Cardiovascular and Non-Cardiovascular death distinction: the utility of Troponin beyond NT-pro BNP. Findings from the BIOSTAT-CHF study

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Abstract

Introduction: Heart failure (HF) patients are at high-risk of cardiovascular (CV) events, including CV death. Nonetheless, a substantial proportion of these patients die from non-CV causes. Identifying patients at higher risk for each individual event may help selecting patients for clinical trials and tailoring cardiovascular therapies.

Aims: The aims of the present study are to: 1) characterize the patients according to CV vs. non-CV death; 2) develop models for the prediction of the respective events; 3) assess the models` performance to differentiate CV from non-CV death.

Methods: This study included 2,309 patients with HF from the BIOSTAT-CHF (A systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure) study. Competing-risk models were used to assess the best combination of variables associated with each cause-specific death. Results were validated in an independent cohort of 1,738 HF patients.

Results: The best model to predict CV death included low blood pressure, eGFR≤60 ml/min, peripheral edema, previous HF hospitalization, ischemic HF, COPD, elevated NT-proBNP, and troponin (c-index=0.73). The non-CV death model incorporated age>75y, anemia and elevated NT-proBNP (c-index=0.71). Both CV and non-CV death rose by quintiles of the risk scores; yet these models allowed the identification of patients in whom the absolute CV death rates clearly outweigh the non-CV death ones. These findings were externally replicated, but performed worse in a less-severely diseased population.

Conclusions: Risk models for predicting CV and non-CV death allowed the identification of patients at higher absolute risk of dying from CV causes (vs. non-CV ones). Troponin helped in predicting CV death only, whereas NT-proBNP helped in the prediction of both CV and non-CV death. These findings can be useful both for tailoring therapies and for patient selection in HF trials in order to attain CV event enrichment.

Key-words: heart failure; risk; events; cardiovascular death; non-cardiovascular death; natriuretic peptides; troponin.

Introduction

Heart failure (HF) patients are at high risk of cardiovascular (CV) events, including CV death[1, 2]. Nonetheless, a substantial proportion of patients die from non-CV causes (e.g., infection, cancer, multiorgan failure)[3]. In HF trials, a composite of CV death or HF hospitalization is generally used. Identifying patients at higher risk for each mode of death (CV vs. non-CV) may help in tailoring specific therapies, developing prevention strategies, providing information to patients and their families, and also in selecting patients for clinical trials (those at higher risk for CV death, may experience more benefit from CV drugs)[4].

Patients` clinical information (medical history, signs and symptoms), plus a few parameters routinely available in clinical practice (blood pressure, heart rate, electrocardiography, echocardiography, and laboratory results such as hemoglobin and renal function) may provide useful, precise and highly discriminatory information with regards to patients` outcome[5, 6]. However, determining if an individual-patient is at higher risk of dying from CV or non-CV causes may be more challenging[7]. Natriuretic peptides (e.g. NT-pro BNP) are strong prognosticators in HF and, consequently, are often used as an "enrichment" criterion in HF trials[8, 9]. However, patients with high natriuretic peptides (NPs) may be at an increased risk for both CV and non-CV death, which may be problematic when testing CV drugs due to the high proportion of competing non-CV events. Therefore, the ability to determine patients` risk for a specific mode of death using clinical data, NPs, and troponin (variables routinely available both in clinical practice and research) may be of high relevance to tailor HF treatments and also for clinical trials, where treating high CV-risk (and ideally low non-CV risk) patients is desirable.

In BIOSTAT-CHF (A systems BIOlogy Study to TAilored Treatment in Chronic Heart Failure) the events were adjudicated and the causes of death (CV vs. non-CV) could be determined. Moreover, clinical parameters are detailed and NT-pro BNP plus Troponin T were determined with up-to-date technology.

The aims of the present study are to: 1) characterize the patients according to CV vs. non-CV death; 2) develop models with good discrimination for the prediction of the respective events; 3) assess the performance of the models to identify and differentiate CV from non-CV death.

Methods

Patient population

BIOSTAT-CHF is a European project that enrolled 2,516 patients with worsening HF on less than guideline-recommended doses of medication from 69 centres in 11 European countries to investigate the factors predicting the response to attempted up-titration of HF therapies. The design and first results of the study and patients have been published[10]. Briefly, patients were aged ≥18 years

with signs and symptoms of worsening HF managed either in an out-patient clinic or hospital ward. The diagnosis of HF was 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 were either treatment naïve with respect to disease-modifying 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[11, 12].

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

The median (pct_{25-75}) follow-up time was 21 (9-26) months.

Study outcomes

The primary outcome was a composite of heart failure hospitalization (HFH) and all-cause mortality (ACM). The adjudication of HFH was performed by the treating physician. After the trial had ended all medical reports of the mortality events were read and adjudicated by *Adriaan A. Voors* based on the (medical registries from the case record forms) and the cause of death (CV or non-CV death) was ascertained and inserted in the dataset. The criteria used for the event adjudication are shown in the *supplemental material (table 8)*.

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

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 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[10].

Statistical analysis, biomarker determination, and bioinformatical approach

Population description and comparison of the patients` characteristics by the occurrence (or not) of events was performed using parametric or non-parametric tests, as appropriate.

Competing-risk models, as described by Fine and Gray[13], were used to build the prognostic models for CV death (with non-CV death as “competing risk”), non-CV death (with CV death as “competing risk”), and hospitalizations (using all-cause death as “competing risk”). The covariates used for model development were chosen from demographic (age and sex), clinical (previous HF hospitalization, NYHA class, concomitant HF treatments, co-morbidities, body mass index, heart rate,

blood pressure, and left ventricular ejection fraction), and laboratory (NT-pro BNP, troponin, hemoglobin, glomerular filtration rate estimated by the CKD-EPI formula[14, 15], and sodium) by their well-established prognostic value in HF[16] and low proportion of missing values in this cohort. Continuous variables were categorized based on clinically relevant cutoffs to build a prognostic model ready for clinical application.

NT-pro BNP and Troponin T-high sensitive (hsTnT) were determined in a central laboratory using Roche Elecsys® cobas analyzer; 87% of the patients had hsTnT levels above the 99th percentile of 0.14 ng/mL (14 ng/dL).

The collection of the clinical, biological and biomarker data presented in this analysis was performed at baseline i.e. in the first study visit. With the exception of NT-pro BNP and hsTnT (analysed centrally) all the other variables were collected and/or analysed in the local laboratories of the respective participating centers. Blood pressure was determined with a calibrated sphygmomanometer in the sitting position after 5 minutes of rest and taking the mean of three measures.

Variables with >20% of missing values were not included in the models and missing values were kept to a minimum (analyses using multiple imputation with chained equations ("MICE") across 10 datasets were also performed with overlapping results). A stepwise (backward) procedure was applied to each model with p-value set at 0.05 for a variable to stay in the model. We repeated these procedures using 1000x bootstrap samples and using Cox regression models (to be concordant with the underlying event rate) providing similar estimates to those presented.

The risk scores were then computed by attributing integer numbers based on the β coefficients of the associations, and subsequently divided in quintiles[17]. We merged both risk scores in a "combined risk" score that incorporates both the variables that predict CV events and also those that predict non-CV events; as NT-pro BNP was the only variable that predicted both event types we assigned it the weight given in the CV death prediction model (assigning the weight of the non-CV death models provided similar estimates). Event-rates, the respective differences and ratios were calculated. The "number needed to enroll" (NNE) for a cardiovascular event to occur was also calculated by computing the inverse of the absolute difference between cardiovascular and non-cardiovascular events (analogous to the number needed to treat). Prespecified interactions between hsTnT and HF etiology (ischemic vs. non-ischemic), hsTnT and NT-pro BNP with LVEF (≤40% vs. >40%) were tested.

Exploratory unsupervised Classification and Regression Tree (CART) analysis were also computed using failure time data and chi-square values for all possible cut-points on the CART covariates.

All the analyses were performed using STATA (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP).

