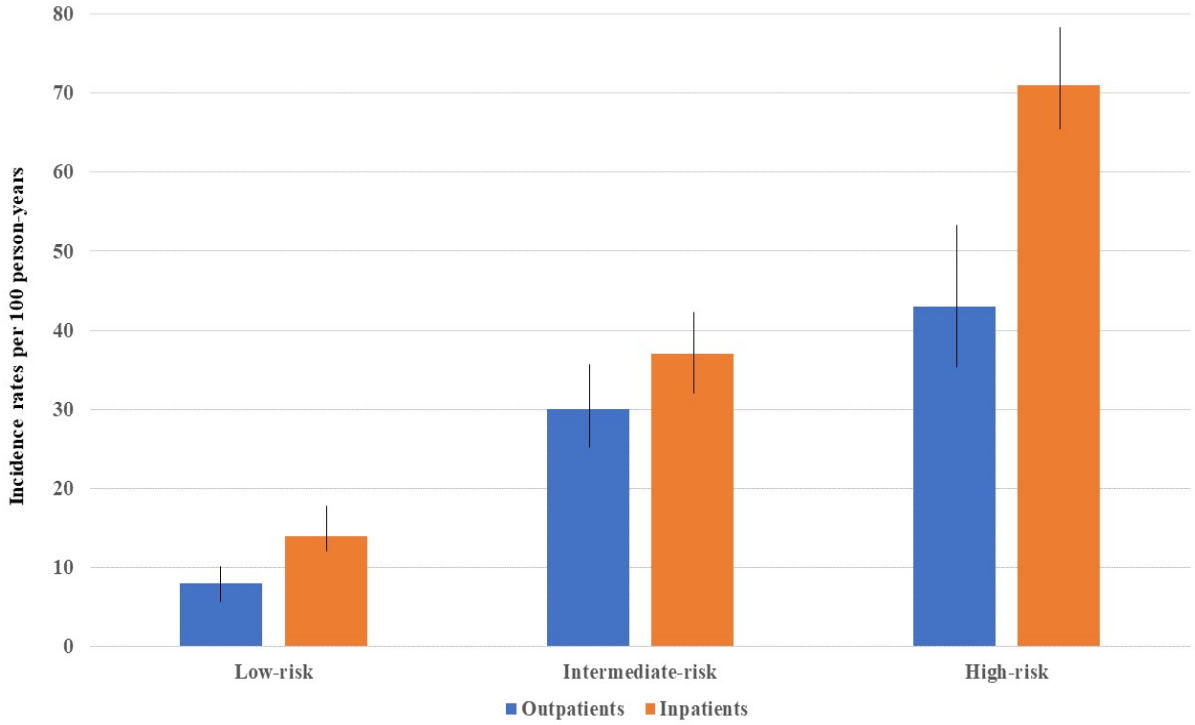
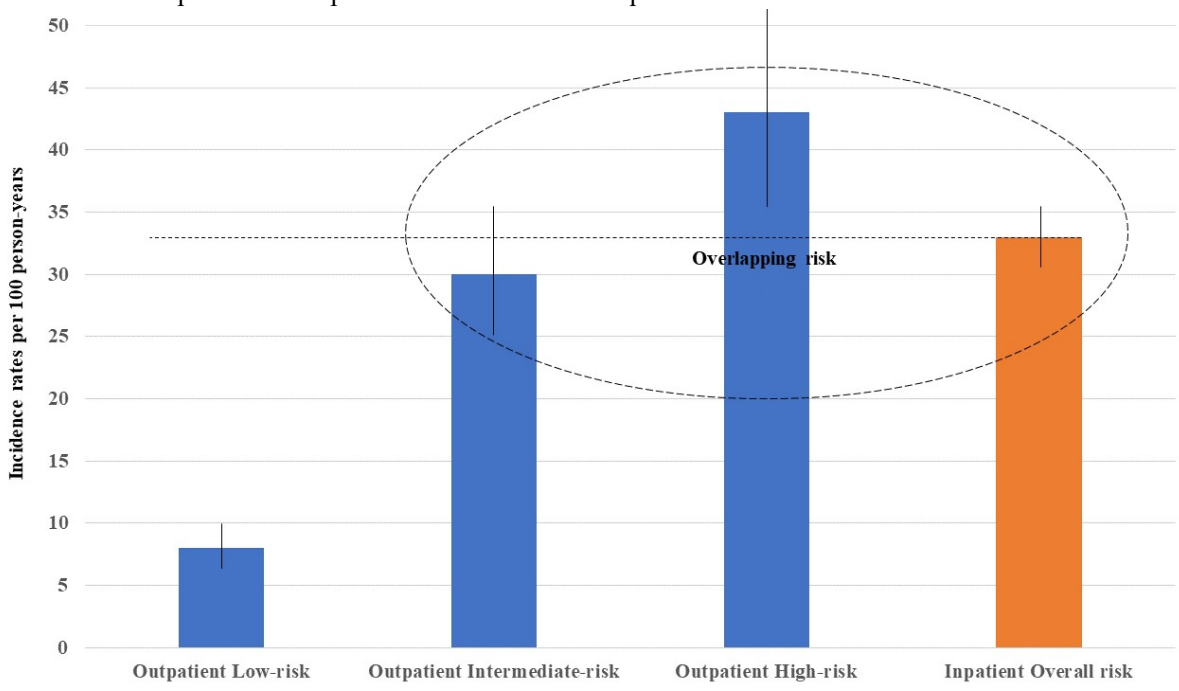


