# Cardiovascular and non-cardiovascular death distinction

Ferreira, Joao Pedro; Ouwerkerk, Wouter; Tromp, Jasper; Ng, Leong; Dickstein, Kenneth; Anker, Stefan; Filippatos, Gerasimos; Cleland, John G.; Metra, Marco; van Veldhuisen, Dirk J.

*Published in:*
European Journal of Heart Failure

*DOI:*
10.1002/ejhf.1654



*Publication date:*
2020

ESC European Society of Cardiology

European Journal of Heart Failure (2019)
doi:10.1002/ejhf.1654

RESEARCH ARTICLE

# Cardiovascular and non-cardiovascular death distinction: the utility of troponin beyond N-terminal pro-B-type natriuretic peptide. Findings from the BIOSTAT-CHF study

**João Pedro Ferreira[1]*, Wouter Ouwerkerk[2,3], Jasper Tromp[2,4], Leong Ng[5], Kenneth Dickstein[6], Stefan Anker[7], Gerasimos Filippatos[8], John G. Cleland[9,10], Marco Metra[11], Dirk J. van Veldhuisen[4], Adriaan A. Voors[4], and Faiez Zannad[1]**

[1]Université de Lorraine, Inserm, Centre d'Investigations Cliniques- Plurithématique 14-33, and Inserm U1116, CHRU, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France; [2]National Heart Centre Singapore, Hospital Drive, Singapore; [3]Department of Dermatology, Amsterdam UMC, Amsterdam Infection & Immunity Institute, University of Amsterdam, Amsterdam, The Netherlands; [4]Department of Cardiology, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands; [5]Department of Cardiovascular Sciences, NIHR Leicester Biomedical Research Centre, Glenfield Hospital, University of Leicester, Leicester, UK; [6]Stavanger University Hospital, University of Bergen, Bergen, Norway; [7]Department of Cardiology (CVK), and Berlin-Brandenburg Center for Regenerative Therapies (BCRT), German Centre for Cardiovascular Research (DZHK) partner site Berlin, Charité Universitätsmedizin, Berlin, Germany; [8]National and Kapodistrian University of Athens, Attikon General Hospital, Athens Greece; and University of Cyprus, School of Medicine, Nicosia, Cyprus; [9]Robertson Centre for Biostatistics and Clinical Trials, University of Glasgow, Glasgow, UK; [10]National Heart and Lung Institute, Imperial College London, London, UK; and [11]Institute of Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy

*Received 13 June 2019; revised 24 September 2019; accepted 27 September 2019*

**Aims** 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. The aims of the present study are to: (i) characterize patients according to CV vs. non-CV death; (ii) develop models for the prediction of the respective events; (iii) assess the models' performance to differentiate CV from non-CV death.

**Methods and results** This study included 2309 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 1738 HF patients. The best model to predict CV death included low blood pressure, estimated glomerular filtration rate $\leq 60$ mL/min, peripheral oedema, previous HF hospitalization, ischaemic HF, chronic obstructive pulmonary disease, elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP), and troponin (c-index = 0.73). The non-CV death model incorporated age $>75$ years, anaemia 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 absolute CV death rates clearly outweigh 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.

**Keywords** Heart failure • Risk • Events • Cardiovascular death • Non-cardiovascular death • Natriuretic peptides • Troponin

*Corresponding author. Centre d'Investigation Clinique 1433 module Plurithématique, CHRU Nancy - Hopitaux de Brabois, Institut Lorrain du Coeur et des Vaisseaux Louis Mathieu, 4 rue du Morvan, 54500 Vandoeuvre les Nancy, France. Tel: +33 3 83157315, Fax: +33 3 83157324, Email: j.ferreira@chru-nancy.fr

# 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 haemoglobin and renal function) may provide useful, precise and highly discriminatory information with regard 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. N-terminal pro-B-type natriuretic peptide (NT-proBNP)] 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 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, natriuretic peptides, 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-proBNP plus troponin T were determined with up-to-date technology.