Results

Patients` characteristics

Patients who died from CV causes had more often HF of ischemic etiology, previous HFH, and lower blood pressure. Those who died from non-CV causes were older, had more often a LVEF >40%, anemia, atrial fibrillation, history of cancer, and an eGFR ≤60 ml/min. **Table 1**. Patients` characteristics adding the mode of hospitalization in those who remained alive during the follow-up is presented in the **Supplemental Table 1**. A total of 657 patients died during the follow-up; of these 441 (67.1%) died from CV causes and 216 (32.9%) from non-CV causes.

Competing-risk clinical models for the specific events

The point-score model to predict CV death included systolic blood pressure (SBP) <110 mmHg, presence of peripheral edema, HF of ischemic etiology, chronic obstructive pulmonary disease (COPD), eGFR ≤60 ml/min, NT-pro BNP, and hsTnT categories. The model presented good discrimination (c-index =0.73). The model to predict non-CV death included age above 75 years, anemia, and NT-pro BNP categories. This model also presented a good discrimination (c-index =0.71). **Table 2**. The same model with using continuous variables presented the same discriminatory capacity and is presented in the **Supplemental Table 2**.

No statistical interactions were found between the etiology of HF (ischemic or non-ischemic) and the predictive value of hsTnT (p for interaction =0.34), LVEF (≤40% vs. >40%) and the predictive value of troponin (p for interaction =0.26) or NT-pro BNP (p for interaction =0.80).

Competing risk models to predict hospitalizations (HF and non-HF) were also developed (presented in the **Supplemental Table 3**). Independent predictors of HF hospitalization included NYHA III or IV, previous HF hospitalization, diabetes, active smoking, eGFR ≤60 ml/min, and elevated NT-pro BNP; with moderate discrimination (c-index =0.68). The model for predicting non-HF hospitalization performed poorly (c-index =0.56), and these patients had much lower risk compared with those hospitalized for HF. **Supplemental Figure 1**.

Risk differentiation between CV and non-CV death

A steep increase in the CV and non-CV death rates was observed by quintiles of the respective risk scores (**Table 3**), with good calibration (**Supplemental Figure 2**).

For example, patients with ≥6 points (i.e. quintile ≥3) in the CV death risk score had >16% CV death events during the follow-up, corresponding to >7 events per 100py. Patients in the top quintile of the CV death risk score (≥10 points) had >44% events during the follow-up, corresponding to >32 events per 100py. **Table 3** & **Figure 1**. The absolute event rate difference (CV minus non-CV death) for patients with ≥6 points in the CV death risk score is ≥5 events per 100py, up to 25 events per 100py in patients with ≥10 points (i.e. "top" quintile of the CV death risk score); consequently, the number of patients needed to enrol (NNE) to have a CV death event (over a non-CV death one) decreases steeply by quintiles of the CV risk score, and is of 20 patients in those with a risk score of 6 or 7, 12 patients if the score is 8 or 9, and 4 patients if the score is 10 or greater. **Table 3**. Below a CV

risk score of 6 (i.e. quintiles 1 and 2) the CV death event rates are much lower (9% during the follow-up; <7 events per 100py) and not that different from the non-CV death ones (event rate difference <2 events per 100py). **Table 3** & **Figure 1**.

The CV-death risk model was also well calibrated for non-CV death i.e. non-CV death event rates increase steeply per each quintile of the CV death risk score; suggesting that when the CV-death risk is enhanced, the non-CV death risk also rises. Consequently, the CV to non-CV death ratio does not illustrate the potential difference between these two event "types", but the absolute difference does. **Table 3** (see also the discussion section).

NT-pro BNP was associated with both CV death and non-CV death; although NT-pro BNP had a stronger association (i.e. "weight") for predicting CV death compared with non-CV death (β estimates for NT-pro BNP between 1500 and 5000 are of 0.52 for CV death and 0.44 for non-CV death; and of 0.84 and 0.62 NT-pro BNP above 5000, respectively). Troponin was an independent predictor of CV-death but not of non-CV death. These findings were also supported by unsupervised CART analyses, depicted in the **Supplemental Figure 3**, where troponin was selected as the top discriminator for CV death but was not considered by the model to classify non-CV death.

Combining the CV and non-CV death risk scores (**Table 3**) allows the computation and comparison of these scenarios for each individual patient in a "real-world" scenario i.e. for risk assessment and/or for CV risk enrichment in clinical trials. For this purpose, an **Online Calculator** is available. The CV vs. non-CV death event rate comparison is visually depicted in the **Figure 2**.

We also analysed the patients at high risk for CV death (≥6 points in the CV death risk score) and low risk for non-CV death (≤2 points in the non-CV death risk score). Patients with a high risk of CV death and low risk of non-CV death represented 21% of the BIOSTAT-CHF study population, whereas patients with a low risk of CV death and high-risk of non-CV death represented 5% of the study population (**Table 4**). Patients with high risk of CV death and low risk of non-CV death have higher levels of NT-pro BNP and hsTnT, and CV death event rates when compared with the other remaining patients. **Supplemental Table 4** & **5**.

External validation

The findings were replicated but performed worse in the validation cohort. With exception of the quintile 2 where few patients/events were present (n =99 for CV death and n =78 for non-CV death); higher event rates were also observed per incremental quintiles of risk in the validation cohort. However, the event rates were overall lower in the validation cohort because this population had less severe HF. Moreover, the validation cohort has a smaller sample size than the derivation one (n=1,738 vs. n =2,309).

The results for the individual components on the risk score for both CV death and non-CV death are presented in the **Supplemental Table 6**. The c-index of the model for CV death is 0.66 and for non-CV death 0.60.

Patients with 7 or more points in the combined risk score had an "excess" of CV death events (over non-CV death i.e. ratio >1) with a steep increase in the event rate difference (and consequently lower "number needed to enrol") in favour of CV death. **Supplemental Table 7**.

Discussion

To our knowledge, this is the first study to show that a distinction between patients at high risk for CV death and non-CV death is possible using a set of routinely available clinical and biochemical variables. The "risk scores" here developed may be used in clinical practice for identifying patients at high risk for CV death, and for clinical trials were a CV over non-CV death enrichment is required to test the efficacy of CV drugs while decreasing the odds for competing non-CV events.

Predicting the occurrence of events throughout the follow-up using models that incorporated biomarkers has been attempted in patients with atrial fibrillation enrolled in the ARISTOTLE trial[18]. In this analysis hsTnT and NT-pro BNP were strongly associated with CV death; however, non-CV death was not assessed and whether these biomarkers could differentiate the modes of death was not determined. A study including 4842 patients hospitalized for acute HF assessed the factors associated with non-CV death[19]. Over a median follow-up of 17 months 1183 patients died, of whom 356 (30%) from non-CV causes. The proportion of non-CV death events was similar to that found in our cohort, and age and low hemoglobin were also independently associated with this mode of death[19]. Notwithstanding, this study did not assess CV death, biomarkers, nor the capacity of clinical variables to identify different modes of death. Serial hsTnT measurements were also performed in the RELAX-AHF study and found to be strongly associated with adverse cardiovascular outcomes, particularly CV death at 180 days[20]; but the potential capacity of hsTnT for differentiating the modes of death was also not assessed. Other reports that studied the association of biomarkers with different modes of death also did not ascertain the capacity of these biomarkers (on top of the clinical variables) to differentiate CV from non-CV death[21].

The present study goes beyond the previous published reports. We developed two calibrated (and easy to compute) risk models able to identify patients at high risk for CV death and also assess which patients will likely have high CV to non-CV death rates difference, potentially benefiting more from CV drugs while less prone to non-CV competing events.

A few examples may illustrate the potential use of these models. Patients with ≥6 points in the CV death risk score have high CV death event rates during follow up (>16%; >7 events per 100py) with a non-CV death difference of more than 5 events per 100py. Even considering the patients at higher risk for non-CV death events (i.e. those in the top quintile of the non-CV death score) versus those with intermediate risk for CV death (i.e. third quintile or 6-7 points in the CV death score), they have at least similar CV to non-CV death event rates. In this regard, the combined (CV and non-CV death) risk score available as *Online Calculator* (and also visualized in the *Figure 2*) allows the computation of these scenarios in a "real-world" setting. In a "practical" example for a hypothetical

HF trial, enrolling patients with signs and symptoms of HF, elevated NT-pro BNP and detectable troponin (while "capping" the enrolment of very old patients and those with anemia) may "enrich" the CV death rates and increase the CV to non-CV death absolute difference i.e. decreases the overall probability on non-CV competing risks. As non-CV death events also increase along with the CV-death ones, looking at the absolute even-rate differences is more informative than the "ratio", as the event-rate difference increases steeply by each quintile of the combined risk score, whereas the ratio does not (e.g., in patients with ≥7 points in the combined risk score *Online Calculator* the event rate difference increases from 4.2 events per 100py in those with 7 or 8 points, to 16.6 events per 100py in those with 11 to 16 points, whereas the event ratio remains around 2).

