Development and validation of multivariable models to predict mortality and hospitalization in patients with heart failure

A.A. Voors, MD, PhD[1], W. Ouwerkerk[2], F. Zannad, MD, PhD[3], D.J. van Veldhuisen, MD, PhD[1], N.J Samani, MD[4], P. Ponikowski, MD, PhD[5], L.L. Ng, MD[4], M. Metra, MD[6], J.M. ter Maaten, MD[1], C.C. Lang, MD[7], H.L. Hillege, MD, PhD[1], P. van der Harst, MD, PhD[1], G. Filippatos, MD[8], K. Dickstein, MD[9,10], J.G. Cleland, MD[11], S.D. Anker, MD, PhD[12], and A.H. Zwinderman, PhD[2]

[1]*University of Groningen, Department of Cardiology, University Medical Center Groningen, The Netherlands*

[2]*Department of Clinical Epidemiology, Biostatistics, and Bioinformatics, Academic Medical Center, University of Amsterdam, 1105 AZ Amsterdam, The Netherlands*

[3]*Inserm CIC 1433, Université de Lorrain, CHU de Nancy, Nancy, France*

[4]*Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, UK and NIHR Leicester Cardiovascular Biomedical Research Unit, Glenfield Hospital, Leicester, LE3 9QP, UK*

[5]*Department of Heart Diseases, Wroclaw Medical University, Poland and Cardiology Department, Military Hospital, Wroclaw, Poland.*

[6]*Institute of Cardiology, Department of medical and surgical specialties, radiological sciences and public health; University of Brescia, Italy*

[7]*School of Medicine Centre for Cardiovascular and Lung Biology, Division of Medical Sciences, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK*

[8]*Department of Cardiology, Heart Failure Unit, Athens University Hospital Attikon, National and Kapodistrian University of Athens, Athens, Greece*

[9]*University of Stavanger, Stavanger, Norway*

[10]*University of Bergen, Bergen, Norway*

[11]*National Heart and Lung Institute, Royal Brompton and Harefield Hospitals, Imperial College, London, United Kingdom.*

[12]*Innovative Clinical Trials, Department of Cardiology and Pneumology, University Medical Center Göttingen (UMG), Göttingen, Germany*

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Corresponding author:

Prof. dr. Adriaan A. Voors

Professor of Cardiology, University Medical Center Groningen

Hanzeplein 1, 9713 GZ Groningen

Phone: +31 (0) 50 361 2355

Abstract

Introduction

Many risk prediction models have been developed for patients with heart failure (HF), but most were from retrospective and selected patient populations and were not appropriately validated.

Methods

BIOSTAT-CHF is a research program designed to develop and externally validate risk-models to predict all-cause mortality and HF-hospitalizations. The index cohort consisted of 2,516 patients with HF from 69 centres in 11 European countries. The external validation cohort consisted of 1,728 comparable patients from 6 centres in Scotland, UK

Results

Patients from the index cohort had a mean age of 69 years, 27% were female, 83% were in NYHA class II-III and the mean left ventricular ejection fraction was 31%. The full prediction models for mortality, HF-hospitalization and the combined outcome, yielded c-statistic values of 0.73, 0.69, and 0.71 respectively. Predictors of mortality and HF-hospitalization were remarkably different. The 5 strongest predictors of mortality were a greater age, higher BUN and NT-proBNP, lower hemoglobin and failure to prescribe a beta-blocker. The 5 strongest predictors of HF-hospitalization were greater age, previous HF-hospitalization, presence of edema, lower SBP and lower eGFR. Patients from the validation cohort were 74 years, 34% were women, 85% were in NYHA II-III and mean LVEF was 41%; c-statistic values for the full and compact model were comparable to the index cohort.

Conclusion

A small number of variables, which are usually readily available in the routine clinical setting,

provide useful prognostic information for patients with heart failure. Predictors of mortality were remarkably different from predictors of HF-hospitalization.

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Introduction

Accurately predicting risk of mortality or heart failure hospitalization in patients with heart failure (HF) might lead to intensified monitoring and treatment (1–7) and help physicians, nurses and patients in making management decisions (8). Also, selecting high risk patients in phase III drug and device trials may enrich clinical event rates and decrease sample size.

Many risk prediction models for patients with HF have been published (9). Of 117 models included in a recent meta-analysis, only 33% were validated in a separate cohort. Most of these models performed only moderately (c-statistic values 0.71, 0.63, and 0.68, for mortality, HF-hospitalization or their composite respectively) (9–13). Patient-data in these models were derived predominantly from randomized controlled intervention trials, which enroll highly selected and motivated patients who volunteer for research, or from administrative data-sets, such as medical insurance claims, that often have diagnostic inaccuracies and fail to record key clinical data such as the blood pressure or a measure of renal function.

BIOSTAT-CHF is a large European project, which was specifically designed to develop and validate risk prediction models in patients with HF (14). In the present report we provide the principle findings of this study.

Methods

The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) recommendation was used as guideline in developing and validating our prediction models (15).

Patient index and validation cohort

Our models were developed using data from the BIOSTAT-CHF cohort (14). In short, BIOSTAT-CHF enrolled an index cohort of 2,516 patients from 69 hospital centers in 11 European countries predominantly during 2010-2014 and a comparable validation cohort of 1,728 patients from 6 centers in Scotland, UK enrolled predominantly during years 2010-2014. Patients were enrolled as in-patients or from outpatient clinics. The median follow-up in each cohort was 21 months with an interquartile range of 15 and 27 months respectively. Patients from the index cohort were aged >18 years with symptoms of new-onset or worsening HF, confirmed either by a left ventricular ejection fraction (LVEF) of ≤40% or B-type Natriuretic Peptide (BNP) and/or (N-terminal pro) B-type natriuretic peptide (NT-proBNP) plasma levels >400 pg/ml or >2,000pg/ml, respectively, treated with either oral or intravenous furosemide ≥40 mg/day or equivalent at the time of inclusion. BIOSTAT-CHF was also designed to establish the effects and response to of initiation and up-titration of and response to guideline directed medical therapy. Therefore, in order to be considered for enrollment in either cohort, patients had either not to be treated with an ACE-inhibitor/ARB and/or beta-blocker or had to treated with ≤50% of target doses of these therapies at the time of inclusion and with an anticipated initiation or up-titration of such therapy by the treating physician.

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.
Patients were regularly contacted, usually by telephone, to collect information on medication and clinical events.

Outcomes and predictor variables

Primary outcomes were time to all-cause mortality, first HF-hospitalization and the composite outcome of all-cause mortality and HF-hospitalization.

The predictive value of 42 demographic, clinical and biochemical variables measured at inclusion in the cohort, previously reported to be associated with mortality and hospitalization, were evaluated with Cox proportional hazards models. An overview of the predictor variables and summary statistics are available in supplemental table (S1).

For all quantitative variables non-linearity of the log-hazard with quantitative values were evaluated using restricted cubic splines (16). For the non-linear variables transformations to linearity were applied (e.g. log-transformation or square root) and re-tested using cubic splines. The proportionality assumption of the Cox model was assessed using Schoenfeld residuals and the Therneau and Grambsch non-proportionality test (17).

Missing predictor values were imputed using multi-chain Monte Carlo methods with Gibbs sampling. We used the R-package 'mice' (18). We imputed missing data five times, performed

the analysis over all five imputations and averaged results using Rubin's rule (18).

Model Development

We conducted stepwise backward regressions on the predictor variables by Akaike information criterion (AIC) in 1000 bootstrap samples for each imputation set. We chose variables for our full model when predictor variables were selected in more than 40% of all 5×1000 bootstrap samples. In addition, to make our models more applicable in medical practice, we developed a reduced compact model with a maximum of five predictor variables in the mortality and HF-hospitalization models and ten in the composite model. We used variables selected in the compact model to develop a simplified risk score, using a decision tree algorithm (19), and calculated survival using Cox proportional hazards for all three outcomes.