The aims of the present study are to: (i) characterize patients according to CV vs. non-CV death; (ii) develop models with good discrimination for the prediction of the respective events; (iii) 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 2516 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 outpatient clinic or hospital ward. The diagnosis of HF was confirmed either by a left ventricular ejection fraction (LVEF) of ≤40% or B-type natriuretic peptide 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 [angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (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 15 December 2012.

The median (25th–75th percentile) follow-up time was 21 (9–26) months.

## Study outcomes

The primary outcome was a composite of HF hospitalization and all-cause mortality. The adjudication of HF hospitalization was performed by the treating physician. After the trial had ended all medical reports of mortality events were read and adjudicated by A.A.V. based on the medical registries from the case record forms, and the cause of death (CV or non-CV) was ascertained and inserted in the dataset. The criteria used for the event adjudication are shown in online supplementary *Table S1*).

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 1738 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 ACEi/ARBs and/or beta-blockers according to the 2008 European Society of Cardiology guidelines.[12] Patients could be enrolled as inpatients or from outpatient clinics.[10]

## Statistical analysis, biomarker determination, and bioinformatic approach

Population description and comparison of the patient 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, New York Heart Association (NYHA) class, concomitant HF treatments, co-morbidities, body mass index, heart rate, blood pressure, and LVEF], and laboratory (NT-proBNP, troponin, haemoglobin, glomerular filtration rate estimated by the Chronic Kidney Disease Epidemiology Collaboration equation,[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-proBNP and high-sensitivity troponin T (hsTnT) were determined in a central laboratory using Roche Elecsys® cobas analyzer (Roche Diagnostics, Mannheim, Germany); 87% of the patients had hsTnT levels above the 99th percentile of 0.14 ng/mL (14 ng/dL).

The collection of clinical, biological and biomarker data presented in this analysis was performed at baseline, i.e. at the first study visit. With the exception of NT-proBNP and hsTnT (analysed centrally), all the other variables were collected and/or analysed in the local laboratories of the respective participating centres. Blood pressure was determined with a calibrated sphygmomanometer in the sitting position after 5 min 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 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 1000× 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 $\beta$ coefficients of the associations, and subsequently divided into 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-proBNP 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 non-CV death models provided similar estimates). Event rates, the respective differences and ratios were calculated. The 'number needed to enrol' (NNE) for a CV event to occur was also calculated by computing the inverse of the absolute difference between CV and non-CV events (analogous to the number needed to treat). Pre-specified interactions between hsTnT and HF aetiology (ischaemic vs. non-ischaemic), hsTnT and NT-proBNP with LVEF (≤ 40% vs. > 40%) were tested.

Exploratory unsupervised Classification and Regression Tree (CART) analysis was 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 (2015 Stata Statistical Software, release 14; StataCorp. LP, College Station, TX, USA).

# Results

## Patient characteristics

Patients who died from CV causes had more often HF of ischaemic aetiology, previous HF hospitalization, and lower blood pressure. Those who died from non-CV causes were older, had more often a LVEF > 40%, anaemia, atrial fibrillation, history of cancer, and an eGFR ≤60 mL/min (*Table 1*). Patient characteristics adding the mode of hospitalization in those who remained alive during the follow-up is presented in online supplementary *Table S2*. 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 <110 mmHg, presence of peripheral oedema, HF of ischaemic aetiology, chronic obstructive pulmonary disease, eGFR ≤60 mL/min, NT-proBNP, and hsTnT categories. The model presented good discrimination (c-index = 0.73). The model to predict non-CV death included age > 75 years, anaemia, and NT-proBNP 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 online supplementary *Table S3*.

No statistical interactions were found between aetiology of HF (ischaemic or non-ischaemic) 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-proBNP (*P* for interaction = 0.80).

Competing risk models to predict hospitalizations (HF and non-HF) were also developed (online supplementary *Table S4*). Independent predictors of HF hospitalization included NYHA class III or IV, previous HF hospitalization, diabetes, active smoking, eGFR ≤ 60 mL/min, and elevated NT-proBNP, 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 (online supplementary *Figure S1*).