In addition to the clinical features, the association of hsTnT with CV death (but not with non-CV death) adds additional differentiation, and should be incorporated when assessing the risk of CV death in HF patients, as even small elevations in hsTnT are associated with increased CV event rates[22]. This observation may be explained by the fact that troponin is cardiac-specific and is detectable in many HF patients even in the absence of clinically apparent myocardial ischemia[22]. It should be emphasized that we did not find heterogeneity ("statistical interaction") between the HF etiology (ischemic vs. non-ischemic) and the predictive value of troponin, supporting the use of troponins for CV death risk assessment also in patients without ischemic HF. On the other hand, NT-pro BNP elevations may be found in association with older age, impaired renal function, infections, cancer, atrial fibrillation and many other cardiac and non-cardiac condition, that preclude this biomarker from differentiating the risk of CV vs. non-CV death[23, 24]. For example, a patient with a hsTnT of 0.06 ng/mL and a NT-pro BNP of 2000 pg/mL already counts "6 points" in the combined score (regardless of the other variables); this individual patient will be at higher risk for CV death (relative to non-CV death) because only patients with NT-pro BNP above 5000 pg/mL, aged above 75 and with anemia would be at similar risk for CV and non-CV death, but unlikely at higher risk.

The model built for identifying patients at higher risk for HF hospitalization, retained variables associated with HF severity, eGFR ≤60 ml/min, diabetes, current smoking and NT-pro BNP but not troponin; suggesting that HF hospitalizations may be driven by several causes beyond the "disease progression" (e.g. infections, arrhythmias, renal dysfunction, drug intolerance, etc) and that adjudication of these events may be very challenging. For example, in our study patients identified as admitted for non-HF causes had a very low event risk, suggesting that these patients were probably admitted for "programmed" procedures. Either way, HF hospitalizations were associated with high overall subsequent death rates (CV and non-CV) and a careful event adjudication is warranted when considering time-to-first composite end points in HF trials.

These findings may have a high impact both for current clinical practice and HF trials. Identifying patients at higher risk for CV death may help in tailoring CV therapies (e.g. drug up-titration, coronary ischemia test or device implant) and in selecting patients for future HF trials, where the tested drugs are targeted at reducing the CV death events, specifically.

Limitations

Several limitations should be acknowledged in this analysis. First, the data from the BIOSTAT-CHF come from European centres only and may not be representative of HF patients in other world regions. Second, all patients enrolled in the BIOSTAT-CHF had severe symptoms and high natriuretic peptide levels, hence these findings cannot be generalized to less symptomatic HF patients. Third, patients enrolled herein were included if they had suboptimal HF treatment, which can also limit the generalization of our results to HF patients with optimized medical treatment. However, the medical treatment in BIOSTAT-CHF was similar to other registries and doctors were instructed to up-titrate treatment during follow-up. Fourth, CV death was adjudicated directly from the clinical record forms and the subspecific modes of death (e.g. sudden, sepsis) are not available in the dataset. Fifth, HF hospitalizations were adjudicated by the investigators at the site-level and may be prone to adjudication bias. Sixth, patients with active malignancies and with infection/sepsis as the cause of admission were excluded from the BIOSTAT-CHF study, these are important variables that may account for high non-CV death risk a "real-world" setting. Seventh, the external validation cohort consisted of a smaller sample of patients with less severe HF, which may have compromised the external performance of the models.

Conclusion

Risk models for predicting CV and non-CV death allowed the identification of patients at higher absolute risk of dying from CV causes (vs. non-CV ones). Troponin helped in predicting CV death only, whereas NT-proBNP helped in the prediction of both CV and non-CV death. In addition to clinical features and NT-pro BNP, troponin should be considered to identify HF patients at high CV-death risk, both for tailoring therapies and for patient selection in future HF trials.

Acknowledgements/Funding

This project was funded by a grant from the European Commission (FP7-242209-BIOSTAT-CHF; EudraCT 2010–020808–29).

JPF and FZ are supported by the French National Research Agency Fighting Heart Failure (ANR-15-RHU-0004), by the French PIA project "Lorraine Université d'Excellence" GEENAGE (ANR-15-IDEX-04-LUE) programmes, and the Contrat de Plan Etat Région Lorraine and FEDER IT2MP.

Disclosures

The authors have nothing to disclose with regards to the present manuscript.

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Table 1. Characteristics of the BIOSTAT-CHF population according to the studied events

Patients` characteristics	Alive	CV death	Non-CV death	p-value	% MV
N.	1859	441	216		
Age, years	67.1 ± 11.9	71.7 ± 11.2	73.3 ± 10.9	<0.001	0
Male	1370 (73.7%)	325 (73.7%)	151 (69.9%)	0.48	0
BMI, kg/m2	28.1 ± 5.5	27.3 ± 5.49	27.2 ± 5.5	0.006	2%
Heart rate, bpm	82 ± 22	82 ± 20	82 ± 22	0.90	1%
SBP, mmHg	126 ± 22	121 ± 22	124 ± 24	<0.001	0
Pulm. congestion/Rales	892 (49.4%)	264 (61.8%)	135 (63.7%)	<0.001	3%
Peripheral edema	839 (54.8%)	281 (73.6%)	136 (72.7%)	<0.001	17%
Orthopnea	599 (32.3%)	189 (43.1%)	91 (42.3%)	<0.001	0
NYHA III or IV	1049 (58.0%)	315 (73.9%)	158 (75.2%)	<0.001	3%
LVEF (%)	30.70 ± 9.84	30.94 ± 12.11	34.04 ± 13.12	<0.001	11%
LVEF >40%	142 (7.6%)	51 (11.6%)	42 (19.4%)	<0.001	-
Ischemic HF	771 (41.5%)	231 (52.4%)	101 (46.8%)	<0.001	0
Previous HF hosp.	531 (28.6%)	187 (42.4%)	76 (35.2%)	<0.001	0
PCI/CABG	579 (31.1%)	174 (39.5%)	89 (41.2%)	<0.001	0
Atrial fibrillation	795 (42.8%)	230 (52.2%)	118 (54.6%)	<0.001	0
Stroke	152 (8.2%)	58 (13.2%)	23 (10.6%)	0.004	0
Peripheral arterial disease	178 (9.6%)	68 (15.4%)	27 (12.5%)	0.001	0
Device therapy	404 (21.7%)	149 (33.8%)	65 (30.1%)	<0.001	0
Hypertension	1154 (62.1%)	275 (62.4%)	140 (64.8%)	0.73	0
Diabetes	577 (31.0%)	162 (36.7%)	80 (37.0%)	0.024	0
Smoking	274 (14.7%)	47 (10.7%)	32 (14.9%)	0.26	0
COPD	279 (15.0%)	109 (24.7%)	48 (22.2%)	<0.001	0
Current malignancy	60 (3.2%)	20 (4.5%)	17 (7.9%)	0.003	0
Hemoglobin, g/dL	13.4 ± 1.8	12.7 ± 1.9	12.3 ± 2.2	<0.001	9%
Anemia	378 (20.3%)	147 (33.3%)	92 (42.6%)	<0.001	-
eGFR, ml/min	65.7 ± 22.4	52.7 ± 23.8	54.1 ± 21.1	<0.001	0
eGFR <60	775 (41.7%)	286 (64.9%)	144 (66.7%)	<0.001	0
Sodium, mmol/L	139.4 ± 3.7	138.2 ± 4.6	139 ± 4.5	<0.001	8%
Potassium, mmol/L	4.3 ± 0.5	4.3 ± 0.6	4.3 ± 0.6	0.77	8%
Glucose, mmol/L	7.1 ± 3.0	7.4 ± 3.3	7.4 ± 3.2	0.11	25%
NTproBNP, pg/mL	2209 (984, 4777)	4515 (2419, 10138)	4022 (1953, 7486)	<0.001	9%
Troponin T, ng/mL	0.27 (0.17, 0.46)	0.48 (0.31, 0.80)	0.42 (0.27-0.79)	<0.001	7%
Beta-blocker	1578 (84.9%)	349 (79.1%)	166 (76.9%)	<0.001	0
ACE/ARB	1378 (74.1%)	294 (66.7%)	148 (68.5%)	0.003	0
MRA	1017 (54.7%)	227 (51.5%)	95 (44.0%)	0.008	0

Legend: CV, cardiovascular; HF, heart failure; BMI, body mass index; SBP, systolic blood pressure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; PCI/CABG, percutaneous coronary intervention/coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ACE/ARB, angiotensin converting enzyme/angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonists; MV, missing values.