Figure 3. Incidence rates per 100 person-years for the primary outcome of heart failure hospitalization or death with comparison of outpatients` risk levels with inpatients overall risk



Supplemental Material

Supplemental Table 1. Validation cohort: multivariate risk model

Final model	**HR (95%CI)**	**Coef.**	**P-value**	**Integer**
Age ≤65 yr	Reference	-	-	-
Age 65 to 75	1.12 (0.89-1.40)	0.11	0.32	-
Age >75	1.30 (1.05-1.62)	0.27	0.018	+1
HFH in the last year	1.39 (1.20-1.62)	0.33	<0.001	+1
Peripheral edema	1.39 (1.19-1.63)	0.33	<0.001	+1
SBP ≤110 mmHg	1.23 (1.06-1.44)	0.21	0.008	+1
eGFR >60 ml/min/1.73m^2	Reference	-	-	-
eGFR 45 to 60	1.10 (0.88-1.38)	0.09	0.38	-
eGFR <45	1.04 (0.86-1.26)	0.04	0.66	+1
Urea <8 mmol/L	Reference	-	-	-
Urea 8 to 16	1.24 (1.04-1.49)	0.22	0.019	+1
Urea >16	1.44 (1.09-1.91)	0.37	0.011	+1
NT-pro BNP 2000-3000 pg/mL	Reference	-	-	-
NT-pro BNP 3000-7000	1.82 (1.53-2.18)	0.60	<0.001	+2
NT-pro BNP >7000	2.07 (1.68-2.56)	0.73	<0.001	+3
Anemia	1.30 (1.12-1.52)	0.27	0.001	+1
HDL <1 mmol/L	1.08 (0.94-1.25)	0.08	0.28	+1
Sodium <135 mmol/L	1.14 (0.90-1.43)	0.13	0.27	-
No beta-blocker at baseline	1.00 (0.86-1.18)	0.004	0.97	+1

Legend: HFH, hospitalization for heart failure; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; NT-pro BNP, N-terminal pro brain natriuretic peptide; HDL, high-density cholesterol.

*The best risk model incorporates the same variables for all the studied outcomes (URL: https://biostat-chf.shinyapps.io/calc/).

Supplemental Table 2. Validation cohort: hazard ratios, incidence rates and respective 95% confidence intervals for the study outcomes

Inpatient vs. Outpatient	Crude HR (95%CI)	P-value	Adjusted HR (95%CI)*	P-value
HFH or death	2.18 (1.89-2.51)	<0.001	1.36 (1.16-1.58)	<0.001
Death	2.33 (1.97-2.78)	<0.001	2.14 (1.80-2.55)	<0.001
HFH	1.76 (1.48-2.09)	<0.001	1.30 (1.08-1.57)	0.005

*Adjusted on the BIOSTAT-CHF risk model including age, heart failure hospitalization in the previous year, peripheral edema, systolic blood pressure, estimated glomerular filtration rate, urea, NT-pro BNP, hemoglobin, HDL cholesterol, sodium, and beta-blocker use.
C-statistic for risk score mortality/HF hospitalization =0.66; mortality only =0.71; HF hospitalization only 0.61

Supplemental Table 3. Validation cohort: event proportion and incidence rates per 100-person years of outpatients and inpatients by categories of the risk score and study outcomes

HFH or death	Total		Outpatients		Inpatients	
Risk category	n. pts/events (%)	Incidence-rate	n. pts/events (%)	Incidence-rate	n. pts/events (%)	Incidence-rate
Low (0-4)	848/285 (34 %)	13.4 (11.9-15.0)	522/156 (27 %)	10.5 (9.0-12.3)	326/129 (35 %)	19.9 (16.8-23.7)
Intermediate (4-6)	446/259 (58 %)	31.4 (27.8-35.5)	201/107 (50 %)	23.2 (19.2-28.0)	245/152 (57 %)	41.9 (35.8-49.2)
High (7-12)	384/267 (70 %)	61.9 (54.9-69.7)	57/36 (58 %)	37.9 (27.4-52.6)	327/231 (70 %)	68.6 (60.3-78.1)
Death	Total		Outpatients		Inpatients	
Risk category	n. pts/events (%)	Incidence-rate	n. pts/events (%)	Incidence-rate	n. pts/events (%)	Incidence-rate
Low (0-4)	848/160 (19 %)	6.1 (5.2-7.1)	522/83 (16 %)	4.8 (3.9-6.0)	326/77 (24 %)	8.7 (6.9-10.8)
Intermediate (4-6)	446/170 (38 %)	14.3 (12.3-16.6)	201/69 (34 %)	11.5 (9.1-14.6)	245/101 (41 %)	17.0 (14.0-20.7)
High (7-12)	384/235 (61 %)	33.3 (29.3-37.9)	57/32 (56 %)	25.5 (18.1-36.1)	327/203 (62 %)	35.0 (30.5-40.2)
HFH	Total		Outpatients		Inpatients	
Risk category	n. pts/events (%)	Incidence-rate	n. pts/events (%)	Incidence-rate	n. pts/events (%)	Incidence-rate
Low (0-4)	848/197 (23 %)	8.5 (7.4-9.7)	522/107 (20 %)	6.8 (5.6-8.2)	326/90 (28 %)	12.2 (9.9-14.9)
Intermediate (4-6)	446/175 (39 %)	17.3 (15.0-20.1)	201/76 (38 %)	14.4 (11.5-18.0)	245/99 (40 %)	20.6 (16.9-25.1)
High (7-12)	384/169 (44 %)	24.3 (20.9-28.2)	57/20 (35 %)	15.2 (9.8-23.6)	327/149 (61 %)	26.4 (22.5-31.0)

Supplemental Table 4. Derivation cohort: hazard ratios, incidence rates and respective 95% confidence intervals for cardiovascular death

Inpatient vs. Outpatient	Crude HR (95%CI)	P-value	Adjusted HR (95%CI)*	P-value
Cardiovascular Death	1.81 (1.45-2.26)	<0.001	1.16 (0.92-1.47)	0.20

*Adjusted on the BIOSTAT-CHF risk model including age, heart failure hospitalization in the previous year, peripheral edema, systolic blood pressure, estimated glomerular filtration rate, urea, NT-pro BNP, hemoglobin, HDL cholesterol, sodium, and beta-blocker use.

Supplemental Table 5. Derivation cohort: cardiovascular death event proportion and incidence rates per 100-person years of outpatients and inpatients by categories of the risk score

Cardiovascular death	Total		Outpatients		Inpatients	
Risk category	n. pts/events (%)	Incidence-rate	n. pts/events (%)	Incidence-rate	n. pts/events (%)	Incidence-rate
Low (0-4)	1,058/88 (8 %)	4.2 (3.4-5.2)	437/29 (7 %)	3.4 (2.4-4.9)	621/59 (10 %)	4.7 (3.7-6.1)
Intermediate (5-6)	746/131 (18 %)	10.7 (9.0-12.7)	233/41 (18 %)	10.2 (7.5-13.8)	513/90 (18 %)	11.0 (8.9-13.5)
High (7-15)	712/222 (31 %)	23.9 (20.9-27.3)	152/30 (20 %)	13.4 (9.4-19.2)	560/192 (34 %)	27.3 (23.7-31.4)