## Risk differentiation between cardiovascular and non-cardiovascular death

A steep increase in CV and non-CV death rates was observed by quintiles of the respective risk scores (*Table 3*), with good calibration (online supplementary *Figure S2*). For example, patients with ≥6 points (i.e. quintile ≥3) in the CV death risk score had >16% CV death events during follow-up, corresponding to >7 events per 100 person-years. Patients in the top quintile of the CV death risk score (≥10 points) had >44% events during follow-up, corresponding to >32 events per 100 person-years (*Table 3* and *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 100 person-years, up to 25 events per 100 person-years 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) CV death event rates are much lower (9% during follow-up; <7 events per 100 person-years) and not different from the non-CV death ones (event rate difference < 2 events per 100 person-years) (*Table 3* and *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*).

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

| Characteristics | Alive (*n* = 1859) | CV death (*n* = 441) | Non-CV death (*n* = 216) | *P*-value | % MV |
|---|---|---|---|---|---|
| Age, years | 67.1 ± 11.9 | 71.7 ± 11.2 | 73.3 ± 10.9 | <0.001 | 0 |
| Male sex | 1370 (73.7%) | 325 (73.7%) | 151 (69.9%) | 0.48 | 0 |
| BMI, kg/m$^2$ | 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 |
| Pulmonary congestion/rales | 892 (49.4%) | 264 (61.8%) | 135 (63.7%) | <0.001 | 3% |
| Peripheral oedema | 839 (54.8%) | 281 (73.6%) | 136 (72.7%) | <0.001 | 17% |
| Orthopnoea | 599 (32.3%) | 189 (43.1%) | 91 (42.3%) | <0.001 | 0 |
| NYHA class 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 | – |
| Ischaemic HF | 771 (41.5%) | 231 (52.4%) | 101 (46.8%) | <0.001 | 0 |
| Previous HF hospitalization | 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 |
| Haemoglobin, g/dL | 13.4 ± 1.8 | 12.7 ± 1.9 | 12.3 ± 2.2 | <0.001 | 9% |
| Anaemia | 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 mL/min | 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% |
| NT-proBNP, pg/mL | 2209 (984– 4777) | 4515 (2419– 10 138) | 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 |
| ACEi/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 |

ACEi, angiotensin-converting enzyme inhibitor; ARB angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; MV, missing values; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.
*P*-value represents any difference between the categories.

NT-proBNP was associated with both CV death and non-CV death; although NT-proBNP had a stronger association (i.e. 'weight') for predicting CV death compared with non-CV death ($\beta$ estimates for NT-proBNP between 1500 and 5000 pg/mL are of 0.52 for CV death and 0.44 for non-CV death; and of 0.84 and 0.62 NT-proBNP >5000 pg/mL, respectively). Troponin was an independent predictor of CV-death but not of non-CV death. These findings were also supported by unsupervised CART analyses (online supplementary *Figure S3*), where troponin was selected as the top discriminator for CV death but was not considered by the model to classify non-CV death.

Combining 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 CV risk enrichment in clinical trials. For this purpose, an online calculator is available. The CV vs. non-CV death event rate comparison is depicted in *Figure 2*.

We also analysed 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

**Table 2 Competing risk clinical models for the specific fatal events**

| 'Best' predictors | SHR (95%CI) | Coefficient | *P*-value | Points |
|---|---|---|---|---|
| CV death | | | | |
| SBP <110 mmHg | 1.28 (1.03–1.59) | 0.25 | 0.027 | +1 |
| Peripheral oedema | 1.46 (1.14–1.86) | 0.38 | 0.002 | +1 |
| Ischaemic HF | 1.35 (1.08–1.67) | 0.30 | 0.007 | +1 |
| Previous HF hospitalization | 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, pg/mL | | | | |
| ≤1500 | 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, ng/mL | | | | |
| ≤0.20 | 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 > 75 years | 2.05 (1.33–3.17) | 0.72 | 0.001 | +2 |
| Anaemia | 1.88 (1.40–2.53) | 0.63 | <0.001 | +2 |
| NT-proBNP, pg/mL | | | | |
| ≤1500 | 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 |

CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure.
C-index: CV death = 0.73; non-CV death = 0.71.
*P* for interaction of troponin*ischaemic HF = 0.34.