The p-value represents any difference between the categories.

Table 2. Competing-risk clinical models for the specific fatal events

"Best" predictors	SHR (95%CI)	Coef.	p-value	Points
CV death				
SBP <110 mmHg	1.28 (1.03-1.59)	0.25	0.027	+1
Per. edema	1.46 (1.14-1.86)	0.38	0.002	+1
Ischemic HF	1.35 (1.08-1.67)	0.30	0.007	+1
Previous HF hosp.	1.38 (1.11-1.72)	0.32	0.004	+1
COPD	1.47 (1.16-1.87)	0.39	0.002	+1
eGFR ≤60 ml/min	1.27 (1.01-1.59)	0.24	0.045	+1
NT-proBNP ≤1500, pg/mL	Reference	-	-	-
>1500 & ≤5000	1.69 (1.21-2.35)	0.52	0.002	+2
>5000	2.31 (1.66-3.22)	0.84	<0.001	+3
Troponin T ≤0.20, ng/mL	Reference	-	-	-
>0.20 & ≤0.50	1.76 (1.19-2.61)	0.57	0.004	+2
>0.50	2.98 (2.01-4.42)	1.09	<0.001	+4
Non-CV death				
Age >75y	2.05 (1.33-3.17)	0.72	0.001	+2
Anemia	1.88 (1.40-2.53)	0.63	<0.001	+2
NT-proBNP ≤1500, pg/mL	Reference	-	-	-
>1500 & ≤5000	1.55 (1.04-2.32)	0.44	0.031	+1
>5000	1.86 (1.23-2.82)	0.62	0.003	+2

Legend: HF, heart failure; CV, cardiovascular; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate;

C-index: CV death =0.73; Non-CV death =0.71.

P for interaction of troponin*ischemic HF =0.34.

Table 3. Risk differentiation between CV and non-CV death

CV death Risk Score (Quintiles)								
Points (from 0 to 13)	Total n.	CV death n. (%)	CV death Inc. Rate	Non-CV death n. (%)	Non-CV death Inc. Rate	Ratio %	Diff.	NNE
0-3	429	28 (6.5)	3.5 (2.4-5.1)	14 (3.3)	1.8 (1.0-2.9)	1.9	1.7	59
4-5	366	33 (9.0)	4.8 (3.4-6.8)	20 (5.5)	2.9 (1.9-4.5)	1.7	1.9	53
6-7	440	71 (16.1)	9.0 (7.1-11.4)	39 (8.9)	4.9 (3.6-6.8)	1.8	5.1	20
8-9	431	112 (26.0)	17.0 (14.1-20.4)	59 (13.7)	8.9 (6.9-11.6)	1.9	8.1	12
10-13	236	105 (44.5)	39.0 (32.2-47.3)	38 (16.1)	14.1 (10.3-19.4)	2.8	24.9	4
Non-CV death Risk Score (Quintiles)								
Points (from 0 to 6)	Total n.	CV death n. (%)	CV death Inc. Rate	Non-CV death n. (%)	Non-CV death Inc. Rate	Ratio %	Diff.	NNE
0	503	33 (6.6)	3.4 (2.4-4.8)	14 (2.8)	1.4 (0.9-2.4)	2.4	2.0	50
1	482	65 (13.5)	7.4 (5.8-9.4)	31 (6.4)	3.5 (2.5-5.0)	2.1	3.9	26
2	456	83 (18.2)	11.2 (9.0-13.8)	37 (8.1)	5.0 (3.6-6.9)	2.2	6.2	16
3-4	645	155 (24.0)	15.3 (13.1-17.9)	75 (11.6)	7.4 (5.9-9.3)	2.1	7.9	13
5-6	208	65 (31.2)	21.7 (17.0-27.7)	40 (19.2)	13.4 (9.8-18.2)	1.6	8.3	12
Combined Risk Score (Quintiles)								
Points (from 0 to 15)	Total n.	CV death n. (%)	CV death Inc. Rate	Non-CV death n. (%)	Non-CV death Inc. Rate	Ratio %	Diff.	NNE
0-4	477	30 (6.3)	3.4 (2.3-4.8)	13 (2.7)	1.4 (0.8-2.5)	2.3	2.0	50
5-6	321	34 (10.5)	5.7 (4.0-7.9)	14 (4.4)	2.3 (1.4-3.9)	2.4	3.4	29
7-8	401	64 (15.9)	9.0 (7.1-11.5)	34 (8.5)	4.8 (3.4-6.7)	1.9	4.2	24
9-10	337	79 (23.4)	15.2 (12.2-19.0)	46 (13.7)	8.9 (6.7-11.9)	1.7	6.3	16
11-16	366	142 (38.8)	29.9 (25.4-35.3)	63 (17.2)	13.3 (10.4-17.0)	2.3	16.6	6

Legend: CV, cardiovascular; Inc. Rate, incidence rate per 100 person-years; Ratio %, incidence rate ratio; Diff., incidence rate difference; NNE, number needed to enrol to have a cardiovascular death event (over a non-cardiovascular one).

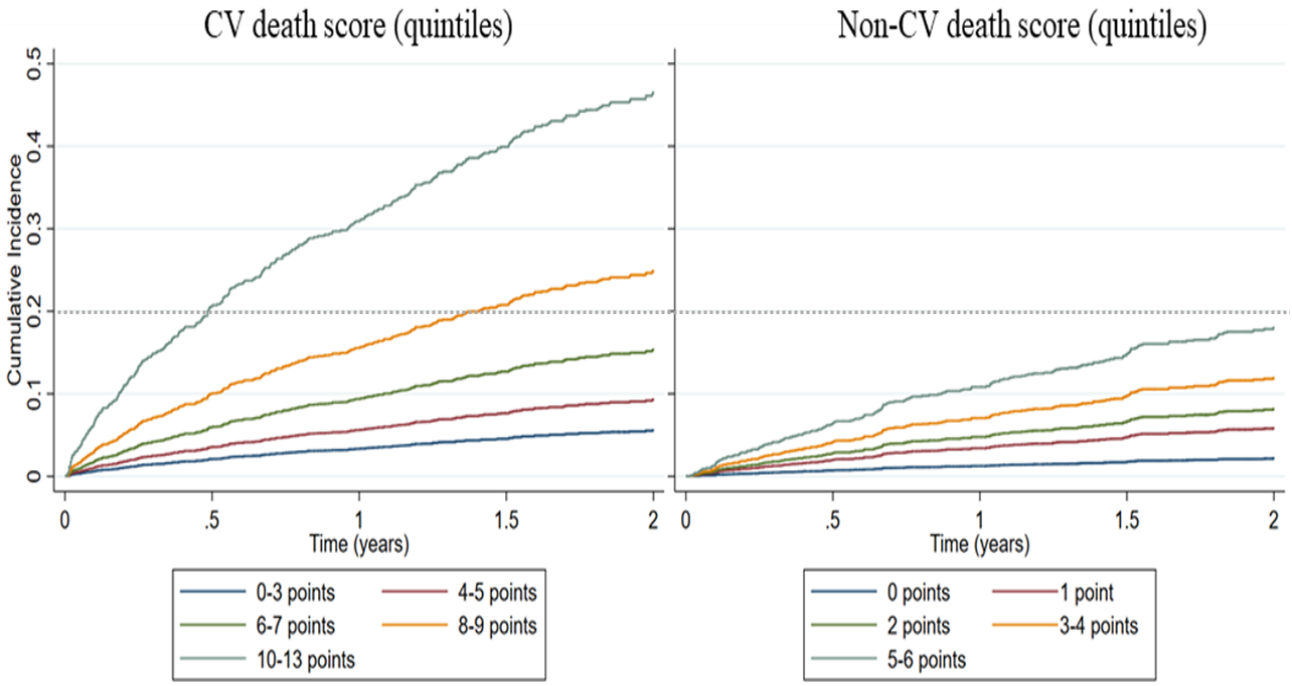
Spearman correlation between the CV and non-CV death scores =0.61.