Model Validation

We first validated our models internally correcting the raw c-statistic for optimism by 1000 bootstrap sampling in the five imputation sets. We used the procedure suggested by Musoro et al (20). Second, we validated our models externally in the validation cohort data. For all patients in this cohort we calculated the risk score using the Cox-regression weights estimated from the index cohort and subsequently calculated the c-statistic for the validation cohort. We then compared the distribution of prediction scores in the index cohort with the distribution of those from the validation cohort. We also applied two prediction models (the Seattle Heart Failure Model (SHFM) (21) and the MAGGIC (22) mortality scores) to the BIOSTAT-CHF cohort and compared c-statistic values to our developed models. Additionally, we compared c-statistic values in our models for patients with either HFrEF or HFpEF in the index and validation cohorts.

Results

Patients in the index cohort (n=2516) had a mean (±SD) age of 69 (±12) years, 27% were female, 83% were in NYHA II-III with a mean (±SD) LVEF of 31 (±11)%, and 162 (7%) had a LVEF>45%. Further details were previously published (14). Most patients were enrolled during an admission for worsening heart failure (55%). During a median follow-up of 21 [15-27] months, 657 (26%) patients died, 613 (24%) were hospitalized at least once for worsening HF and 1,019 (41%) had a first event of either death or HF-hospitalization. Patients in the validation cohort (n=1738) had a mean (±SD) age of 74 (±11) years, 34% was female. 85% were in NYHA II-III with a mean (±SD) LVEF of 41(±13)%, and 529 (34%) had a LVEF>45% (14). Most patients in this cohort were enrolled as out-patients (46%). During a median follow-up of 21 [11-32] months, 589 (34%) patients died and 610 (35%) were hospitalized for worsening of HF, and 894 (51%) had a first event of either death or HF-hospitalization.

Model Development index cohort

Full models

The final full models included those variables that appeared in >40% of the bootstrap analyses (supplementary figure S1), which for mortality consisted of 16 variables (Table 1) and yielded a raw c-statistic of 0.73 (0.73 after correction for optimism). The relation of each variable with the outcome parameters are presented in supplementary table S2. The final full model to predict HF-hospitalization incorporated 10 variables, which achieved a raw c-statistic of 0.69 (0.68 after correction for optimism). The final full model to predict the composite outcome

consisted of 15 variables, which had a raw c-statistic of 0.71 (0.70 corrected for optimism).

Compact models

The final compact mortality model included 5 variables that appeared in more than 70% of the bootstrap analyses. Greater age, higher blood urea nitrogen (BUN) and NT-proBNP, lower hemoglobin and failure to prescribe a beta-blocker predicted a higher mortality with a raw c-statistic of 0.69 (0.69 after correction for optimism). The final compact model to predict HF-hospitalization included 5 variables that appeared in more than 60% of the bootstrap analyses. Greater age, HF-hospitalization in year prior to inclusion, presence of edema, lower systolic blood pressure (SBP) and lower estimated glomerular filtration rate (eGFR) predicted an increased risk of HF hospitalization with a raw c-statistic of 0.67, and 0.66 after correcting for optimism. The final compact model to predict the combined endpoint included 9 variables that appeared in more than 70% of the bootstrap analyses. Greater age, HF-hospitalization in the year prior to inclusion, presence of edema, higher NT-proBNP, lower SBP, hemoglobin, HDL-cholesterol, and serum sodium concentration and failure to prescribe a beta-blocker predicted the composite outcome with a raw and optimism corrected c-statistic value of 0.69.

Point score model

For the risk score we used the variables from the compact model. The decision tree algorithm selected the following cut-off points for optimal classification: NT-proBNP >4000 pg/ml, BUN >11 mmol/l, HDL <1.05 mmol/l, age >70 years, sodium <140 mmol/l, hemoglobin (HB) <12 g/dL, eGFR (CKD-EPI formula) <40 ml/min and SBP <140 bpm.

A score for each patient was subsequently calculated by adding one point for each 'adversely' affected variable, resulting in a score range of 0-5, 0-5, 0-9 for mortality, hospitalization, and

the combined endpoint respectively. Kaplan Meier survival curves for each score were then calculated (figure 1). The risk scores can be calculated using the online calculator which can be found at: http://www.biostat-chf.eu

In the validation cohort, the c-statistic for the full models were 0.73, 0.64, and 0.68 for mortality, HF-hospitalization and their composite, respectively and 0.72, 0.61, and 0.67 for the compact models. The two-year event rates for risk scores were almost uniformly higher in the validation cohort (figure 1). Calibration plots are presented in supplementary figures S2 and S3. Applying the SHFM and MAGGIC mortality scores to our cohort achieved a similar c-statistic (0.68) to the BIOSTAT compact model.

Difference between HFrEF and HFpEF

In the index cohort, for mortality, HF-hospitalization, and their composite, the final full models yielded c-statistics of 0.73, 0.69, and 0.71 for HFrEF and 0.65, 0.61 and 0.62 for HFpEF and for the compact models 0.69, 0.67, and 0.70 for HFrEF and 0.64, 0.62 and 0.61 for HFpEF. These differences between HFrEF and HFpEF patients in the index cohort were not present in the validation cohort, as presented in table 4. The final full mortality, HF-hospitalization, and their composite models yielded c-statistic values 0f 0.74, 0.63, and 0.68 for HFrEF and 0.72, 0.64 and 0.69 for HFpEF and for the compact models 0.72, 0.62, and 0.67 for HFrEF and 0.71, 0.61 and 0.67 for HFpEF.

Discussion

This analysis demonstrates that a small number of readily available clinical variables predict

outcome consistently and with reasonable accuracy in two patient populations with symptomatic HF representative of current clinical practice. Predictors of mortality were remarkably different from predictors of HF-hospitalization.

We recently published a meta-analysis on all available risk-prediction models in patients with HF (9). In 117 models, 249 different variables were used. The mean c-statistic across all models was 0.71, 0.63 and 0.68 for predicting mortality, HF-hospitalization, or their composite, respectively. The BIOSTAT-CHF prediction model for mortality therefore performed slightly better than average. This is remarkable, since BIOSTAT-CHF included much broader and more heterogeneous populations, closer to routine clinical practice, than the populations providing the data for most other HF risk prediction models (8).

We also compared our risk scores to two other more complex models based mainly on clinical trial populations; the Seattle Heart Failure Model (SHFM) (21) and the MAGGIC (22) which reported c-statistics of 0.72 and 0.75 respectively for predicting mortality (21; 22). C-statistic values of the SHFM and MAGGIC mortality scores to our cohort achieved a similar c-statistic (0.68) to the BIOSTAT compact model. This supports the hypothesis that our patient population is more heterogeneous, making it more difficult to achieve accurate predictions.

The majority of currently existing prognostic models in patients with heart failure are based on data from randomized controlled trials or extracted from administrative data-sets, such as medical insurance claims. Patients selected for clinical trials are generally a highly selected group of volunteers that have few serious co-morbidities and a high disease burden. Administrative datasets often do not include the detailed medical data needed to develop

accurate prediction models. BIOSTAT-CHF included a broad cohort of patients in Europe, with a very limited number of in- and exclusion criteria. And therefore better reflects patients with HF in daily clinical practice.