**Table 3 Risk differentiation between cardiovascular and non-cardiovascular death**

| Points | Total, *n* | CV death, *n* (%) | CV death inc. rate | Non-CV death, *n* (%) | Non-CV death inc. rate | Ratio, % | Diff. | NNE |
|---|---|---|---|---|---|---|---|---|
| CV death risk score (quintiles) | | | | | | | | |
| 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) | | | | | | | | |
| 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) | | | | | | | | |
| 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 |

CV, cardiovascular; Diff., incidence rate difference; inc. rate, incidence rate per 100 person-years; NNE, number needed to enrol to have a cardiovascular death event (over a non-cardiovascular one); Ratio %, incidence rate ratio.
Spearman correlation between the CV and non-CV death scores = 0.61.

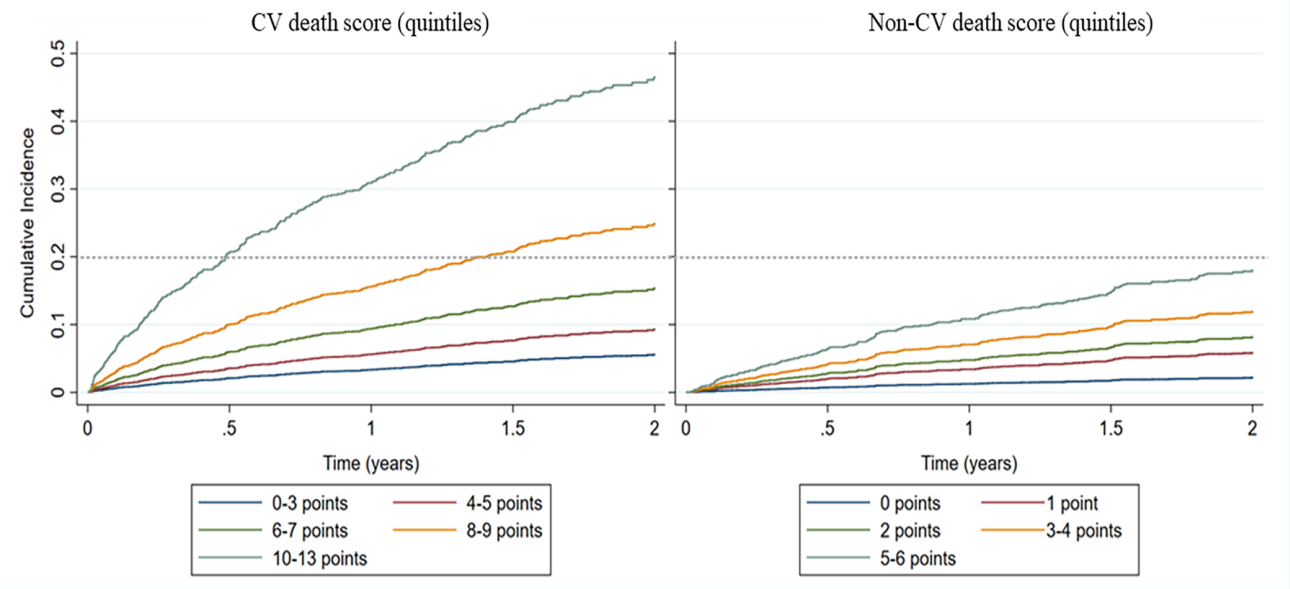


**Figure 1** Cardiovascular (CV) death vs. non-CV death event rate comparison by quintiles of the respective risk scores. Patients with ≥6 points in the CV death risk score have similar or greater CV death event rates than the patients at the highest risk for non-CV death.