Table 4. Cross-tabulation of cardiovascular (CV) vs. Non-CV death

Mode of death / Risk score points		**Non-CV death**				
		0	**1**	**2**	**3-4**	**5-6**
CV death	**0-3**	289	44	66	29	1
	4-5	87	115	63	91	10
	6-7	35	133	90	141	41
	8-9	5	86	97	173	70
	10-13	0	13	61	108	54

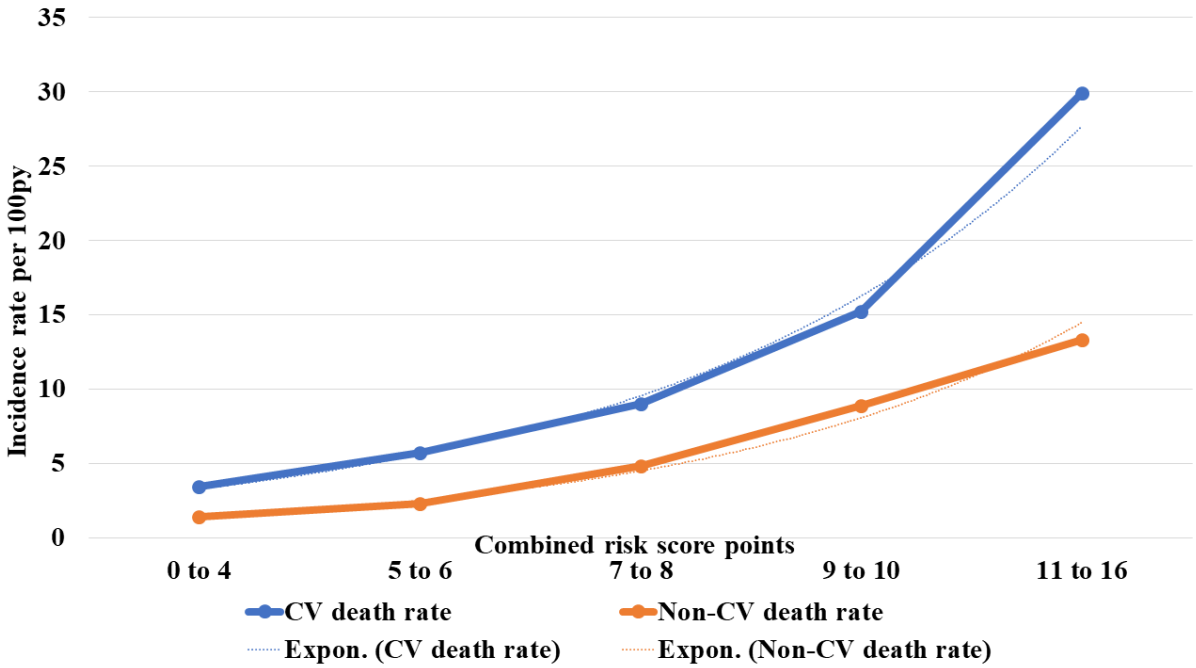
Green: patients with a high CV death risk and low non-CV death risk (n =520; 21%).
Yellow: patients with a high non-CV death risk and low CV death risk (n=131; 5.2%).

Figure 1. CV death vs. Non-CV death event rates comparison by quintiles of the respective risk scores



Legend: CV, cardiovascular.
Patients with ≥6 points in the CV death risk score have similar or greater CV death event rates than the patients at highest risk for non-CV death.

Figure 2. Cardiovascular and Non-Cardiovascular death event rates per 100py by the quintiles of the combined risk score



Legend: CV, cardiovascular.
Note: see also the Table 3.

Supplemental Material

Supplemental Table 1. Characteristics of the BIOSTAT-CHF population according to the studied events, including hospitalizations

Patients` characteristics	No event	HF hosp.	Non-HF hosp.	CV death	Non-CV death	p-value
N.	965	360	534	441	216	
Age, years	66.32 ± 12.33	69.91 ± 11.19	66.45 ± 11.49	71.68 ± 11.24	73.26 ± 10.89	<0.001
Male	687 (71.2%)	269 (74.7%)	414 (77.5%)	325 (73.7%)	151 (69.9%)	0.068
BMI, kg/m2	28.10 ± 5.39	27.81 ± 5.45	28.29 ± 5.65	27.30 ± 5.49	27.25 ± 5.59	0.017
Heart rate, bpm	82.07 ± 21.66	81.74 ± 19.64	83.51 ± 23.13	82.00 ± 19.69	81.92 ± 21.81	0.70
SBP, mmHg	126.74 ± 20.67	123.28 ± 23.79	125.79 ± 21.32	120.68 ± 21.98	123.65 ± 24.02	<0.001
Pulm. congestion/Rales	454 (48.5%)	200 (57.6%)	238 (45.5%)	264 (61.8%)	135 (63.7%)	<0.001
Peripheral edema	408 (52.0%)	201 (64.6%)	230 (52.9%)	281 (73.6%)	136 (72.7%)	<0.001
Orthopnea	283 (29.3%)	144 (40.0%)	172 (32.3%)	189 (43.1%)	91 (42.3%)	<0.001
NYHA III or IV	501 (53.6%)	252 (71.6%)	296 (56.5%)	315 (73.9%)	158 (75.2%)	<0.001
LVEF (%)	30.26 ± 9.20	30.69 ± 11.48	31.51 ± 9.75	30.94 ± 12.11	34.04 ± 13.12	<0.001
LVEF >40%	55 (5.7%)	34 (9.4%)	53 (9.9%)	51 (11.6%)	42 (19.4%)	<0.001
Ischemic HF	384 (39.8%)	172 (47.8%)	215 (40.3%)	231 (52.4%)	101 (46.8%)	<0.001
Previous HF hosp.	238 (24.7%)	154 (42.8%)	139 (26.0%)	187 (42.4%)	76 (35.2%)	<0.001
PCI/CABG	275 (28.5%)	133 (36.9%)	171 (32.0%)	174 (39.5%)	89 (41.2%)	<0.001
Atrial fibrillation	395 (40.9%)	183 (50.8%)	217 (40.6%)	230 (52.2%)	118 (54.6%)	<0.001
Stroke	69 (7.2%)	37 (10.3%)	46 (8.6%)	58 (13.2%)	23 (10.6%)	0.006
Peripheral arterial disease	75 (7.8%)	34 (9.4%)	69 (12.9%)	68 (15.4%)	27 (12.5%)	<0.001
Device therapy	187 (19.4%)	113 (31.4%)	104 (19.5%)	149 (33.8%)	65 (30.1%)	<0.001
Hypertension	597 (61.9%)	234 (65.0%)	323 (60.5%)	275 (62.4%)	140 (64.8%)	0.64
Diabetes	258 (26.7%)	151 (41.9%)	168 (31.5%)	162 (36.7%)	80 (37.0%)	<0.001
Smoking	138 (14.3%)	54 (15.0%)	82 (15.4%)	47 (10.7%)	32 (14.9%)	0.096
COPD	134 (13.9%)	67 (18.6%)	78 (14.6%)	109 (24.7%)	48 (22.2%)	<0.001
Current malignancy	22 (2.3%)	18 (5.0%)	20 (3.7%)	20 (4.5%)	17 (7.9%)	0.001
Hemoglobin, g/dL	13.57 ± 1.80	12.99 ± 1.71	13.45 ± 1.84	12.67 ± 1.91	12.35 ± 2.18	<0.001
Anemia	164 (17.0%)	99 (27.5%)	115 (21.5%)	147 (33.3%)	92 (42.6%)	<0.001
eGFR, ml/min	68.91 ± 21.83	57.47 ± 22.62	65.56 ± 21.98	52.70 ± 23.78	54.05 ± 21.09	<0.001
eGFR <60	345 (35.8%)	211 (58.6%)	219 (41.0%)	286 (64.9%)	144 (66.7%)	<0.001
Sodium, mmol/L	139.50 ± 3.62	138.88 ± 4.15	139.67 ± 3.56	138.16 ± 4.64	138.79 ± 4.53	<0.001
Potassium, mmol/L	4.29 ± 0.57	4.24 ± 0.56	4.22 ± 0.49	4.28 ± 0.60	4.28 ± 0.61	0.18
Glucose, mmol/L	6.95 ± 2.94	7.34 ± 3.21	7.09 ± 2.88	7.42 ± 3.30	7.36 ± 3.18	0.10