Similar to many other risk prediction models, we found that the accuracy to predict mortality was moderate, but the model was less accurate at predicting HF-hospitalization. This might be because worsening evidence of HF is not the sole or even dominant factor precipitating hospitalization. Co-morbidity, frailty, community heart failure services, ability to manage life-style and medications, social support networks and cultural factors poorly related to disease severity may all be important determinants of hospitalization. Accordingly, no relation has been found between early readmissions and mortality after a first hospitalization (23-26)

The predictors of mortality were very different from those of HF-hospitalization. The only variable included in all compact models was age. The majority of our predictors of HF-hospitalization have been described in other models as well. In particular, a previous HF-hospitalization identifies patients at greater risk of (re)hospitalization; it was associated with a more than doubled risk of repeat HF-hospitalization (27). This variable therefore might identify an especially vulnerable patient-group in which fluid balance is easily disrupted, hence causing signs and symptoms of congestion warranting admission and intravenous diuretic treatment. The finding that edema is also a marker of increased hospitalization risk but not of mortality supports this notion and suggests that the underlying pathology might differ significantly (28).

In our mortality model, BUN was an independent predictor, while eGFR was a predictor of re-hospitalizations. BUN is one of the strongest predictors of adverse outcome in HF, and the

information captured by this marker is often thought to encompass more than renal function alone (29; 30). However, eGFR and BUN are strongly correlated and this in part explains the absence of BUN in the hospitalization model and the absence of eGFR in the mortality model.

Interestingly, serum sodium and HDL are only included in the compact models for the combined endpoint. The inclusion of HDL in these models was not expected beforehand, yet in one report on a small population of patients with advanced HF, HDL was the strongest predictor of an adverse outcome (31). Traditionally, HDL has been associated with the risk of atherosclerosis, however recent evidence showed that the HDL proteome also plays an important role in inflammation (32). Hyponatremia is a well-recognized predictor of poor outcome in both acute and chronic HF and it is therefore not surprising that low serum sodium is associated with an increased risk of the combined endpoint (33; 34). Failure to prescribe a beta-blocker at baseline was associated with a lower risk of mortality and the combined endpoint. The inclusion of beta-blocker use in our model might be confounded by disease severity influencing tolerability of beta-blockers creating a potential selection bias. In addition, suboptimal medical treatment was an inclusion criterion for our study. However, it may also confirm the importance of the use of beta-blockers in HF and its effect on improved outcome. Further analyses of the BIOSTAT-CHF study will attempt to determine the determinants and clinical outcome related to inadequate up-titration of ACE-inhibitors and/or beta-blockers.

Limitations and Strengths

The BIOSTAT-CHF cohort is a European multi-national prospective cohort. Healthcare systems and patient treatment between the different European countries vary greatly. This might influence management, outcome and prediction, although all investigators were encouraged to

follow the recommendations of the ESC HF Guidelines. However, because of the multi-national character of this cohort, the results will be highly generalizable. Our validation cohort consisted only of patients from Scotland. This cohort might not resemble the heterogeneity of the European patient population. However, this cohort was a completely independent validation cohort with no ties to the index cohort.

Both in the index and validation cohorts, BIOSTAT-CHF included patients with HFrEF and HFpEF. This can be regarded as both a strength and a limitation. The HFpEF patients in the index cohort were limited to those patients with NT-proBNP levels >2000 pg/mL, thereby increasing the reliability of the diagnosis but reducing its prevalence and excluding milder cases. There were small differences in c-statistic values between HFrEF and HFpEF in the index cohort, but in the validation cohort, the prediction model performed similarly in patients with either HFpEF or HFrEF. Therefore, the current risk prediction model is representative for the overall HF population, which was not the case in the majority of the previously published models that only included selected patients with HFrEF.

Conclusion

We developed and validated models for predicting mortality, HF-hospitalization and the combined outcome of mortality and HF-hospitalization. Predictors of mortality were remarkably different from predictors of HF-hospitalization. In addition, we presented a simplified risk score for use in clinical practice. In comparison with well-known existing prediction scores, our developed models performed better in this patient population.

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References

[1] Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJV, Ponikowski P, Poole-Wilson PA, et al. 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. Eur Heart J. 2008 oct;29(19):2388–442.

[2] McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. 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. Eur J Heart Fail. 2012;14:803–869.

[3] McAlister FA, Stewart S, Ferrua S, McMurray JJJV. Multidisciplinary strategies for the management of heart failure patients at high risk for admission: A systematic review of randomized trials. J Am Coll Cardiol. 2004;44:810–819.

[4] Whellan DJ, Hasselblad V, Peterson E, O'Connor CM, Schulman KA. Metaanalysis and review of heart failure disease management randomized controlled clinical trials. Am Heart J. 2005;149:722–729.

[5] Jaarsma T, van der Wal M, Lesman-Leegte I, Luttik ML, Hogenhuis J, Veeger N, et al. Effect of moderate or intensive disease management program on outcome in patients with heart failure: Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart failure (COACH). Arch Intern Med . 2008;168:316–324.

[6] de la Porte PW, Lok DJ, van Veldhuisen DJ, van Wijngaarden J, Cornel JH, Zuithoff NP, et al. Added value of a physician-and-nurse-directed heart failure clinic: results from the Deventer-Alkmaar heart failure study. Heart. 2007;93:819–825.

[7] Fonarow GC, Albert NM, Curtis AB, Gattis Stough W, Gheorghiade M, Heywood JT, et al. Improving evidence-based care for heart failure in outpatient cardiology practices: Primary results of the registry to improve the use of evidence-based heart failure therapies in the outpatient setting (IMPROVE HF). Circulation. 2010;122:585–596.

[8] Steyerberg EW. Applications of Prediction Models. In: Clinical Prediction Models A Practical Approach to Development, Validation, and Updating, New York, Springer New York; 2009

[9] Ouwerkerk W, Voors AA, Zwinderman AH. Factors Influencing the Predictive Power of Models for Predicting Mortality and/or Heart Failure Hospitalization in Patients With Heart Failure. JACC Heart Fail. 2014;2:429–436.

[10] Ross JS, Mulvey GK, Stauffer BD, Patlolla V, Bernheim SM, Keenan PS, et al. Statistical Models and Patient Predictors of Readmission for Heart Failure. Arch Intern Med. 2008;168:1371–1386.

[11] Giamouzis G, Kalogeropoulos A, Georgiopoulou V, Laskar S, Smith AL, Dunbar S, et al. Hospitalization epidemic in patients with heart failure: risk factors, risk prediction, knowledge gaps, and future directions. J Card Fail. 2011 ;17:54–75.

[12] Kansagara D, Englander H, Salanitro A, Kagen D, Theobald C, Freeman M, et al. Risk PredictionModels forHospitalReadmission A Systematic Review. JAMA. 2011;306:1688–98.

[13] Betihavas V, Davidson PM, Newton PJ, Frost Sa, Macdonald PS, Stewart S. What are the factors in risk prediction models for rehospitalisation for adults with chronic heart failure? Aust Crit Care. 2012;25:31–40.

[14] Voors AA, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, et al. A systems biology study to tailored treatment in chronic heart failure: rationale, design, and baseline characteristics of BIOSTAT-CHF. Eur J Heart Fail. 2016;in press.

[15] Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD Statement. BMC Med. 2015;13:1–10.

[16] Harrell F. Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis; New York: Springer New York; 2001.

[17] Grambsch PM, Therneau TM. Proportional hazards test and diagnostics based on weighted residuals. Biometrika. 1994;81:515–526.

[18] van Buuren S, Groothuis-oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. J Stat Softw. 2011;45:1—-67.

[19] Breiman L, Freidman JH, Olshen RA, Stone CJ. Classification and Regression. New York: Chapman & Hall; 1984.

[20] Musoro JZ, Zwinderman AH, Puhan Ma, ter Riet G, Geskus RB. Validation of prediction models based on lasso regression with multiply imputed data. BMC Med Res Methodol. 2014;14:116.

[21] Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation. 2006;113:1424–33.

[22] Pocock SJ, Ariti Ca, McMurray JJV, Maggioni A, Køber L, Squire IB, et al. Predicting survival in heart failure: A risk score based on 39 372 patients from 30 studies. Eur Heart J. 2013;34:1404–1413.