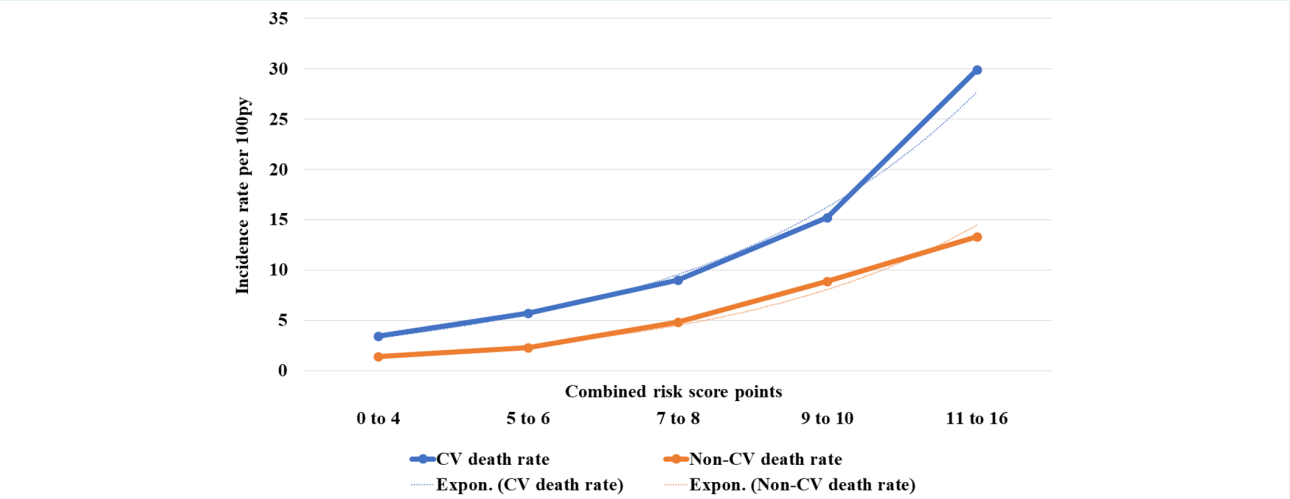


**Figure 2** Cardiovascular (CV) and non-CV death event rates per 100 person-years (py) by the quintiles of the combined risk score [see also *Table 3*].

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-proBNP and hsTnT, and CV death event rates when compared with the remaining patients (online supplementary *Tables S5* and *S6*).

## 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 ($n = 1738$ vs. $n = 2309$).

The results for the individual components on the risk score for both CV death and non-CV death are presented in online supplementary *Table S7*. The c-index of the model for CV death is 0.66 and for non-CV death 0.60.

Patients with ≥7 points in the combined risk score had an 'excess' of CV death events (over non-CV death, i.e. ratio > 1)

**Table 4 Cross-tabulation of cardiovascular vs. non-cardiovascular 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 |

CV, cardiovascular.
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%).

with a steep increase in the event rate difference (and consequently lower NNE) in favour of CV death (online supplementary *Table S8*).

## 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-proBNP 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 haemoglobin 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 CV 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 evaluated 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 rate 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 100 person-years) with a non-CV death difference of more than 5 events per 100 person-years. 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) vs. those with intermediate risk for CV death (i.e. in the third quintile or with 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 (*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-proBNP and detectable troponin (while 'capping' the enrolment of very old patients and those with anaemia) may 'enrich' 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 event 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 100 person-years in those with 7 or 8 points, to 16.6 events per 100 person-years in those with 11–16 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 ischaemia.[22] It should be emphasized that we did not find heterogeneity ('statistical interaction') between HF aetiology (ischaemic vs. non-ischaemic) and the predictive value of troponin, supporting the use of troponins for CV death risk assessment also in patients without ischaemic HF. On the other hand, NT-proBNP elevations may be found in association with older age, impaired renal function, infections, cancer, atrial fibrillation and many other cardiac and non-cardiac conditions 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-proBNP 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-proBNP >5000 pg/mL, aged >75 years and with anaemia 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-proBNP but

not troponin, suggesting that HF hospitalizations may be driven by several causes beyond '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 endpoints 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 ischaemia test, or device implant) and in selecting patients for future HF trials, where the tested drugs are targeted at reducing CV death events, specifically.