NTproBNP, pg/mL	1912 (789, 4242)	3429 (1733, 7344)	2072.00 (1039, 4522)	4515 (2419, 10138)	4022 (1953, 7486)	<0.001
Beta-blocker	842 (87.3%)	293 (81.4%)	443 (83.0%)	349 (79.1%)	166 (76.9%)	<0.001
ACE/ARB	741 (76.8%)	243 (67.5%)	394 (73.8%)	294 (66.7%)	148 (68.5%)	<0.001
MRA	546 (56.6%)	204 (56.7%)	267 (50.0%)	227 (51.5%)	95 (44.0%)	0.003

Legend: BMI, body mass index; SBP, systolic blood pressure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; PCI/CABG, percutaneous coronary intervention/coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ACE/ARB, angiotensin converting enzyme/angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonists.

Supplemental Table 2. Competing-risk clinical models for the specific fatal events using continuous instead of categorical variables (BIOSTAT-CHF derivation)

"Best" predictors	SHR (95%CI)	p-value
Cardiovascular death		
SBP per 10 mmHg higher	0.94 (0.88-0.99)	0.027
Per. Edema (yes)	1.51 (1.18-1.94)	0.001
Ischemic HF (yes)	1.37 (1.09-1.71)	0.006
Previous HF hosp. (yes)	1.30 (1.03-1.64)	0.028
COPD (yes)	1.49 (1.16-1.91)	0.002
eGFR per 10 ml/min higher	0.90 (0.85-0.95)	<0.001
NT-proBNP per log	1.39 (1.24-1.56)	<0.001
Troponin T per log	1.55 (1.28-1.87)	<0.001
Non-Cardiovascular death		
Age per 10 years older	1.34 (1.16-1.54)	<0.001
Anemia	1.83 (1.36-2.46)	<0.001
NT-proBNP per log	1.23 (1.09-1.40)	0.001

Supplemental Table 3. Competing-risk clinical models for the hospitalization events (BIOSTAT-CHF derivation)

"Best" predictors	SHR (95%CI)	p-value
HF hospitalization		
NYHA III or IV	1.33 (1.03-1.73)	0.030
Previous HF hosp.	1.42 (1.12-1.79)	0.003
Diabetes	1.48 (1.18-1.85)	0.001
Smoking	1.43 (1.01-2.03)	0.047
eGFR ≤60 ml/min	1.33 (1.05-1.69)	0.020
Log NT-proBNP, pg/mL	1.13 (1.03-1.23)	0.012
Non-HF hospitalization		
Male	1.29 (1.01-1.65)	0.043
HR, per 10bpm increase	1.07 (1.02-1.11)	0.004
LVEF >40%	1.40 (1.00-1.95)	0.050
Age, per 10yr increase	0.88 (0.81-0.96)	0.003
Per. edema	0.76 (0.60-0.91)	0.004
Log NT-proBNP, pg/mL	0.88 (0.81-0.95)	0.001

Legend: HF, heart failure; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; HR, heart rate.

C-index: HF hosp. =0.68; Non-HF hosp. =0.56.

Supplemental Table 4. Patients` characteristics by the combination of high CV risk and low non-CV risk vs. the rest of the BIOSTAT-CHF population

Patients` characteristics	Others	High CV and low non-CV risk	p-value
N.	1996	520	
Age, years	69.41 ± 12.37	64.52 ± 9.28	<0.001
Male	1414 (70.8%)	432 (83.1%)	<0.001
BMI, kg/m2	27.70 ± 5.37	28.60 ± 5.93	<0.001
Heart rate, bpm	81.16 ± 20.97	86.70 ± 22.36	<0.001
SBP, mmHg	125.84 ± 21.76	120.42 ± 21.93	<0.001
Pulm. congestion/Rales	986 (51.0%)	305 (59.6%)	<0.001
Peripheral edema	890 (56.4%)	366 (70.4%)	<0.001
Orthopnea	653 (32.8%)	226 (43.5%)	<0.001
NYHA III or IV	1157 (59.8%)	365 (71.3%)	<0.001
LVEF (%)	31.79 ± 10.63	28.10 ± 9.90	<0.001
LVEF >40%	205 (10.3%)	30 (5.8%)	0.002
Ischemic HF	843 (42.2%)	260 (50.0%)	0.001
Previous HF hosp.	602 (30.2%)	192 (36.9%)	0.003
PCI/CABG	653 (32.7%)	189 (36.3%)	0.12
Atrial fibrillation	903 (45.2%)	240 (46.2%)	0.71
Stroke	174 (8.7%)	59 (11.3%)	0.065
Peripheral arterial disease	210 (10.5%)	63 (12.1%)	0.30
Device therapy	475 (23.8%)	143 (27.5%)	0.081
Hypertension	1233 (61.8%)	336 (64.6%)	0.23
Diabetes	616 (30.9%)	203 (39.0%)	<0.001
Smoking	249 (12.5%)	104 (20.0%)	<0.001
COPD	314 (15.7%)	122 (23.5%)	<0.001
Current malignancy	83 (4.2%)	14 (2.7%)	0.12
Hemoglobin, g/dL	12.98 ± 1.94	13.96 ± 1.51	<0.001
Anemia	598 (30.0%)	19 (3.7%)	<0.001
eGFR, ml/min	62.65 ± 23.55	61.68 ± 21.94	0.40
eGFR <60	931 (46.6%)	274 (52.7%)	0.014
Sodium, mmol/L	139.22 ± 3.98	138.85 ± 4.12	0.071
Potassium, mmol/L	4.26 ± 0.55	4.28 ± 0.61	0.43
Glucose, mmol/L	7.08 ± 3.01	7.41 ± 3.21	0.053
NTproBNP, pg/mL	2366 (998, 5061)	3995 (2087, 7330)	<0.001
Troponin T, ng/mL	0.30 (0.20, 0.50)	0.50 (0.30-0.70)	<0.001
Beta-blocker	1670 (83.7%)	423 (81.3%)	0.21
ACE/ARB	1441 (72.2%)	379 (72.9%)	0.75
MRA	1005 (50.4%)	334 (64.2%)	<0.001

Legend: BMI, body mass index; SBP, systolic blood pressure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; PCI/CABG, percutaneous coronary intervention/coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ACE/ARB, angiotensin converting enzyme/angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonists.

Supplemental Table 5. Event-rate comparison between patients at high risk for CV death / low risk for non-CV death and rest of the study population.

Subpopulations	Total n.	CV death n. (%)	CV death Inc. Rate	Non-CV death n. (%)	Non-CV death Inc. Rate	Ratio %	Diff.	NNE
Other	1996	328 (16.4)	9.7 (8.7-10.8)	175 (8.8)	5.2 (4.5-6.0)	1.9	4.5	22
High CV / Low Non-CV risk	520	113 (21.7)	13.0 (10.8-15.7)	41 (7.9)	4.7 (3.5-6.4)	2.8	8.3	12

Legend: CV, cardiovascular; Inc. Rate, incidence rate per 100 person-years; Ratio %, incidence rate ratio; Diff., incidence rate difference; NNE, number needed to enrol to have a cardiovascular death event (over a non-cardiovascular one).