[23] Dharmarajan K, Hsieh AF, Lin Z, Bueno H, Kim N, Bernheim SM, et al. NIH Public Access. 2013;309:355–363.

[24] Krumholz HM, Lin Z, Keenan PS, Chen J, Ross JS, Drye EE, et al. Relationship of Hospital Performance with Readmission and Mortality Rates for Patients Hospitalized with Acute Myocardial Infarction, Heart Failure, or Pneumonia. Jama. 2013;309:587–593.

[25] Heidenreich Pa, Sahay A, Kapoor JR, Pham MX, Massie B. Divergent trends in survival and readmission following a hospitalization for heart failure in the Veterans Affairs health care system 2002 to 2006. J Am Coll Cardiol. 2010;56:362–8.

[26] Kociol RD, Liang L, Hernandez AF, Curtis LH, Heidenreich PA, Yancy CW, et al. Are we targeting the right metric for heart failure? comparison of hospital 30-day readmission rates and total episode of care inpatient days. Am Heart J. 2013;165:987–994.e1.

[27] Bello NA, Claggett B, Desai AS, McMurray JJV, Granger CB, Yusuf S, et al. Influence of previous heart failure hospitalization on cardiovascular events in patients with reduced and preserved ejection fraction. Circ Heart Fail. 2014;7:590–595.

[28] Gheorghiade M, Follath F, Ponikowski P, Barsuk JH, Blair JEA, Cleland JG, et al. Assessing and grading congestion in acute heart failure: A scientific statement from the acute heart failure committee of the heart failure association of the European society of cardiology and endorsed by the European society of intensive care medicine. Eur J Heart Fail. 2010;12(5):423–433.

[29] Cleland JG, Chiswell K, Teerlink JR, Stevens S, Fiuzat M, Givertz MM, et al. Predictors of Postdischarge Outcomes From Information Acquired Shortly After Admission for Acute Heart Failure: A Report From the Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized W. Circ Hear Fail. 2014;7:76–87.

[30] Filippatos G, Rossi J, Lloyd-Jones DM, Stough WG, Ouyang J, Shin DD, et al. Prognostic Value of Blood Urea Nitrogen in Patients Hospitalized With Worsening Heart Failure: Insights From the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) Study. J Card Fail. 2007;13(5):360–364.

[31] Mehra MR, Uber PA, Lavie CJ, Milani RV, Park MH, Ventura HO. High-density Lipoprotein Cholesterol Levels and Prognosis in Advanced Heart Failure. J Heart Lung Transplant. 2009;28:876–880.

[32] Connelly MA, Shalaurova I, Otvos JD. HDL and Inflammation in Cardiovascular Disease. Transl Res. 2016;p. 1–12.

[33] Gheorghiade M, Abraham WT, Albert NM, Gattis Stough W, Greenberg BH, O'Connor CM, et al. Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: An analysis from the OPTIMIZE-HF registry. Eur Heart J. 2007;28:980–988.

[34] Khazanie P, Heizer GM, Hasselblad V, Armstrong PW, Califf RM, Ezekowitz J, et al. Predictors of clinical outcomes in acute decompensated heart failure: Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure outcome models. Am Heart J. 2015;170:290–297.e1.

Table 1: Cox Proportional Hazards for final full models

	Mortality			HF-Hospitalization			Combined endpoint		
	logHR	se(logHR)	p	logHR	se(logHR)	P	logHR	se(logHR)	p
Age (years)	0.03	0.004	<0.0001	0.01	0.004	0.0005	0.02	0.004	<0.0001
Ischemic etiology	0.31	0.084	0.0002						
Heart failure hospitalization in last year				0.52	0.084	<0.0001	0.38	0.068	<0.0001
Smoking									
No							-	-	-
Past							0.11	0.071	0.1267
Current							0.35	0.107	0.0012
DM				0.28	0.086	0.0009			
COPD	0.25	0.093	0.0084				0.16	0.078	0.0374
NYHA class									
NYHA class I							-	-	-
NYHA class II							0.16	0.292	0.5822
NYHA class III							0.38	0.287	0.1813
NYHA class IV							0.35	0.302	0.2441
Peripheral edema	0.28	0.090	0.0021	0.25	0.091	0.0052	0.22	0.073	0.0020
Elevated Jugular venous pressure									
No	-	-	-	-	-	-		-	-
Yes	0.22	0.110	0.0482	0.29	0.098	0.0029	0.20	0.078	0.0084
Uncertain	0.13	0.179	0.4498	0.27	0.197	0.1725	0.15	0.172	0.3984
DBP (mmHg)	-0.01	0.004	0.0037						
SBP (mmHg)	-0.00	0.003	0.2962	-0.01	0.002	<0.0001	-0.01	0.002	0.0003
eGFR (CKD-EPI formula)(ml/min)				-0.01	0.002	<0.0001	-0.01	0.002	0.0064

Log-BUN (mmol/L)	0.33	0.064	<0.0001				0.15	0.066	0.0233
Log-NT-proBNP (ng/L)	0.26	0.047	<0.0001	0.11	0.048	0.0205	0.13	0.040	0.0009
Hemoglobin (g/dL)	-0.23	0.077	0.0034				-0.09	0.018	<0.0001
Hematocrit (g/dL)	0.05	0.027	0.0626						
Sodium (mmol/L)	-0.03	0.010	0.0099				-0.02	0.008	0.0026
Log-Total Bilirubin (μmol/L)	0.08	0.085	0.3589				0.10	0.057	0.0798
Log-Alkaline Phosphatase (μg/L)	0.32	0.097	0.0011				0.25	0.084	0.0035
HDL (mmol/L)	-0.39	0.147	0.0075	-0.37	0.126	0.0031	-0.33	0.116	0.0042
Use of beta-blocking agent at baseline	-0.29	0.087	0.0009	-0.30	0.089	0.0007	-0.27	0.070	0.0064

Abbreviations: BUN: blood urea nitrogen; COPD: Chronic Obstructive Pulmonary Disease; DBP: Diastolic Blood Pressure; DM: Diabetes Mellitus; eGFR: estimated Glomerular Filtration Rate; HDL: high density lipoprotein; HF: heart failure; HR: hazard ratio; NT-proBNP: N terminal pro Brain Natriuretic Peptide; SBP: Systolic Blood Pressure

Table 2: Cox Proportional Hazards for final compact models

	Mortality			HF-Hospitalization			Combined endpoint		
	logHR	se(logHR)	p	logHR	se(logHR)	p	logHR	se(logHR)	p
Age (years)	0.02	0.004	<0.0001	0.01	0.004	0.0039	0.03	0.003	<0.0001
Heart failure hospitalization in last year				0.55	0.083	<0.0001	0.42	0.067	<0.0001
Peripheral edema				0.43	0.083	<0.0001	0.34	0.068	<0.0001
SBP (mmHg)				-0.01	0.002	<0.0001	-0.01	0.002	<0.0001
eGFR (CKD-EPI formula)(ml/min)				-0.01	0.002	<0.0001			
Log-BUN (mmol/L)	0.42	0.062	<0.0001						
Log-NT-proBNP (ng/L)	0.34	0.044	<0.0001				0.21	0.038	<0.0001
Hemoglobin (g/dL)	-0.12	0.022	<0.0001				-0.10	0.018	<0.0001
HDL (mmol/L)							-0.49	0.120	<0.0001
Sodium (mmol/L)							-0.03	0.008	0.0002
Use of beta-blocking agent at baseline	-0.27	0.086	0.0019				-0.29	0.069	<0.0001

Abbreviations: BUN: blood urea nitrogen; eGFR: estimated Glomerular Filtration Rate; HDL: high density lipoprotein; HF: Heart Failure; HR: Hazard Ratio; NT-proBNP: N terminal pro Brain Natriuretic Peptide