## Limitations

Several limitations should be acknowledged in this analysis. First, data from BIOSTAT-CHF come from European centres only and may not be representative of HF patients in other world regions. Second, all patients enrolled in 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 in 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-proBNP, 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.

# Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Criteria used for event adjudication.

**Table S2.** Characteristics of the BIOSTAT-CHF population according to the studied events, including hospitalizations.

**Table S3.** Competing risk clinical models for the specific fatal events using continuous instead of categorical variables (BIOSTAT-CHF derivation).

**Table S4.** Competing risk clinical models for hospitalization events (BIOSTAT-CHF derivation).

**Table S5.** Patient characteristics by the combination of high cardiovascular risk and low non-cardiovascular risk vs. the rest of the BIOSTAT-CHF population.

**Table S6.** Event rate comparison between patients at high risk for cardiovascular death/low risk for non-cardiovascular death and rest of the study population.

**Table S7.** Competing risk clinical models for the specific events in the validation cohort ($n = 1738$).

**Table S8.** Risk differentiation between cardiovascular and non-cardiovascular death in the validation cohort ($n = 1738$).

**Figure S1.** Death rates after a hospitalization.

**Figure S2.** Cardiovascular death and non-cardiovascular death model calibration.

**Figure S3.** Unsupervised classification and regression trees (CART) for the studied events.

## Funding

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

**Conflict of interest:** none declared.

## References

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, 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. *Eur J Heart Fail* 2016;**18**: 891–975.
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA Guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2013;**128**: 1810–1852.
3. Lee DS, Gona P, Albano I, Larson MG, Benjamin EJ, Levy D, Kannel WB, Vasan RS. A systematic assessment of causes of death after heart failure onset in the community: impact of age at death, time period, and left ventricular systolic dysfunction. *Circ Heart Fail* 2011;**4**:36–43.

4. Vaduganathan M, Patel RB, Michel A, Shah SJ, Senni M, Gheorghiade M, Butler J. Mode of death in heart failure with preserved ejection fraction. *J Am Coll Cardiol* 2017;**69**:556–569.
5. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Kober L, Squire IB, Swedberg K, Dobson J, Poppe KK, Whalley GA, Doughty RN. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. *Eur Heart J* 2013;**34**:1404–1413.
6. 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, Zwinderman AH. Development and validation of multivariable models to predict mortality and hospitalization in patients with heart failure. *Eur J Heart Fail* 2017;**19**:627–634.
7. Mozaffarian D, Anker SD, Anand I, Linker DT, Sullivan MD, Cleland JG, Carson PE, Maggioni AP, Mann DL, Pitt B, Poole-Wilson PA, Levy WC. Prediction of mode of death in heart failure: the Seattle Heart Failure Model. *Circulation* 2007;**116**:392–398.
8. Gardner RS, Ozalp F, Murday AJ, Robb SD, McDonagh TA. N-terminal pro-brain natriuretic peptide. A new gold standard in predicting mortality in patients with advanced heart failure. *Eur Heart J* 2003;**24**:1735–1743.
9. Voors AA. Sense and sensibility of the use of NT-proBNP for eligibility in clinical trials. *JACC Heart Fail* 2018;**6**:257–259.
10. 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, Metra M. A systems BIOlogy Study to TAilored treatment in Chronic Heart Failure: rationale, design, and baseline characteristics of BIOSTAT-CHF. *Eur J Heart Fail* 2016;**18**:716–726.
11. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012;**14**: 803–869.
12. 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, 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). *Eur Heart J* 2008;**29**:2388–2442.
13. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;**94**:496–509.
14. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–612.
15. Ferreira JP, Girerd N, Pellicori P, Duarte K, Girerd S, Pfeffer MA, McMurray JJ, Pitt B, Dickstein K, Jacobs L, Staessen JA, Butler J, Latini R, Masson S, Mebazaa A, Rocca HP, Delles C, Heymans S, Sattar N, Jukema JW, Cleland JG, Zannad F, Rossignol P. Renal function estimation and Cockcroft-Gault formulas for predicting cardiovascular mortality in population-based, cardiovascular risk, heart failure and post-myocardial infarction cohorts: the Hear 'OMics' in AGEing (HOMAGE) and the high-risk myocardial infarction database initiatives. *BMC Med* 2016;**14**:181.
16. Collier TJ, Pocock SJ, McMurray JJ, Zannad F, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pitt B. The impact of eplerenone at different levels of risk in patients with systolic heart failure and mild symptoms: insight from a novel risk score for prognosis derived from the EMPHASIS-HF trial. *Eur Heart J* 2013;**34**:2823–2829.
17. Ferreira JP, Girerd N, Gregson J, Latar I, Sharma A, Pfeffer MA, McMurray JJ, Abdul-Rahim AH, Pitt B, Dickstein K, Rossignol P, Zannad F. Stroke risk in patients with reduced ejection fraction after myocardial infarction without atrial fibrillation. *J Am Coll Cardiol* 2018;**71**:727–735.
18. Sharma A, Hijazi Z, Andersson U, Al-Khatib SM, Lopes RD, Alexander JH, Held C, Hylek EM, Leonardi S, Hanna M, Ezekowitz JA, Siegbahn A, Granger CB, Wallentin L. Use of biomarkers to predict specific causes of death in patients with atrial fibrillation. *Circulation* 2018;**138**:1666–1676.
19. Wakabayashi K, Ikeda N, Kajimoto K, Minami Y, Keida T, Asai K, Munakata R, Murai K, Sakata Y, Suzuki H, Takano T, Sato N. Trends and predictors of non-cardiovascular death in patients hospitalized for acute heart failure. *Int J Cardiol* 2018;**250**:164–170.
20. Felker GM, Mentz RJ, Teerlink JR, Voors AA, Pang PS, Ponikowski P, Greenberg BH, Filippatos G, Davison BA, Cotter G, Prescott MF, Hua TA, Lopez-Pintado S, Severin T, Metra M. Serial high sensitivity cardiac troponin T measurement in acute heart failure: insights from the RELAX-AHF study. *Eur J Heart Fail* 2015;**17**:1262–1270.
21. Zhang Y, Zhang R, An T, Huang Y, Guo X, Yin S, Wang Y, Ji S, Lv R, Zhang J, Maisel A. The utility of galectin-3 for predicting cause-specific death in hospitalized patients with heart failure. *J Card Fail* 2015;**21**:51–59.
22. Kociol RD, Pang PS, Gheorghiade M, Fonarow GC, O'Connor CM, Felker GM. Troponin elevation in heart failure prevalence, mechanisms, and clinical implications. *J Am Coll Cardiol* 2010;**56**:1071–1078.
23. Lenz M, Krychtiuk KA, Goliasch G, Distelmaier K, Wojta J, Heinz G, Speidl WS. N-terminal pro-brain natriuretic peptide and high-sensitivity troponin T exhibit additive prognostic value for the outcome of critically ill patients. *Eur Heart J Acute Cardiovasc Care* 2018 Apr 1. https://doi.org/10.1177/2048872618768808 [Epub ahead of print].
24. Karthikeyan G, Moncur RA, Levine O, Heels-Ansdell D, Chan MT, Alonso-Coello P, Yusuf S, Sessler D, Villar JC, Berwanger O, McQueen M, Mathew A, Hill S, Gibson S, Berry C, Yeh HM, Devereaux PJ. Is a pre-operative brain natriuretic peptide or N-terminal pro-B-type natriuretic peptide measurement an independent predictor of adverse cardiovascular outcomes within 30 days of noncardiac surgery? A systematic review and meta-analysis of observational studies. *J Am Coll Cardiol* 2009;**54**:1599–1606.