Supplemental Table 6. Competing-risk clinical models for the specific events in the validation cohort (n =1,738)

"Best" predictors	SHR (95%CI)	p-value
CV death (n =320)		
SBP <110 mmHg	1.39 (1.09-1.77)	0.008
Per. edema	1.31 (1.03-1.66)	0.031
Ischemic HF	1.16 (0.90-1.50)	0.24
Previous HF hosp.	1.30 (1.03-1.67)	0.030
COPD	1.09 (0.83-1.41)	0.56
eGFR ≤60 ml/min	8.33 (1.92-33.3)	0.005
NT-proBNP ≤1500, pg/mL	Reference	-
>1500 & ≤5000	1.36 (1.01-1.84)	0.042
>5000	2.08 (1.49-2.88)	<0.001
Troponin T ≤0.20, ng/mL	Reference	-
>0.20 & ≤0.50	1.26 (0.87-1.82)	0.22
>0.50	1.60 (1.06-2.42)	0.025
Non-CV death (n =209)		
Age >75y	1.39 (1.03-1.86)	0.030
Anemia	1.23 (0.93-1.64)	0.15
NT-proBNP ≤1500, pg/mL	Reference	-
>1500 & ≤5000	1.19 (0.87-1.64)	0.28
>5000	1.09 (0.76-1.57)	0.63

Legend: HF, heart failure; CV, cardiovascular; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate;
C-index: CV death =0.66; Non-CV death =0.60.

Supplemental Table 7. Risk differentiation between CV and non-CV death in the validation cohort (n =1,738)

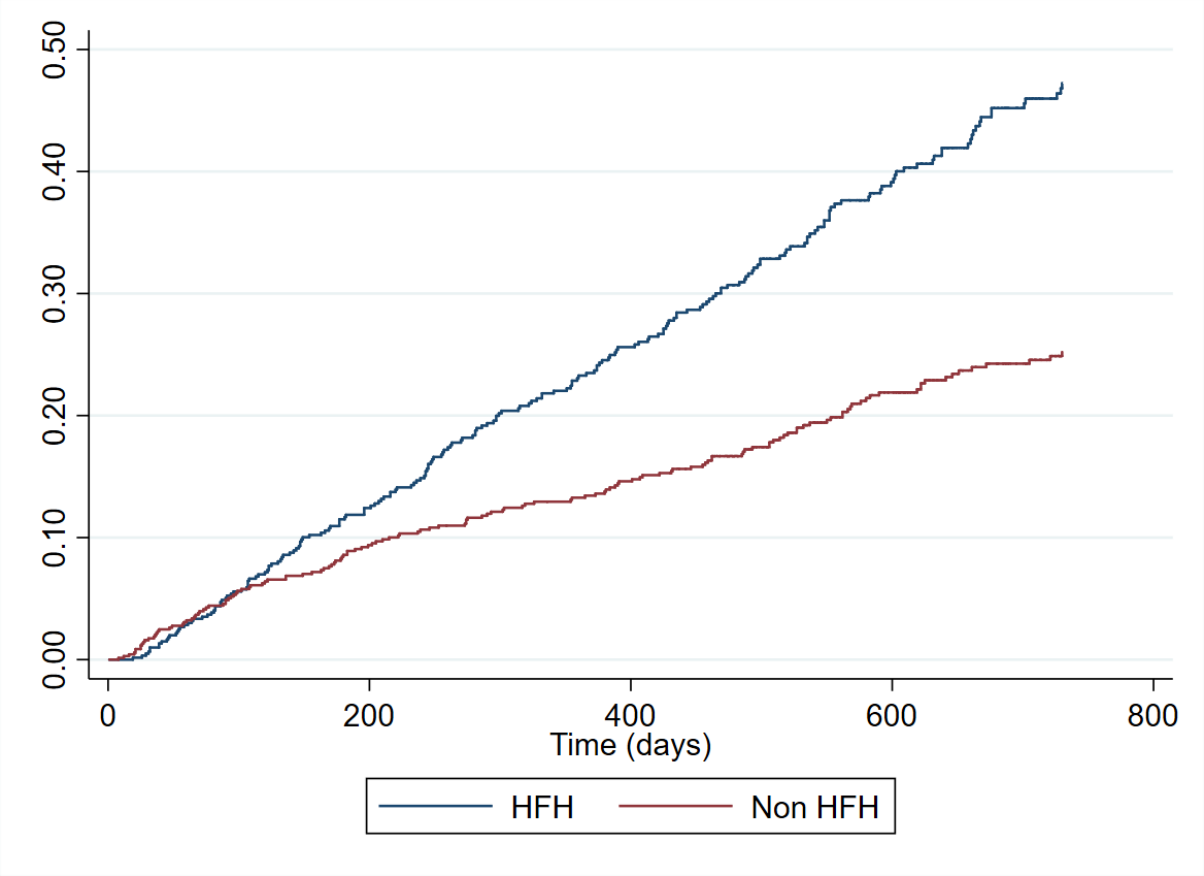
CV death Risk Score (Quintiles)								
Points (from 0 to 13)	Total n.	CV death n. (%)	CV death Inc. Rate	Non-CV death n. (%)	Non-CV death Inc. Rate	Ratio %	Diff.	NNE
0-3	633	38 (6.0)	2.7 (1.9-3.7)	42 (6.6)	3.0 (2.2-4.0)	0.9	-0.3	345
4-5	99	49 (49.4)	48.0 (35.8-62.7)	25 (25.2)	24.5 (16.1-35.4)	2.0	23.5	4
6-7	405	65 (16.0)	8.0 (6.2-10.1)	48 (11.9)	5.9 (4.4-7.7)	1.3	2.1	48
8-9	330	69 (20.9)	12.3 (9.6-15.4)	50 (15.2)	8.9 (6.7-11.6)	1.4	3.4	29
10-13	271	99 (36.5)	24.1 (19.6-29.1)	44 (16.2)	10.7 (7.8-14.2)	2.3	13.4	7
Non-CV death Risk Score (Quintiles)								
Points (from 0 to 6)	Total n.	CV death n. (%)	CV death Inc. Rate	Non-CV death n. (%)	Non-CV death Inc. Rate	Ratio %	Diff.	NNE
0	130	10 (7.7)	3.4 (1.7-6.0)	14 (10.8)	4.8 (2.7-7.8)	0.7	-1.4	73
1	78	19 (24.4)	13.7 (8.5-20.9)	15 (19.2)	10.9 (6.2-17.3)	1.3	2.9	35
2	628	88 (14.0)	6.8 (5.4-8.3)	50 (8.0)	3.8 (2.9-5.0)	1.8	2.9	34
3-4	680	138 (20.3)	11.3 (9.5-13.3)	97 (14.3)	7.9 (6.5-9.6)	1.4	3.4	30
5-6	222	65 (29.3)	20.1 (15.6-25.3)	33 (14.9)	10.2 (7.1-14.1)	2.0	9.9	10
Combined Risk Score (Quintiles)								
Points (from 0 to 15)	Total n.	CV death n. (%)	CV death Inc. Rate	Non-CV death n. (%)	Non-CV death Inc. Rate	Ratio %	Diff.	NNE
0-4	399	22 (5.5)	2.5 (1.6-3.7)	24 (6.0)	2.7 (1.8-3.9)	0.9	-0.2	455
5-6	267	110 (41.2)	32.0 (26.4-38.4)	50 (18.7)	14.6 (10.9-19.0)	2.2	17.4	6
7-8	375	45 (12.0)	5.6 (4.2-7.5)	35 (9.3)	4.4 (3.1-6.0)	1.3	1.3	80
9-10	379	67 (17.7)	9.2 (7.2-11.6)	48 (12.7)	6.6 (4.9-8.7)	1.4	2.6	38
11-16	318	76 (23.9)	14.4 (11.4-17.9)	52 (16.4)	9.8 (7.4-12.7)	1.5	4.6	22

Legend: CV, cardiovascular; Inc. Rate, incidence rate per 100 person-years; Ratio %, incidence rate ratio; Diff., incidence rate difference; NNE, number needed to enrol to have a cardiovascular death event (over a non-cardiovascular one).