Table 3: C-statistic values of all models for mortality, hospitalization and the combined endpoint

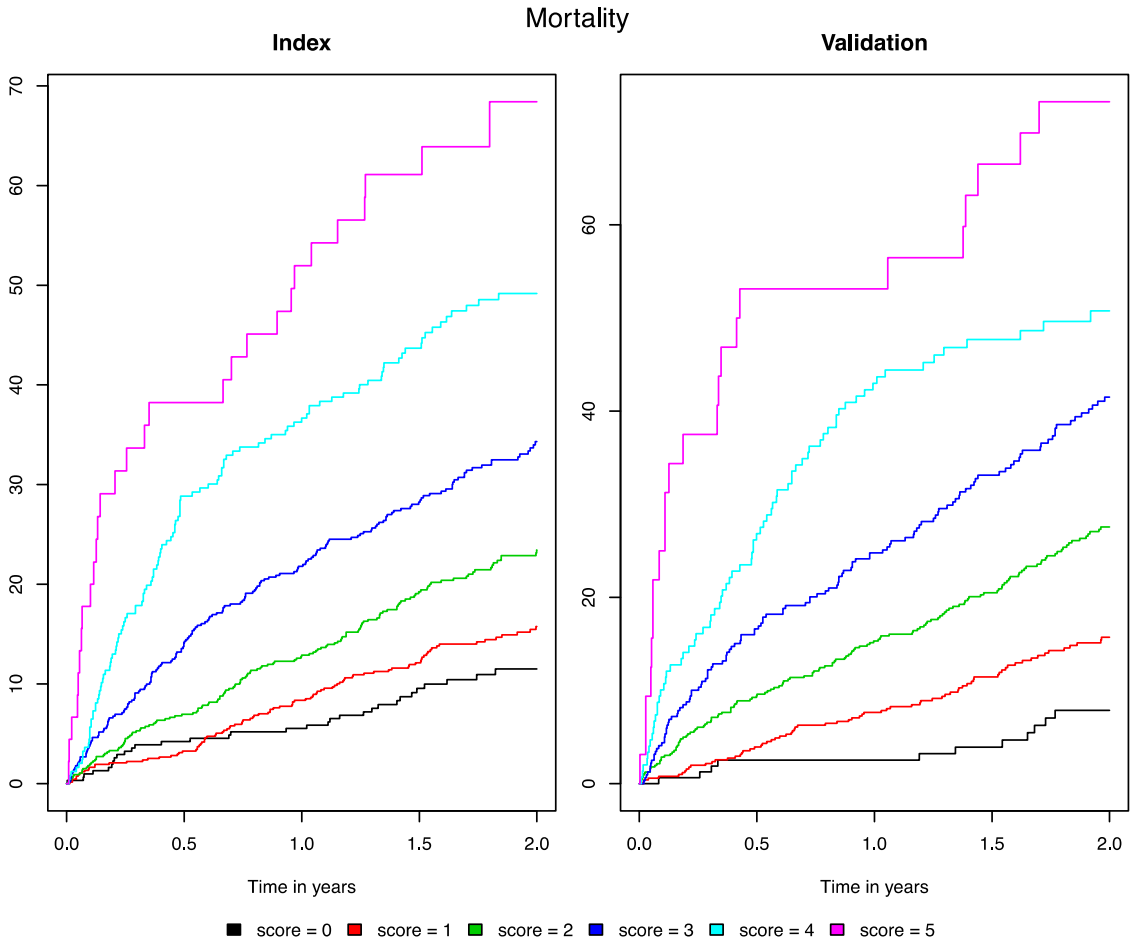
	Model development		Model validation			
	Index cohort		Internal		External	
	Full	Compact	Full	Compact	Full	Compact
Mortality	0.73	0.69	0.73	0.69	0.73	0.73
HF- Hospitalization	0.69	0.67	0.68	0.66	0.63	0.63
Combined endpoint	0.71	0.69	0.70	0.69	0.68	0.68

Table 4: C-statistic values of all models for mortality, hospitalization and the combined endpoint in HFrEF and HFpEF patients

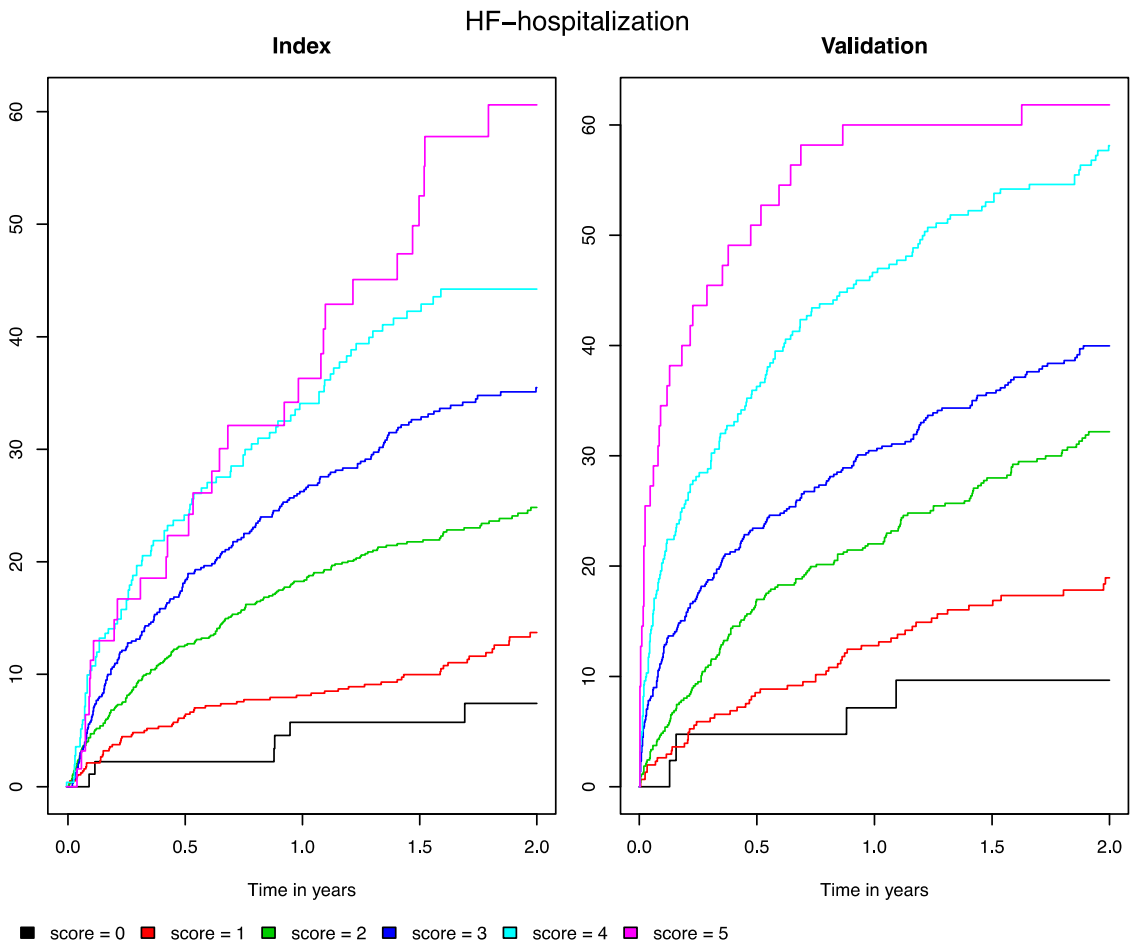
	Index cohort				Validation cohort			
	Full		compact		Full		compact	
	HFrEF	HFpEF	HFrEF	HFpEF	HFrEF	HFpEF	HFrEF	HFpEF
Mortality	0.73	0.65	0.69	0.64	0.74	0.72	0.72	0.71
HF- Hospitalization	0.69	0.61	0.67	0.62	0.63	0.64	0.62	0.61
Combined endpoint	0.71	0.62	0.70	0.61	0.68	0.69	0.67	0.67

Figure 1: Kaplan Meier survival curves for the point scale models (A: Mortality, B:HF-hospitalization, c: Combined endpoint)

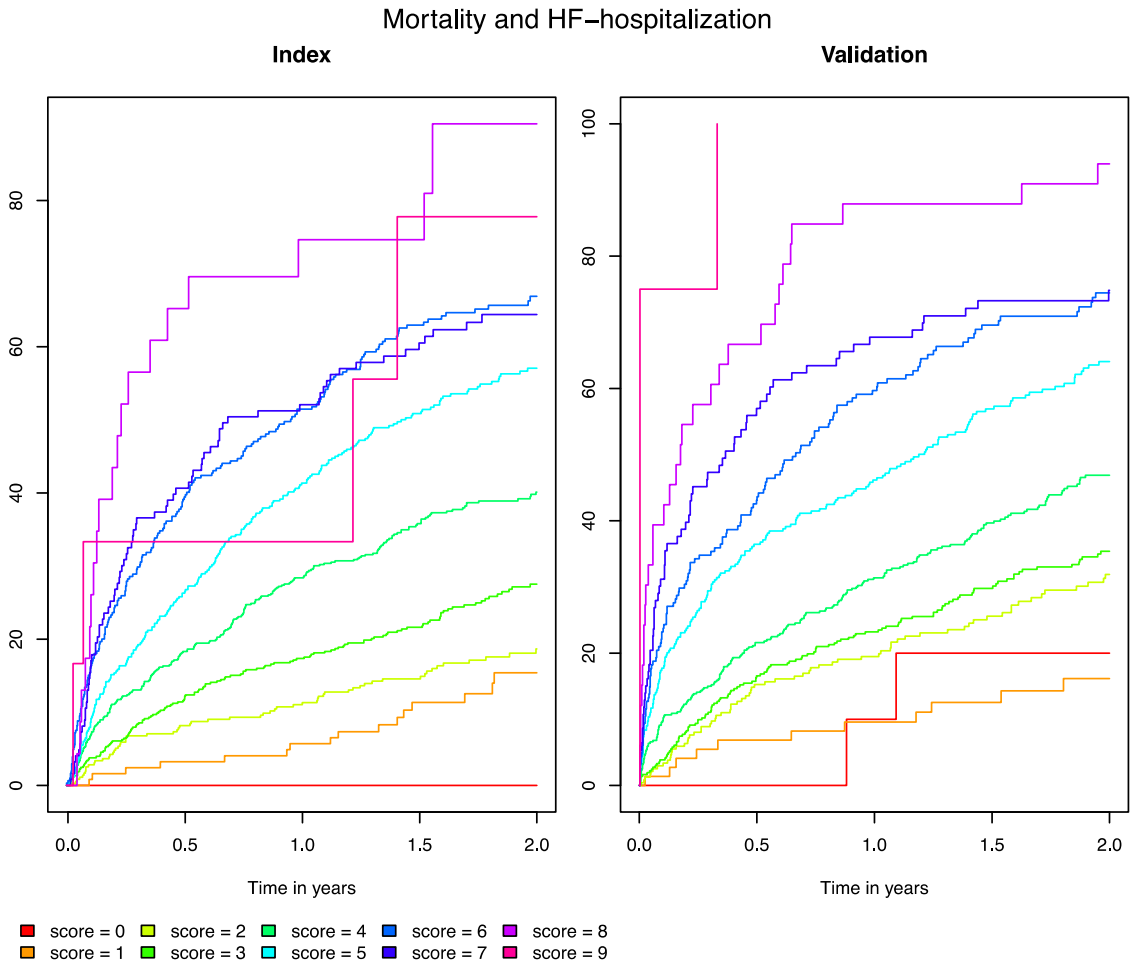
A



B


HF−hospitalization
Index
Validation
0
10
20
30
40
50
60
0.0
0.5
1.0
1.5
2.0
Time in years
score = 0
score = 1
score = 2
score = 3
score = 4
score = 5

C


Mortality and HF–hospitalization
Index
Validation
0
20
40
60
80
100
0.0
0.5
1.0
1.5
2.0
Time in years
score = 0
score = 1
score = 2
score = 3
score = 4
score = 5
score = 6
score = 7
score = 8
score = 9

Supplementary data

Table S1: Description of each variable used in model development (% (number), mean (sd) or median (interquartile range)

	Index	Validation
Sex (% Male(n))	73.4 (1846)	65.9 (1145)
Age (years)	68.9 (±12)	73.7 (±10.7)
Smoking		
Past	48 (*1220*)	35 (602)
Current	14 (353)	13.7 (236)
Alcohol usage	28 (700)	47 (790)
Body mass index (kg/m2)	27.9 (±5.5)	28.1 (±6.4)
Heart rate (bmp)	80 (±19.5)	74.2 (±16.6)
Systolic blood pressure (mmHg)	124.7 (±21.9)	125.9 (±22.6)
Diastolic blood pressure (mmHg)	74.9 (±13.4)	69.2 (±13.2)
Left ventricular ejection fraction (%)	31 (±10.6)	41 (±13.0)
HFpEF (LVEF>45%) (%)	7 (162)	34 (529)
NYHA class		
I	2.2 (56)	1.0 (17)
II	34.5 (868)	41.0 (712)
III	48.8 (1228)	44.4 (772)
IV	11.7 (294)	13.6 (236)
Ischemic heart disease (%(n))	60.5 (1358)	64.9 (1128)
Hospitalization in past year before baseline (%(n))	31.6 (794)	26.5 (460)
History of atrial fibrillation (%(n))	45.4 (1143)	43.7 (760)
Diabetes mellitus	32.6 (819)	32.3 (561)
Hypertension (%(n))	62.4 (1569)	57.9 (1007)
eGFR (CKD-EPI formula)(ml/min)	64.4 (47.5-83.4)	66.1 (47.5-83.4)

Myocardial infarction (%(n))	38.3 (963)	48.8 (849)
Coronary Artery Bypass Graft (%(n))	17.2 (433)	17.7 (308)
Percutaneous coronary intervention (%(n))	21.6 (544)	18.7 (325)
Stroke (%(n))	9.3 (233)	18.1 (315)
Peripheral artery disease (%(n))	10.9 (273)	21.5 (374)
Chronic Obstructive Pulmonary Disease (%(n))	17.3 (436)	18.4 (319)
Pulmonary congestion		
Single base	12.7 (311)	5.7 (95)
Bi-basilar	40.1 (980)	38.7 (639)
Edema (%(n))	29.7 (624)	54.9 (955)
Elevated Jugular venous pressure (%(n))	22 (554)	25.9 (450)
Hepatomegaly (%(n))	14.3 (358)	3.5 (60)
Rales >1/3 up lung fields (%(n))	19.2 (248)	2.9 (50)
Baseline medication		
Agents acting on the renin-angiotensin system (%(n))	72.3 (1820)	70.1 (1218)
Beta-blocking agents (%(n))	83.2 (2093)	72.7 (1264)
Hematocrit (%)	40.1 (36.3-43.7)	40.5 (37.0-44.3)
BUN (mmol/l)	11.1 (7.4-17.6)	8.6 (6.5-11.9)
NT-proBNP (pg/ml)	4275 (2360-8485.5)	1376 (510-3548)
Sodium (mmol/l)	140 (137-142)	139.0 (137.0-141.0)
Potassium (mmol/l)	4.2 (3.9-4.6)	4.3 (4.0-4.6)
Bilirubin (μmol/l)	14 (10-21)	10 (7-15)
HDL cholesterol (mmol/l)	1 (0.8-1.3)	1 (0.9-1.4)
Alkaline Phosphatase (μg/L)	84 (65-117)	89 (72-116)
Hemoglobin (g/dL)	13.3 (11.9-14.5)	13.2 (11.8-14.5)
Albumine (g/L)	33 (27-38)	38 (34-42)
Alanine aminotransferase (U/L)	25 (19-35)	22 (17-33)
Aspartate aminotransferase (U/L)	25 (17-38)	23 (18-31)
Glucose (mmol/L)	6.3 (5.5-7.9)	6.3 (5.2-8.4)

Abbreviations: BUN: blood urea nitrogen*; eGFR: estimate Glomerular Filtration Rate; HDL: High Density Lipoprotein; HFpEF: Heart failure with preserved ejection fraction, NYHA: New York Heart Association class; NT-proBNP: N terminal pro Brain Natriuretic Peptide*

Figure S1: Percentage of times each variables selected in bootstrap models

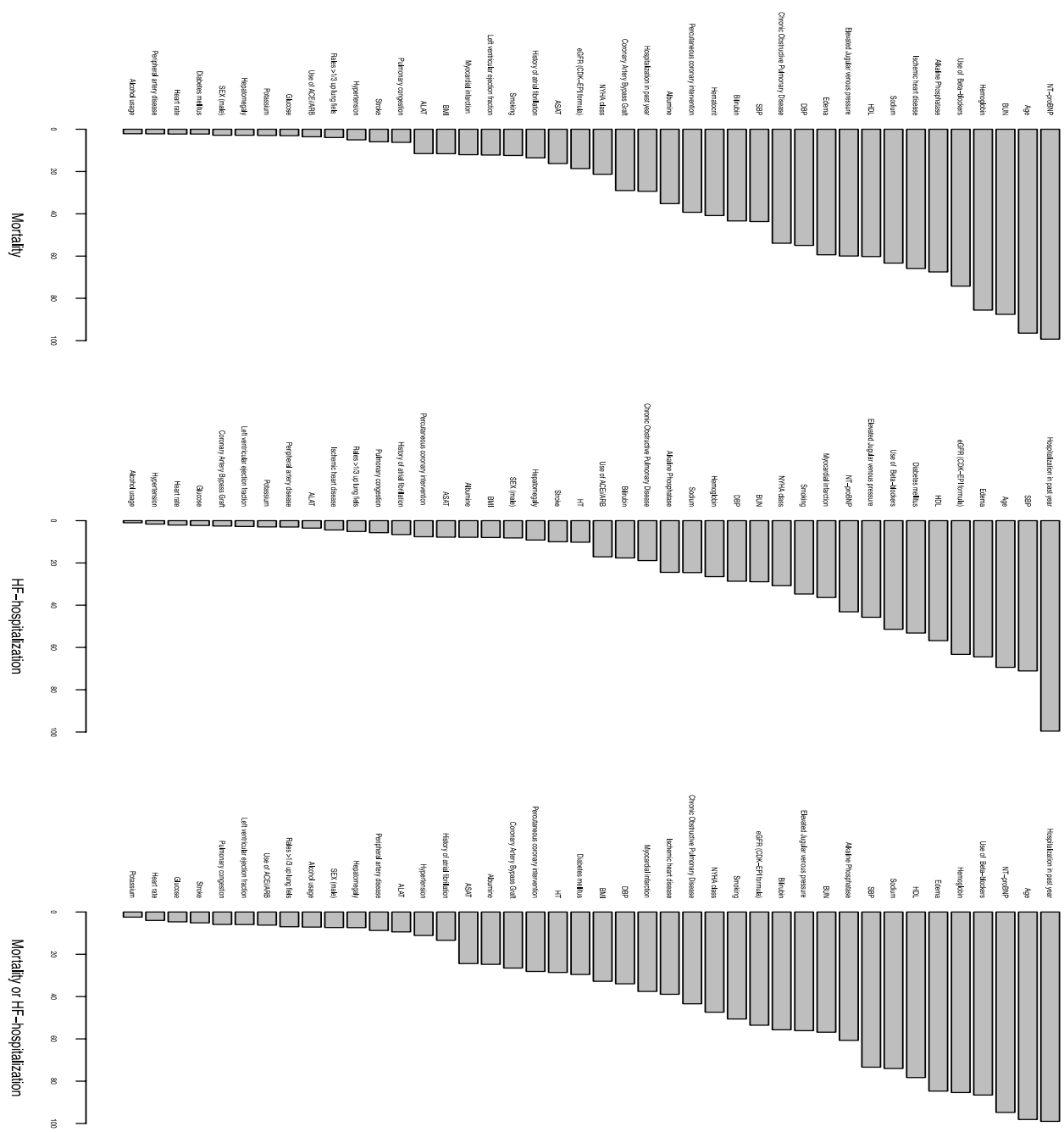


Figure S2: Calibration plot of the compact model in the Index cohort

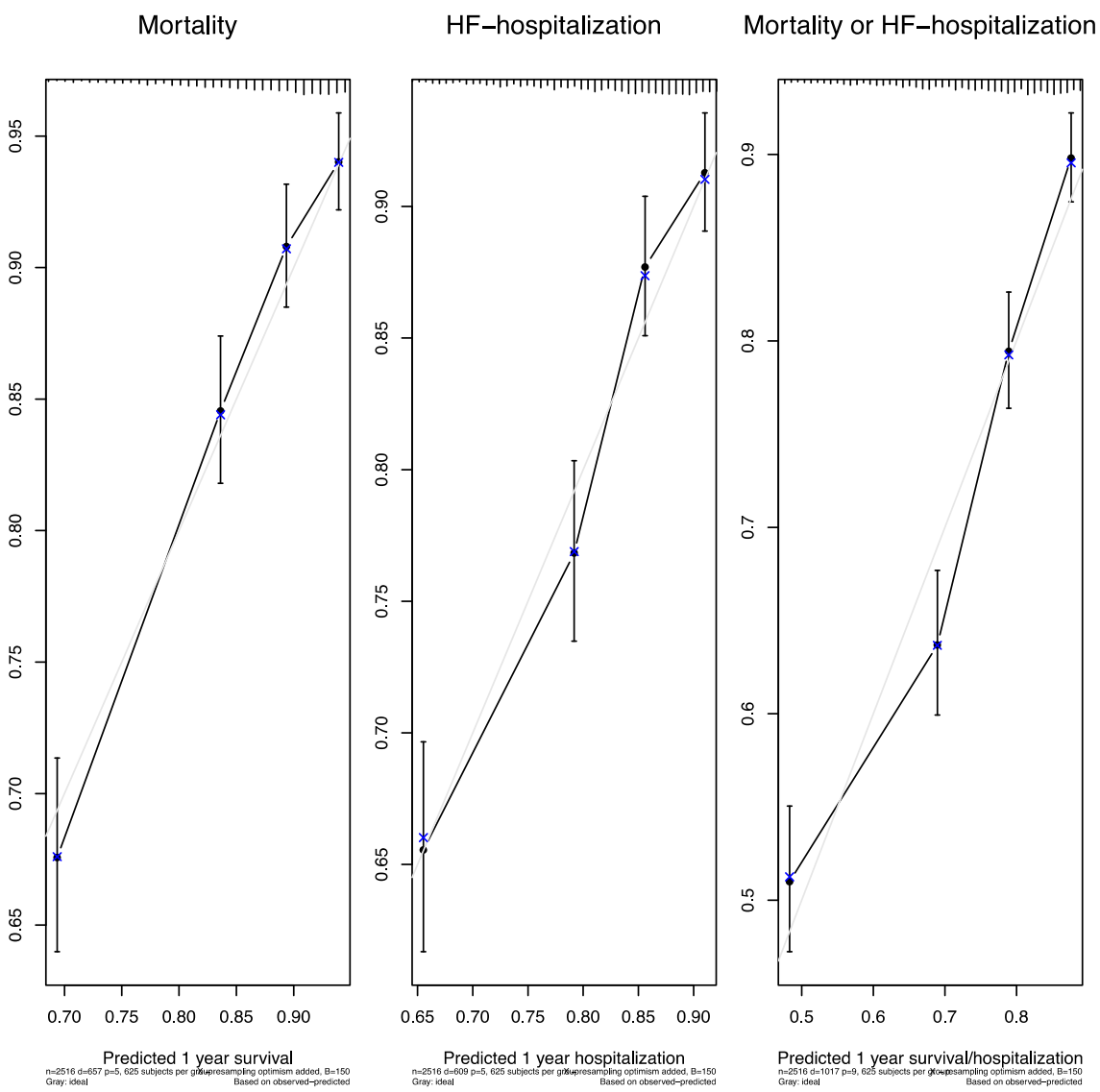


Figure S3: Calibration plot of the compact model in the validation cohort

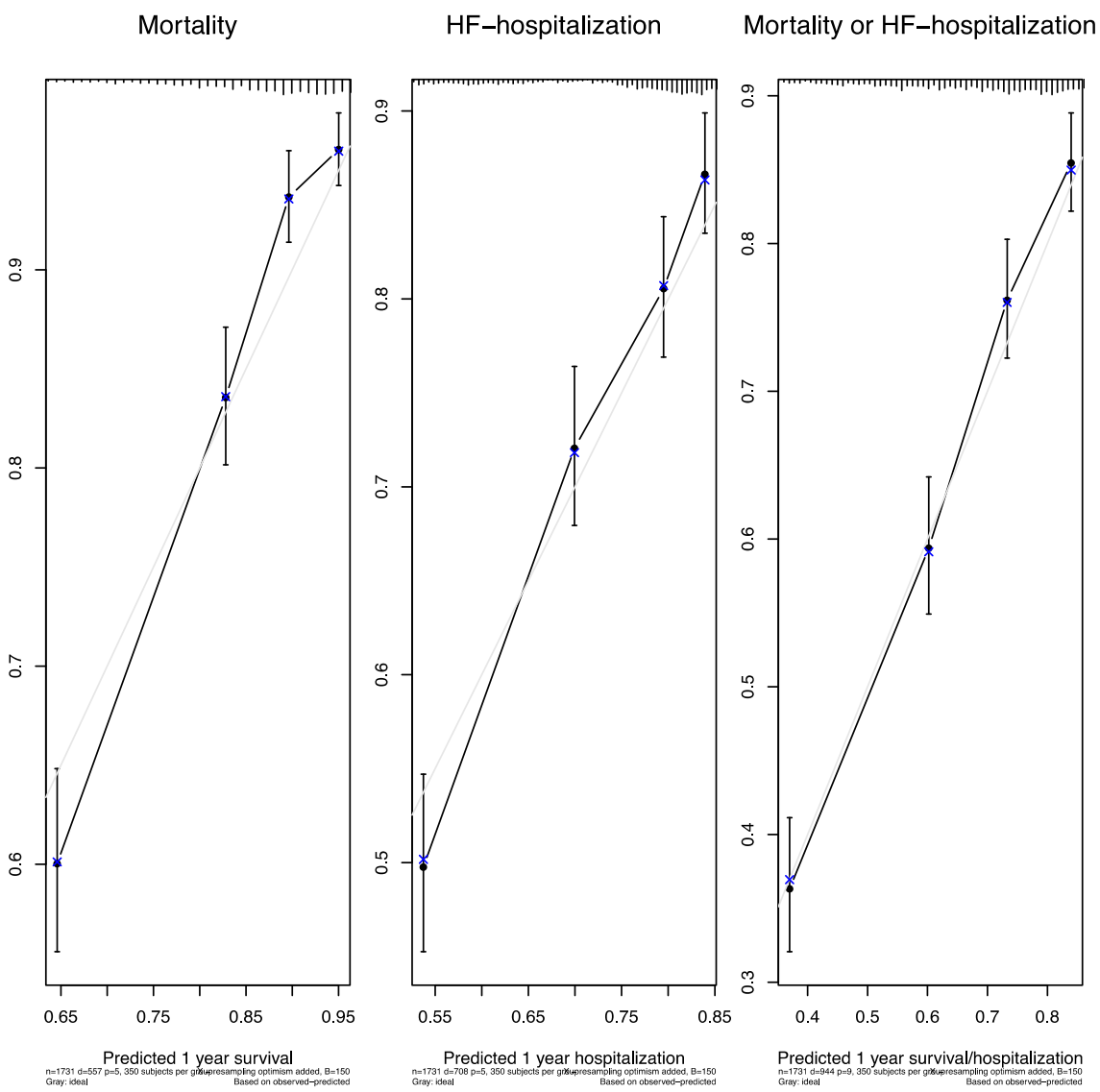


Table S2: Univariate analysis

	Mortality			HF-Hospitalization			Combined endpoint		
	logHR	se(logHR)	p	logHR	se(logHR)	P	logHR	se(logHR)	p
Age (years)	0.03	<0.01	<0.01	0.02	<0.01	<0.01	0.03	<0.01	<0.01
Ischemic etiology	0.41	0.08	<0.01						
Heart failure hospitalization in last year				0.54	0.06	<0.01	0.54	0.06	<0.01
Smoking									
No							-	-	-
Past							0.06	0.07	0.38
Current							-0.04	0.10	0.71
DM				0.44	0.08	<0.01			
COPD	0.5	0.09	<0.01				0.42	0.08	<0.01
NYHA class									
NYHA class I							-	-	-
NYHA class II							0.26	0.28	0.35
NYHA class III							0.85	0.28	<0.01
NYHA class IV							1.01	0.29	<0.01
Peripheral edema	0.62	0.08	<0.01	0.5	0.08	<0.01	0.56	0.06	<0.01
Elevated Jugular venous pressure									
No	-	-	-	-	-	-		-	-
Yes	0.62	0.10	<0.01	0.56	0.09	<0.01	0.56	0.07	<0.01
Uncertain	0.35	0.16	0.03	0.42	0.17	0.01	0.31	0.14	0.02
DBP (mmHg)	-0.03	0.03	<0.01						
SBP (mmHg)	-0.01	<0.01	<0.01	-0.01	<0.01	<0.01	-0.01	<0.01	<0.01
eGFR (CKD-EPI formula)(ml/min)				-0.02	<0.01	<0.01	-0.02	<0.01	<0.01
Log-BUN (mmol/L)	0.61	0.06	<0.01				0.54	0.05	<0.01
Log-NT-proBNP (ng/L)	0.45	0.04	<0.01	0.27	0.04	<0.01	0.35	0.04	<0.01
Hemoglobin (g/dL)	-0.21	0.02	<0.01				-0.18	0.02	<0.01
Hematocrit (g/dL)	-0.06	0.01	<0.01						

Sodium (mmol/L)	-0.06	0.01	<0.01				-0.06	0.01	<0.01
Log-Total Bilirubin (μmol/L)	0.18	0.09	0.01				0.17	0.06	<0.01
Log-Alkaline Phosphatase (μg/L)	0.44	0.11	<0.01				0.33	0.10	<0.01
HDL (mmol/L)	-0.57	0.15	<0.01	-0.57	0.13	<0.01	-0.53	0.12	<0.01
Use of beta-blocking agent at baseline	-0.32	0.08	<0.01	-0.30	0.09	<0.01	-0.30	0.07	<0.01

Abbreviations: *eGFR: estimate Glomerular Filtration Rate; HDL: High Density Lipoprotein; NYHA: New York Heart Association class; NT-proBNP: N terminal pro Brain Natriuretic Peptide*