Supplemental Table 8. Criteria used for event adjudication.

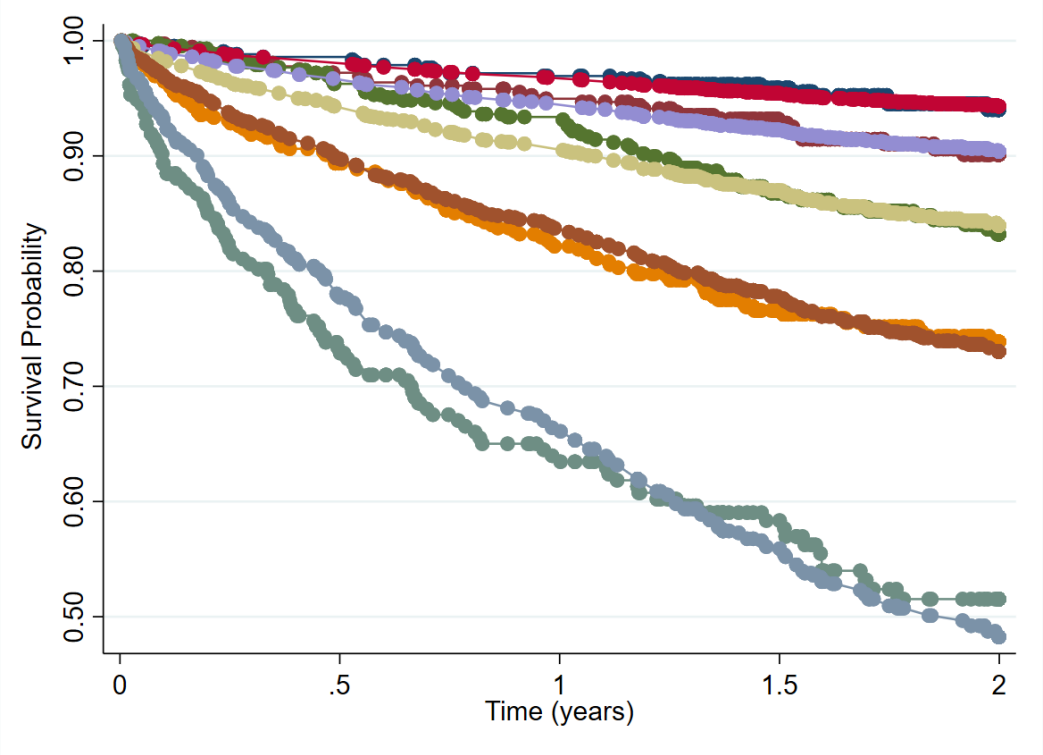
Cardiovascular
ACS/ AMI
Sudden Cardiac Death
Heart Failure
Cardio Renal
Stroke
Haemorrhage
Due to CV treatments
PE
Other
Non-Cardiovascular
Cancer
Respiratory
Renal (not cardio-renal)
Trauma
Infection
Other
Indeterminate

Supplemental Figure 1. Death rates after a hospitalization

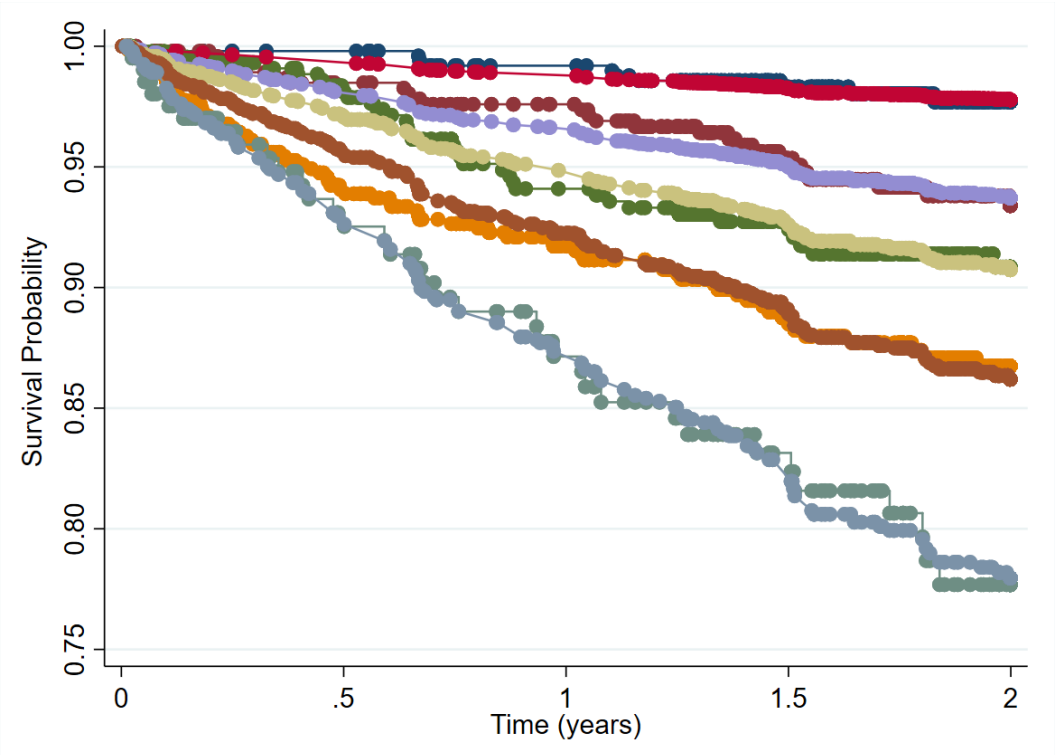


Supplemental Figure 2. CV death and non-CV death model calibration

CV death:



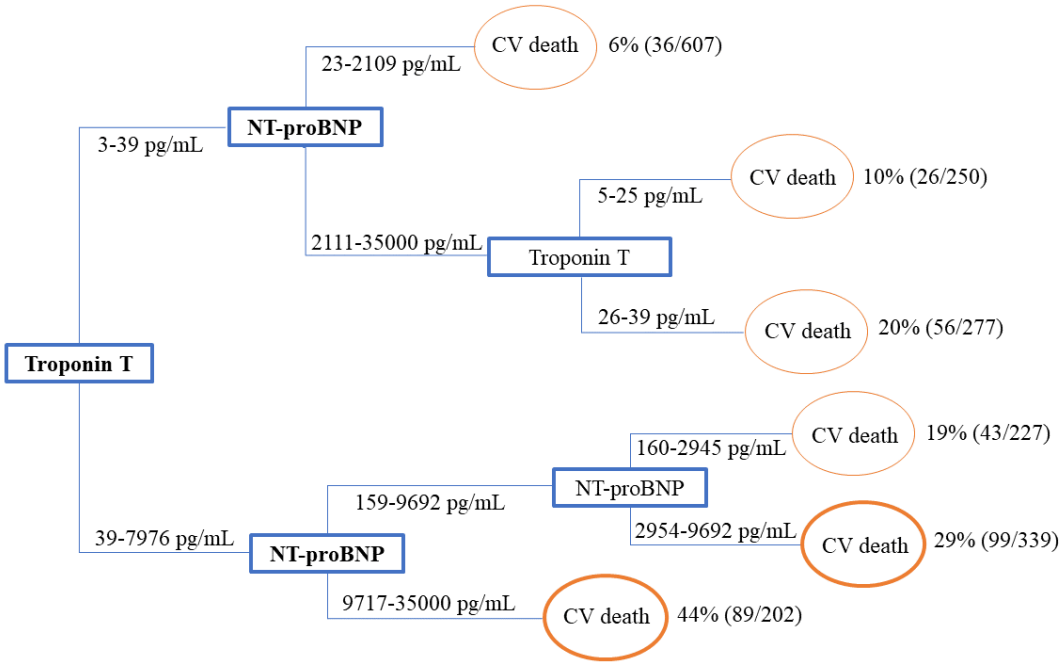
Non-CV death:



The models were well calibrated: good overlap between observed and predicted events.
Legend: CV, cardiovascular.

Supplemental Figure 3. Unsupervised classification and regression trees (CART) for the studied events

CV death:



Non-CV death: