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ORIGINAL ARTICLE

Biomarker prognostication across Universal Definition of Heart Failure stages

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Abstract

Aim The Universal Definition of Heart Failure (UDHF) provides a framework for staging risk for HF events. It is not clear whether prognostic biomarkers have different meaning across UDHF stages. We sought to evaluate performance of biomarkers to predict HF events among high-risk patients undergoing coronary and/or peripheral angiography categorized into UDHF stages.

Methods One thousand two hundred thirty-five individuals underwent coronary and/or peripheral angiography were enrolled. Study participants were categorized into UDHF Stage A (at risk), Stage B (pre-HF), and Stage C or D (HF, including end stage) and grouped into Stage A/B and C/D. Biomarkers and clinical variables were used to develop prognostic models. Other measures examined included total HF hospitalizations.

Results Over a median of 3.67 years of follow-up, 155 cardiovascular (CV) deaths occurred, and 299 patients were hospitalized with acute HF. In patients with Stage A/B, galectin-3 (HR = 1.52, $P = 0.03$), endothelin-1 (HR = 2.16, $P = 0.001$), and *N*-terminal pro-B-type natriuretic peptide (NT-proBNP; HR = 1.43, $P < 0.001$) were associated with incident CV death/HF hospitalization. In Stage C/D, NT-proBNP (HR = 1.26, $P = 0.006$), soluble urokinase-type plasminogen activator receptor (suPAR; HR = 1.57, $P = 0.007$) and high-sensitivity C-reactive protein (hs-CRP; HR = 1.15, $P = 0.01$) were associated with these outcomes. Higher biomarker concentrations were associated with greater total burden of HF events in Stages A/B and C/D.

Conclusions Among higher risk individuals undergoing angiographic procedures, different biomarkers improve risk stratification in different UDHF stages of HF. More precise prognostication may offer a window of opportunity to initiate targeted preventive measures.

Keywords Heart failure; Biomarker; Risk model; Coronary angiography; Mortality

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Introduction

Heart failure (HF) is an increasingly prevalent disorder affecting 6 million individuals in the USA[1] with substantial variation in severity and prognosis[2] but with a progressive course once fully established. Given this, every effort for earlier detection and more precise treatment is necessary, with the goal to reduce risk for progression to more symptomatic, harder-to-treat disease. Identifying those at heightened risk for incident HF or complication of pre-existing diagnosis should be a major aspect of the approach to HF care, but it may be challenging: Risk for progression of HF is complex, as the diagnosis may be marked by various biological processes including neurohormonal activation, inflammation, vascular remodelling, myocardial injury, and renal impairment.[3] Better characterization of individuals at defined stages of the diagnostic journey of HF is needed, particularly when at-risk patients may be identified in an expeditious fashion. For example, we recently reported significant rates of future HF events among patients

evaluated with coronary and/or peripheral angiography,[4] a population whose risk remains very high despite invasive evaluation and management.

Among the tools leveraged to inform better risk stratification for HF events is measurement of circulating biomarkers.[5] Biomarkers add important prognostic information in HF not otherwise available at the bedside and allow for a better understanding of the complex pathophysiology of the diagnosis. Besides *N*-terminal pro-B-type natriuretic peptide (NT-proBNP),[6] numerous biomarkers have been examined aiming to identify novel insights to the complex mechanisms of the diagnosis, including prediction of both incident HF and complication of pre-existing disease.[7]

The recent Universal Definition and Classification of HF (UDHF) articulates an approach that places individuals into four stages of the diagnosis: 'at risk' (Stage A), 'pre-HF' (Stage B), past or present symptomatic HF (Stage C), and end-stage HF (Stage D). These stages are meant to allow for more accurate gauging of risk and planning of intervention. How such staging applies to higher risk categories of individuals such as those undergoing coronary and/or peripheral angiography has not been examined, and where different biomarkers provide prognostic information in such patients in each stage is unclear. To address this, we examined concentrations of several biomarkers from samples obtained from a cohort of individuals undergoing coronary and/or peripheral angiography categorized as a function of UDHF stages. The goal of the study was to use recently articulated staging as a means by which to portray the patterns of biomarkers at these various steps along the way in the diagnosis of HF. Efforts like this will help to add an individualized description of the milieu in each stage. We hypothesized that in this high-risk population, different biomarkers might inform risk depending on where in the HF journey each patient rests.

Methods

All study procedures were approved by the Mass General/Brigham Institutional Review Board.

Study design and participants

The design of the Catheter Sampled Blood Archive in Cardiovascular Diseases (CASABLANCA) study has been described previously (ClinicalTrials.gov Identifier: NCT00842868).[8] In this heavily phenotyped cohort analysis, 1251 persons undergoing coronary and/or peripheral angiography with or without intervention between 2008 and 2011 were prospectively enrolled at the Massachusetts General Hospital in Boston, MA. Patients were referred for angiography for various acute and non-acute indications including acute coronary syndromes, HF, abnormal stress tests, stable chest pain, claudication, and routine pre-operative evaluation. As previously reported,[8] at the time of enrolment, the details of each individual study participant were queried at the bedside and supported by data extraction from the medical records; all information was verified.

Extensive historical information makes this study unique to classify stage of HF. Utilizing all available information, including past history and history at the time of angiography, results of invasive evaluations (including filling pressures and left ventricular angiograms), along with concentrations of NT-proBNP (Siemens Diagnostics, Newark, DE) and high-sensitivity cardiac troponin I (hs-cTnI, Abbott Diagnostics, Abbott Park, IL), study participants were categorized into the 2021 Universal Definition and Classification of Heart Failure Stages[9] (*Table S1*):

- **Stage A**: Persons with no past or present history of HF, no symptoms of dyspnoea, no structural cardiac changes with a left ventricular ejection fraction ≥50%, no history of acute myocardial infarction, significant aortic or mitral valve disease or history of valvular surgery, no implantable cardioverter defibrillator placement, normal filling pressures (pulmonary capillary wedge pressure <15 mmHg, left ventricular end-diastolic pressure < 13 mmHg), NT-proBNP < 300 ng/L, and hs-cTnI <99th percentile (male ≥34 ng/L; female ≥16 ng/L)
- **Stage B**: Persons with no past or present history of HF and no symptoms of dyspnoea, but with any of the following: abnormal cardiac structural changes, elevated filling pressures or abnormal biomarker concentrations (NT-proBNP ≥ 300 ng/L), and hs-cTnI ≥99th percentile (male ≥34 ng/L; female ≥16 ng/L).
- **Stage C/D**: Persons with past or present medical history of HF or end-stage HF.

Given the extensive background information available on study subjects, few remained unclassified. Two physicians independently reviewed the uncertain cases and assigned the correct stage.

Follow-up

Median follow-up was 3.67 years with a maximum follow-up of 8 years. Medical record extraction using natural language processing from the Massachusetts General Hospital electronic health record from time of enrolment to end of follow-up was performed. For identification of clinical endpoints, review of medical records as well as phone follow-up with patients and/or managing physicians was performed. The Social Security Death Index and/or postings of death announcements were used to confirm vital status. A detailed definition of endpoints for CASABLANCA was previously published.[8]

Specific to this analysis, HF events were defined as signs and symptoms of HF in a patient with or without a previous diagnosis of chronic HF and at least one of the following: (i) initiation or increase in dosage of diuretic or (ii) radiographic evidence for pulmonary congestion or (iii) structural heart disease with documentation of left ventricular ejection fraction $<$40% or (iv) diastolic dysfunction or (v) elevated natriuretic peptides. For any recurring events, each discrete event was recorded. Our primary endpoint was the composite of CV death and HF hospitalization.

Biomarker testing

Blood samples were collected immediately prior to cardiac catheterization and were drawn from the access site (either femoral or radial) used for the procedure. For each blood draw, 15 mL of blood was obtained into chilled tubes containing ethylenediaminetetraacetic acid (EDTA) or no anticoagulant and transported on ice to the lab for processing. Blood was subsequently centrifuged for 10 min at 3000 g, and plasma or serum was divided into 500 μL aliquots and stored at −80°C until analysis None of the aliquots used for this study were previously thawed. When assays were run, they were done all off of the same lot of reagent, batching samples into a single run. In this study, we evaluated hs-cTnI (Abbott Diagnostics, Abbott Park IL), galectin-3 (Abbott Diagnostics, Abbott Park IL), soluble urokinase plasminogen activator receptor (suPAR; ViroGates, Birkeroed, Denmark), NT-proBNP (Siemens Inc, Newark DE), high-sensitivity C-reactive protein (hs-CRP; Siemens, Newark, DE), cystatin-C (Siemens, Newark, DE), myeloperoxidase (MPO; Siemens, Newark, DE), soluble ST2 (sST2; Critical Diagnostics, San Diego, CA), Kidney Injury Molecule-1 (KIM-1; Singulex Inc, Alameda CA), and endothelin-1 (ET-1; Singulex, Alameda, CA).

Statistical analysis

Baseline characteristics were stratified by HF Stages A, B, and C/D. For continuous variables, an ANOVA test for significance was performed if data were approximately normally distributed and a Kruskal–Wallis test if data were non-normally distributed. For categorical variables, a chi-square test for significance was performed if all expected cell counts were greater than or equal to 5 and Fisher's exact test was performed otherwise. All biomarker concentrations were log-transformed (base 10) for prognostic analyses.

Overall, 1.78% of the data were missing, with variables with missingness including dyslipidaemia (0.2% missing), smoking (1.0%), hs-cTnI (0.2%), KIM-1 (0.2%), cystatin-C (21.1%), hs-CRP (5.4%), NT-proBNP (0.2%), LDL-C (6.1%), HDL-C (5.4%), MPO (20.3%), galectin (0.5%), suPAR (0.5%), and sST2 (9.6%). We used multivariate imputation via chained equations (MICE) package in R for data imputation.

To select the final variables from candidates [age, sex, race, hypertension, diabetes mellitus, body mass index, hyperlipidaemia, smoking status, CVA/TIA, eGFR (cystatin-based), LDL-C, HDL-C, hyperthyroid, atrial fibrillation, PAD, CKD, COPD, history of MI, history of CAD, history of CABG, history of PCI, log sST2, log NT-proBNP, log suPAR, log hs-cTnI, log galectin-3, log KIM-1, log hs-CRP, log ET-1, log MPO], the least absolute shrinkage and selection operator (LASSO) method was used. LASSO may outperform standard methods (stepwise approach) when dealing with high-dimensional data. We used the value of 'lambda', the tuning parameter, giving the most regularized model such that deviance is within one standard error of the minimum, which is less prone to overfitting. The R package 'glmnet' (version: 4.1-3) was used. Using variables from the LASSO method, Cox proportional hazards models assessed the relationship between final variables and composite primary outcome (incident HF admission and CV death). Final adjusted Cox models were developed that included age, sex, log NT-proBNP, log ET-1, log galectin-3, and log suPAR concentrations for Stage A/B and age, sex, diabetes, log NT-proBNP, log ET-1, log suPAR, log hs-cTnI, log hs-CRP, and log sST2 for Stage C/D. We used the following criteria to report the performance of each prognostic model: Harrell's C statistic was reported as the discrimination ability of the models, whereas calibration was assessed using Hosmer–Lemeshow χ^2 test and Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC).

From these Cox models, predicted risk scores were calculated for each individual by applying the model coefficient values to their covariate distribution. Median risk scores were determined to stratify individuals into risk groups. Kaplan–Meier curves for the composite endpoint of HF hospitalization and CV death were plotted after creating risk groups to demonstrate survival profiles over time, with time points that had fewer than five subjects remaining at risk excluded from plotting.

To assess the association between biomarker concentrations and total burden of events, mean cumulative count methodology was used; this approach quantifies recurrent event rates (hospitalization for HF) in the presence of a competing risk (all-cause mortality). The mean cumulative count estimates the average number of recurrent events within a given time frame using Nelson's mean cumulative function.[10] Competing risks are accounted for by terminating a subject's at-risk status for having the recurrent event. Mean cumulative count analyses were performed for UDHF Stages A/B and C/D comparing lower risk vs. higher risk groupings from the Cox models above. 95% confidence intervals for the mean cumulative count were calculated by creating 1000 bootstrapped datasets and then taking the 2.5th and 97.5th percentiles of each time point estimate, following the percentile bootstrapping method. Although a first HF event in a

study participant in Stage A or B would qualify them as transitioning to Stage C or D, the point of this analysis was to emphasize ability of a cross-sectionally measured biomarker to predict future burden of disease regardless of the subsequent staging. Lastly, to further account for competing risk, we implemented the sub-distribution hazard function introduced by Fine and Gray.[11]

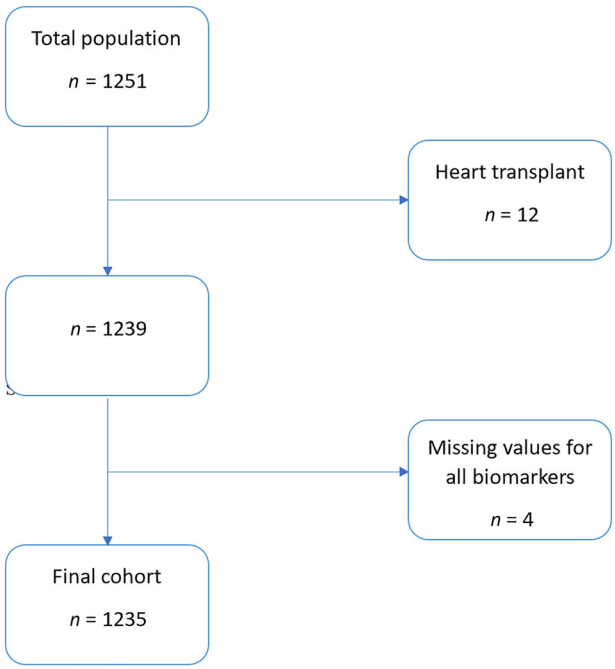
All hypotheses were two-sided with a P value < 0.05 considered statistically significant. All statistical analyses were performed using the R Version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

Results

A study flow diagram is detailed in *Figure 1*. After exclusions, the study sample was 1235 patients. Following categorization into UDHF stages, there were 77 (6.2%) individuals in Stage A, 733 (59.4%) in Stage B, and 425 (34.4%) in Stage C/D. After using all available information, only eight patients with 'dyspnoea' as the cause of being in the lab required further categorization and were assigned.

Baseline characteristics of study population across UDHF Stages A, B, and C/D are presented in *Table 1*, whereas characteristics as a function of UDHF stages and CV death/HF hospitalization events are shown in *Table S2*. Patients with Stage C/D UDHF were older, had higher prevalence of Type 2 diabetes, chronic kidney disease, coronary artery disease, myocardial infarction, coronary artery bypass graft, smoking, and atrial fibrillation. With the exception of MPO, a stepwise increase in biomarker concentrations was seen across UDHF stages.

Figure 1 CONSORT diagram for the present analysis. Excluding those with prior heart transplantation and those missing biomarker results, the study sample was 1235 participants.



During follow-up, among Stage A subjects, there were four (5.2%) first HF events and two (2.6%) CV deaths. Stage B subjects experienced 118 (16.1%) first HF events and 65 (8.9%) CV deaths. In order to maximize analytical power, Stage A/B was pooled for subsequent analyses. Among Stage A/B subjects, there were a total of 281 first and recurrent HF events observed among 810 subjects with 88 (10.9%) subjects reaching the terminal endpoint of all-cause mortality. Stage C/D subjects experienced 177 (41.6%) first HF events and 88 (20.7%) CV deaths; there were a total of 489 first and recurrent HF events observed among 425 subjects with 104 (24.5%) subjects reaching the terminal endpoint of all-cause mortality.

Figure 2 details variables of influence for the composite endpoint of CV death or HF hospitalization in Stages A/B (*Figure 2A*) and C/D (*Figure 2B*). Notably, biomarkers had differing importance depending on UDHF stage category. For example, whereas NT-proBNP was a relatively similar predictor of future events across both categories, ET-1 appeared more prognostically meaningful in Stage A/B than Stage C/D.

The varying importance of biomarkers for prognosticating the composite outcome of first HF/CV death in a fully adjusted Cox proportional hazards model including clinical and biomarker variables is detailed in *Table 2*. For individuals with Stage A/B (*Table 2*) in multivariable adjustment, increase in one unit of log NT-proBNP (HR = 1.43; 95% CI = 1.21–1.68, $P < 0.001$), log ET-1 (HR = 2.16; 95% CI = 1.36–3.41, $P = 0.001$) and log galectin-3 (HR = 1.52; 95% CI = 1.04–2.21, $P = 0.03$) remained predictive of increased risk of HF hospitalization or CV death. In those with Stage C/D HF (*Table 2*), NT-proBNP remained prognostic, suPAR concentrations were associated with greater prognostic association than in Stage A/B, and concentrations of hs-CRP and sST2 both were retained as predictors. Restricted cubic spline cox models showing the shape of association between each biomarker with HF hospitalization/CV death are presented in *Figure S1*. Moreover, associations of each clinical and biomarker variable with HF hospitalization/CV death are shown in *Table S3A* and *S3B*.

In final adjusted Cox models for prognosticating outcomes in Stage A/B, variables included were age, sex, log NT-proBNP, log ET-1, log galectin-3, and log suPAR concentrations, whereas for Stage C/D the variables were age, sex, diabetes, log NT-proBNP, log ET-1, log suPAR, log hs-cTnI, log hs-CRP, and log sST2. *Table S4* shows the discrimination and calibration for each biomarker model. Combination of the biomarkers resulted in a significant increase in the discrimination ability of the model with preservation of acceptable calibration (P value > 0.2). Both final models had modest dis-

Table 1 Baseline characteristics of the study population by Universal Definition of Heart Failure stages

	Stage A HF (n = 77)	Stage B HF (n = 733)	Stage C/D HF (n = 425)	P value[a]
Age, mean (SD)	57.3 (8.90)	66.0 (11.3)	68.8 (11.5)	<0.001
Male sex, *n* (%)	62 (80.52%)	515 (70.26%)	303 (71.29%)	0.17
Caucasian race, *n* (%)	69 (89.61%)	683 (93.18%)	402 (94.59%)	0.24
Medical history, *n* (%)				
Type 2 diabetes	13 (16.88%)	171 (23.33%)	132 (31.06%)	0.003
Hypertension	55 (71.43%)	546 (74.49%)	331 (77.88%)	0.30
Hyperlipidaemia	52 (67.53%)	502 (68.58%)	271 (64.07%)	0.29
CKD	0 (0%)	80 (10.91%)	81 (19.06%)	<0.001
RRT	0 (0%)	18 (2.46%)	14 (3.29%)	0.24
CAD	27 (35.06%)	383 (52.25%)	240 (56.47%)	0.002
MI	0 (0%)	156 (21.28%)	131 (30.82%)	<0.001
COPD	12 (15.58%)	116 (15.85%)	91 (21.41%)	0.05
PAD	15 (19.48%)	199 (27.15%)	109 (25.65%)	0.33
CVA/TIA	5 (6.49%)	75 (10.23%)	57 (13.41%)	0.10
PCI	15 (19.48%)	214 (29.2%)	114 (26.82%)	0.17
DES	1 (50%)	13 (59.09%)	2 (33.33%)	0.53
CABG	8 (10.39%)	124 (16.92%)	96 (22.59%)	0.01
Current smoker	9 (11.84%)	126 (17.38%)	44 (10.45%)	0.005
Atrial fibrillation	5 (6.49%)	82 (11.19%)	143 (33.65%)	<0.001
Haemodynamic data				
LVEDP	9.00 (0–12.0)	16.0 (0–36.0)	17.0 (0–45.0)	<0.001
PCWP	6.50 (3.00–14.0)	12.0 (2.00–34.0)	15.0 (2.00–40.0)	<0.001
LVEF	65.5 (58.0–78.0)	64.0 (32.0–86.0)	51.0 (11.0–81.0)	<0.001
Angiography results				
≥30% coronary stenosis in ≥2 vessels	33 (42.9%)	417 (56.9%)	249 (58.6%)	0.04
≥30% coronary stenosis in ≥3 vessels	26 (33.8%)	323 (44.1%)	197 (46.4%)	0.12
≥50% coronary stenosis in ≥2 vessels	28 (36.4%)	343 (46.8%)	195 (45.9%)	0.22
≥50% coronary stenosis in ≥3 vessels	14 (18.2%)	232 (31.7%)	138 (32.5%)	0.04
≥70% coronary stenosis in ≥2 vessels	17 (22.1%)	263 (35.9%)	154 (36.2%)	0.05
≥70% coronary stenosis in ≥3 vessels	9 (11.7%)	156 (21.3%)	81 (19.1%)	0.11
Medications				
Aspirin	63 (81.82%)	593 (81.12%)	300 (71.09%)	<0.001
Clopidogrel	20 (25.97%)	195 (26.64%)	85 (20.19%)	0.05
Warfarin	5 (6.49%)	63 (8.62%)	119 (28.2%)	<0.001
Statin	54 (70.13%)	552 (75.51%)	299 (70.85%)	0.17
ACE inhibitors	33 (43.42%)	286 (39.02%)	182 (43.03%)	0.36
ARB	9 (11.69%)	97 (13.27%)	84 (19.91%)	0.007
Beta-blocker	36 (46.75%)	513 (70.08%)	321 (76.07%)	<0.001
MRA	3 (3.9%)	21 (2.87%)	30 (7.11%)	0.003
Loop diuretic	2 (2.6%)	72 (9.84%)	185 (43.84%)	<0.001
Thiazide diuretic	15 (19.48%)	129 (17.67%)	60 (14.25%)	0.25
Ca channel blocker	17 (22.08%)	197 (26.95%)	100 (23.64%)	0.36
Nitrates	10 (12.99%)	148 (20.22%)	80 (19%)	0.30
Biomarkers, median (Q1–Q3)				
sST2	36 (28–47)	35 (27–47)	41 (30–58)	<0.001
NT-proBNP	170 (100–240)	1,200 (540–2,800)	3,000 (1,300–7,500)	<0.001
suPAR	2.6 (2.1–3.6)	3.4 (2.5–4.8)	4.3 (2.9–6.0)	<0.001
hs-cTnI	1.7 (1.2–3.3)	4.2 (2.1–12.0)	6.3 (2.8–15.0)	<0.001
Galectin-3	17 (15–19)	19 (15–24)	21 (16–27)	<0.001
KIM-1	110 (77–180)	150 (95–230)	180 (120–290)	<0.001
hs-CRP	1.8 (0.9–3.8)	2.5 (1.0–5.2)	3.3 (1.3–7.1)	<0.001
Cystatin C	0.74 (0.64–0.80)	0.78 (0.68–0.96)	0.87 (0.75–1.20)	<0.001
MPO	390 (310–520)	420 (320–590)	430 (310–600)	0.50
ET-1	2.1 (1.8–2.6)	2.4(2.0–3.0)	3.0 (2.1–3.3)	<0.001

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVA/TIA, cerebrovascular accident/transient ischaemic attack; DES, drug-eluting stent, ET-1, endothelin1;hs-CRP, high-sensitivity C-reactive protein; hs-cTnI, high-sensitive troponin I; Kim-1, Kidney Injury Molecule-1; LVEDP, left ventricular end diastolic pressure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MPO, myeloperoxidase; MRA, mineralocorticoid antagonist; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PCWP, pulmonary capillary wedge pressure; RRT, renal replacement therapy; sST2, soluble ST2; suPAR, soluble urokinase-type plasminogen activator receptor.

[a]For continuous variables, an ANOVA test was used to compare groups if data were approximately normally distributed, and a Kruskal–Wallis test was used if data were non-normally distributed. For categorical variables, Pearson's chi-square test was used if all expected cell counts were >5 and Fisher's exact test was used otherwise.

Figure 2 Influential variables predicting cardiovascular death or heart failure hospitalization. Patients were categorized as Universal Definition of Heart Failure (A) Stage A/B and (B) Stage C/D. hxcopd, history of chronic obstructive pulmonary disease; Hxdm2, history of diabetes mellitus; Log ET-1, log-transformed endothelin 1; log ET-1, log-transformed endothelin-1; log Gal3, log-transformed galectin-3; log hs-CRP, log-transformed high-sensitivity C-reactive protein; log hs-cTnI, log-transformed high-sensitivity cardiac troponin I; Log NTproBNP, log-transformed *N*-terminal prohormone of B-type natriuretic peptide; log ST2, log-transformed soluble ST2; log suPAR, log-transformed soluble urokinase plasminogen activator receptor.

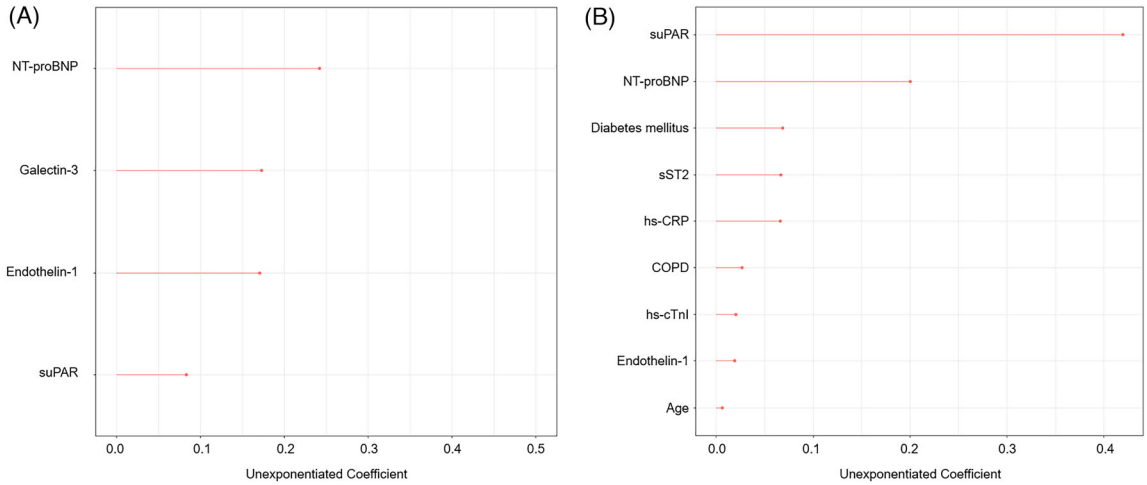


Table 2 Cox modelling results for predictors of heart failure hospitalization or CV death among individuals based on Universal Definition of Heart Failure: Stage A/B or C/D

	Univariable		Multivariable	
Variables	HR (%95 CI)	*P* value	HR (%95 CI)	*P* value
Stage A/B				
Age, per year	1.04 (1.03–1.06)	<0.001	1.02 (1.01–1.04)	0.006
Male sex	1.39 (0.97–2.01)	0.08	1.68 (1.16–2.43)	0.006
Log NT-proBNP[a]	1.90 (1.68–2.16)	<0.001	1.43 (1.21–1.68)	<0.001
Log ET-1[a]	5.45(3.65–8.15)	<0.001	2.16 (1.36–3.41)	0.001
Log galectin-3[a]	3.07 (2.38–3.97)	<0.001	1.52 (1.04–2.21)	0.03
Log suPAR[a]	3.01 (2.32–3.92)	<0.001	1.32 (0.88–1.97)	0.17
Stage C/D				
Age, per year	1.04 (1.03–1.05)	<0.001	1.02 (1.01–1.04)	0.001
Male sex	1.12 (0.83–1.52)	0.45	1.46 (1.07–1.98)	0.02
Type 2 diabetes	1.68(1.28–2.22)	<0.001	1.60 (1.19–2.13)	0.002
Log NT-proBNP[a]	1.71 (1.51–1.93)	<0.001	1.26 (1.07–1.49)	0.006
Log ET-1[a]	2.85 (2.08–3.91)	<0.001	1.29 (0.87–1.92)	0.20
Log suPAR[a]	3.01 (2.34–3.87)	<0.001	1.57 (1.13–2.18)	0.007
Log hs-cTnI[a]	1.28 (1.19–1.38)	<0.001	1.10 (0.99–1.21)	0.07
Log hs-CRP[a]	1.33 (1.21–1.46)	<0.001	1.15 (1.03–1.29)	0.01
Log sST2[a]	1.76 (1.42–2.19)	<0.001	1.19 (0.95–1.49)	0.14

ET-1, endothelin-1; hs-CRP, high-sensitivity C-reactive protein; hs-cTnI, high-sensitivity cardiac troponin I; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; sST2, soluble ST2; suPAR, soluble urokinase-type plasminogen activator receptor.
[a]Per log unit change.

crimination ability as evident by Harrell's C-statistics 0.76 and 0.73 for Stages A/B and C/D, respectively (*Table S5*). Moreover, to account for competing risk, sub-distribution hazard ratios (SHR) of each biomarker for primary outcome are shown in *Table S6*. Similar associations between biomarkers and adverse clinical outcomes were found except that in Stage A/B, SHR of galectin-3 and in Stage C/D, SHR of hs-CRP and hs-cTnI for incident HF/CV death were statistically non-significant.

In an effort to translate results of the multivariable model to a predictive tool for risk of HF events in those with Stage A/B or C/D undergoing angiographic procedures, the coefficients from the models for each scenario were applied to develop a risk stratification tool and divided at the median value for the continuous output of the risk model. For Stage A/B, this was 0.77, whereas for Stage C/D, it was 0.75. Outcomes of CV death or HF hospitalization across median split are depicted for Stages A/B (*Figure 3*) and C/D (*Figure 4*).

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Figure 3 Kaplan–Meier curve predicting heart failure hospitalization or CV death in Universal Definition of Heart Failure Stage A/B based on high and low risk. For Stage A/B risk modelling, variables included age, sex, log NT-proBNP, log ET-1, log galectin-3, and log suPAR concentrations.

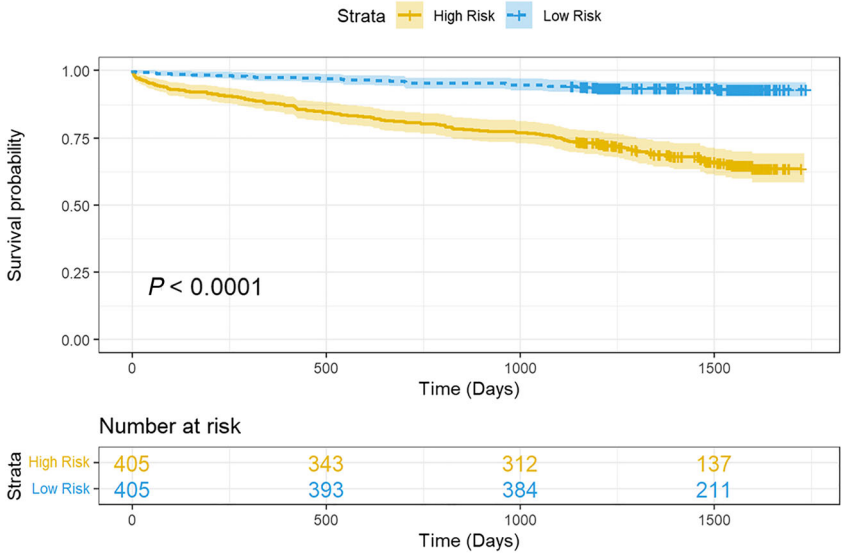
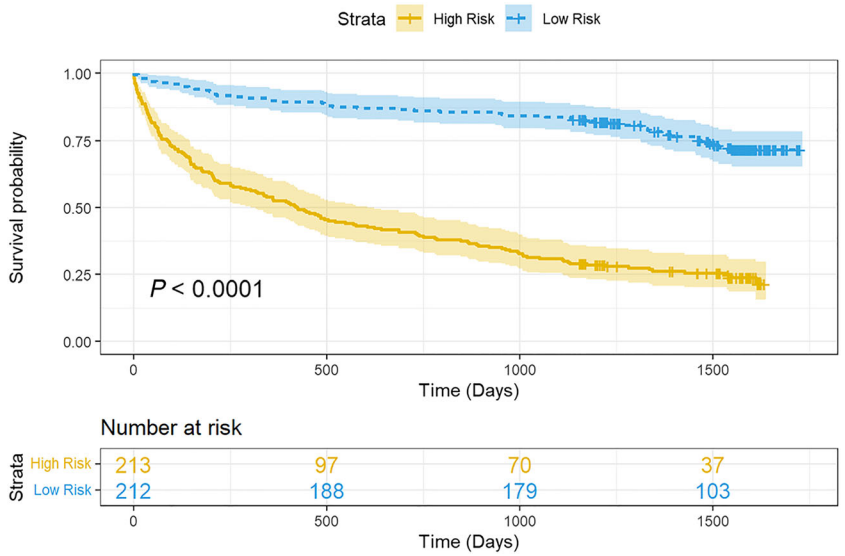
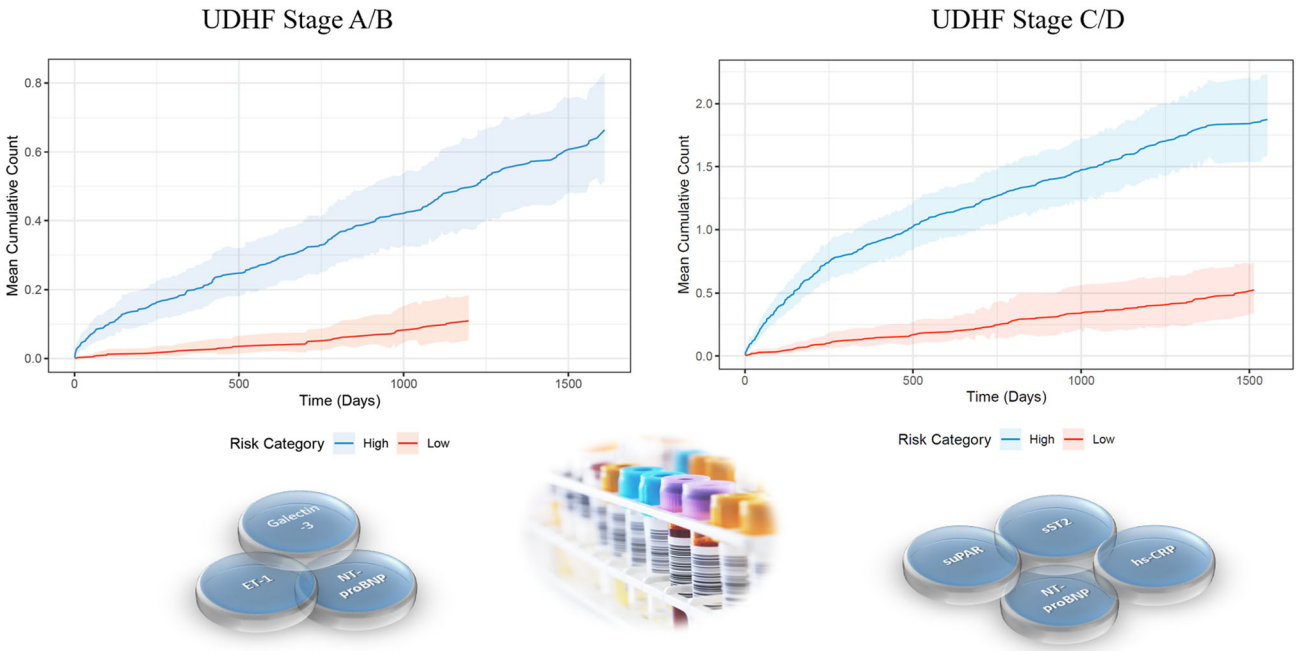


Figure 4 Kaplan–Meier curve predicting heart failure hospitalization or CV death in Universal Definition of Heart Failure Stage C/D based on high and low risk categories. For Stage C/D risk modelling, variables included were age, sex, diabetes, log NT-proBNP, log ET-1, log suPAR, log hs-cTnI, log hs-CRP, and log sST2.



Besides predicting first events, higher biomarker concentrations (leading to higher risk categories in the Cox models) were associated with total burden of HF events. The average number of first and recurrent HF events is shown over time for high- and low-risk groups in *Figure 5*. In Stage A/B, for the high-risk group at the end of follow-up (1610 days), the average number of recurrent events was 66 HF hospitalizations per every 100 individuals (95% CI: 53–89 events). For the low-risk group at the end of follow-up (1197 days), the average number of recurrent events was 11 per every 100 individuals (95% CI: 5–19 events); thus, the average number of recurrent events for the high-risk group in Stage A/B is approximately six times higher than that of the low-risk group at the end of each group's follow-up. Among the low-risk individuals in Stage A/B with HF events (N = 19), most (N = 11; 58%) experienced only one event, whereas 57% high-risk par-

Figure 5 Average number of first and recurrent heart failure events over time expressed as a function of high and low risk groups as derived from Cox regression models.



ticipants in Stage A/B experienced more than one outcome event. In Stage C/D, for the high-risk group at the end of follow-up (1554 days), the average number of recurrent events was 187 per every 100 individuals (95% CI: 156–224 events). For the low-risk group at the end of follow-up (1514 days), the average number of recurrent events was 52 per every 100 individuals (95% CI: 34–74 events). Therefore, the average number of recurrent events for the high-risk group in Stage C/D is approximately 3.5 times higher than that of the low-risk group at the end of each group's follow-up. For low-risk individuals in Stage C/D (n = 212), a total of 104 first and recurrent HF events were observed, while for higher risk Stage C/D study participants (n = 213), a nearly fourfold higher (N = 385) total HF event count was observed. Similar to Stage A/B, lower risk individuals in Stage C/D were more likely to have single events (61%), whereas higher risk Stage C/D individuals had the opposite finding, with 64% experiencing first and recurrent events.

Discussion

The recent UDHF consensus provides important guidance regarding staging of HF, something that is applicable to individuals not only in the community but also under medical care, such as hospitalized individuals or those undergoing evaluation in the catheterization laboratory. In this heavily phenotyped cohort of patients referred for angiographic procedures, we demonstrated the distribution of UDHF Stages, finding a high number of at-risk Stage A and particularly Stage B (or 'pre-HF') individuals along with a comparably large number of Stage C/D HF. Consistent with the concept of the UDHF, those with Stage B or C/D HF had worse overall risk factors and higher prognostic biomarkers compared with those with Stage A. When grouped as Stage A/B or C/D, we also found differential prognostic impact of various biomarkers when added to prognostication models across the UDHF risk continuum as defined by the UDHF. For example, among those with earlier stages, biomarkers reflective of myocardial strain and remodelling and pulmonary hypertension (NT-proBNP, galectin-3, ET-1) were predictive; in those with prevalent HF, NT-proBNP again remained prognostic, but was joined by biomarkers reflecting immune activation and inflammation (hs-CRP, suPAR) and by sST2, a biomarker well-known to be associated with HF-related events.[12] We extended our results by evaluating how risk models might be applied to individuals undergoing angiographic procedures depending on their UDHF stage, with discrimination for CV death or HF hospitalization by the predictive rules developed from risk models at each stage, and finally show how higher biomarker concentrations are associated not only with first events but total burden of events. These results show how the UDHF staging system reliably risk stratifies high-risk individuals undergoing angiography and emphasize importance of biomarkers to more precisely panel risk across the UDHF,

not only for first events but also for total burden of disease-related outcomes.

The findings of this study identify clear opportunities to identify risk in those thought to be lower risk (e.g. Stage A/B) and categorize risk in those with established Stage C/D HF. As those undergoing evaluation in the catheterization laboratory represent a population easily identified and treated, the approach we have taken might be expected to assist in more precise application of care: Given established treatments to reduce risk for incident HF events, improved understanding of risk strata may lead to interventions to reduce such risk with less delay.[13] Biomarkers may be used as a low-cost, low-risk tool to build prognostic models and understand HF.[14] However, a biomarker-leveraged approach for patient risk assessment is only now gaining support. Part of the challenge with prior studies is application of biomarker testing in a 'one size fits all' approach to individual patients with varying baseline risks. Our results suggest prognostic meaning of mechanisms involved in HF (including inflammation, neurohormonal activation, myocardial stretch, myocyte injury, and matrix remodelling) may vary in those at different UDHF stages[15,16]; depending on the stage of diagnosis and clinical setting where measured, the relative importance of different biomarkers may shift, reflecting progression in the pathophysiologic pathways involved in HF.

Among those with Stage A/B HF, concentrations of NT-proBNP, ET-1, and galectin-3 remained significant in adjusted models. Although the role of NT-proBNP is well established to predict HF events in those at risk for the diagnosis, our results show important findings relative to ET-1 and galectin-3. ET-1 is a pulmonary vasoconstrictor, and endothelin signalling has been proposed to be a marker of pulmonary hypertension.[17] Previous studies have been inconsistent about the association of elevated levels of ET-1 with outcomes in patients with coronary artery disease.[18,19] In our analysis, ET-1 was associated with HF hospitalization and CV death in Stage A/B, but this independent association was diminished in patients with Stage C/D. Galectin-3 is a macrophage lectin associated with fibrotic conditions including myocardial fibrosis.[20] Studies have demonstrated that higher levels of galectin-3 are associated with an increased risk for HF and mortality events; however, the link between galectin-3 and outcomes has been inconsistent, particularly in Stage C/D HF.[21,22] In this study, among higher risk Stage A/B (but not C/D) study participants, galectin-3 was independently associated with risk of CV death or HF hospitalization. This finding is consistent with the notion that processes leading to fibrosis may precede clinical manifestations of HF by many years. The identification of galectin-3 activation in UDHF Stage A/B before impairment of LV function may offer a window of opportunity to initiate targeted preventive treatment early in the course of the disease, particularly as therapies to inhibit galectin-3-mediated fibrosis are under development.[23]

In those with Stage C/D HF, once again, NT-proBNP remained a predictor of outcome; higher NT-proBNP concentrations in established HF inform presence and significance of cardiac remodelling and more congestion,[18,24] helping to understand how this biomarker predicts future CV events.[18,25] Setting Stage C/D patients apart from earlier stages however was the emergence of importance of inflammatory biomarkers; chronic inflammation is an important pathophysiological aspect of HF.[26] SuPAR is released from activated monocytes, neutrophils, T cells, and endothelial cell from proteolytic cleavage and release of the membrane-bound receptor into the plasma.[27] Three prospective cohort studies have extended the prognostic significant role of suPAR for prediction of adverse outcomes in HF patients.[28] In a similar fashion, concentrations of hs-CRP remained prognostic in this analysis, even in adjusted models. Although hs-CRP has had mixed results with respect to predicting incident HF events in some studies, among those with Stage C/D HF undergoing angiographic procedures—an arguably higher risk patient population—this biomarker remained robust as a risk predictor. Lastly, sST2 represents the intersection of inflammation and tissue fibrosis; it is an interleukin 1 receptor family member whose concentrations are strongly linked to tissue fibrosis, cardiac remodelling, and HF events.

A noteworthy finding in the present analysis is the association between biomarker concentration and total burden of HF hospitalization/CV death events. Recent studies have shown that some therapies not only reduce first but also total HF events,[29] a finding with both clinical and financial relevance. The results of this study suggest that biomarkers may not only identify those more likely to develop events but also identify those with higher likelihood for a greater burden of such events; in the present analysis, those in the higher risk groupings had a fourfold to fivefold excess of HF hospitalization/CV death events compared with lower risk individuals and greater propensity towards recurrent events. Whether more targeted therapeutic intervention would be expected to reduce such risk remains uncertain but bears further evaluation.

Lastly, when we performed the competing risk analysis considering non-CV death as a competing factor, we found slight changes in the associations of biomarkers with the primary outcome. The associations of galectin-3 in Stage A/B and hs-CRP and hs-cTnI in Stage C/D with primary outcome were attenuated or diminished. These findings may be interpreted with caution, given that the SHR is not ideal for studying disease aetiology and causal inference, but has the advantage of precise predicting individuals' risk in the presence of competing risk.[30–32]

This study has limitations. First, there were only 77 cases of Stage A UDHF in this population of individuals undergoing coronary and/or peripheral angiography. No antecedent data exist to predict the prevalence of Stage A HF in the catheterization laboratory; however, given the underlying reason for

being in this environment, it is improbable there would be many. This is exactly why the results of this study are important: The catheterization laboratory affords an obvious opportunity to identify individuals at risk for HF, even the few with Stage A. Due to small number of patients with Stage A UDHF, we combined Stages A and B into a single group, and we were unable to assess the predictors of progression from Stage A to B. Another potential issue is the risk for mis-staging individuals with Stage A HF as Stage B. Given the low expected prevalence of such patients together with the extensive phenotyping of individuals in the CASABLANCA study (including available NT-proBNP and hs-cTnI in every individual), this seems highly improbable. Furthermore, given limited numbers of those in Stage D, we combined Stages C and D. Based on previous studies,[33,34] a small number in Stage D (a highly specialized patient population) would be entirely expected. We had high percentage of missing values for cystatin c and MPO; this might have weakened their associations with primary outcome and ultimately precluded their inclusion into our final models. Future studies need to re-assess the prognostic role of these two biomarkers. Although the CASABLANCA population is unique in its detailed phenotyping, there are few study participants with available results from invasive haemodynamic measurements. Furthermore, our study included patients who underwent coronary or peripheral angiography. Future studies may need to examine the role of proposed biomarkers in the entire population with UDHF Stages A–D besides those seen in the cardiac catheterization laboratory, who represent a generally higher risk group of individuals with more Stage B–D HF. Still, those coming through the catheterization laboratory are an ideal population in some ways for this type of analysis, given the detailed assessment and follow-up typically seen after their procedure. Our study was conducted in era before angiotensin receptor/neprilysin inhibitors and sodium glucose cotransporter 2 inhibitors as treatment option for patients with HF. Improved survival as result of these novel treatments cannot be assessed in this study. Although the goal of this study was not to create new tools for predicting outcomes, the discrimination ability of our models was similar to the existing prognostic HF scores.[35] Lastly, our study lacks external validation. Future studies are needed to test generalizability of our models in independent cohorts.

In conclusion, we have shown how the UDHF stages of HF are able to categorize individuals undergoing angiographic procedures in the Cardiac Catheterization Laboratory and how biomarkers may provide specific risk stratification to those at risk/preclinical and those with established HF. Therapies now exist to improve prognosis at each stage of the UDHF classification; such treatments remain grossly underutilized. The increased focus on earlier detection of risk for HF provides an opportunity to change this treatment gap. Emphasis on detection of risk and application of preventive treatments would be expected to improve outcomes from those at risk for or affected by HF. The results of this analysis suggest more precise prognostication across UDHF stages may be possible.

Conflict of interest

Ms Laurel Jackson, **Dr Susan Gawel**, and **Dr Gillian Murtagh** are full-time employees and shareholders of Abbott. **Dr Gaggin** has received research grant support from Roche Diagnostics, Jana Care, Ortho Clinical, Novartis, Pfizer, Alnylam, and Akcea; consulting income from Amgen, Eko, Merck, Roche Diagnostics, and Pfizer; stock ownership for Eko; and research payments for clinical endpoint committees from Radiometer. She has also received research payment for clinical endpoint committees from Baim Institute for Clinical Research for Abbott, Siemens, and Beckman Coulter. **Dr Januzzi** is supported by the Hutter Family Professorship; is a Trustee of the American College of Cardiology; is a board member of Imbria Pharmaceuticals; has received grant support from Abbott Diagnostics, Applied Therapeutics, Innolife, and Novartis; has received consulting income from Abbott Diagnostics, Boehringer-Ingelheim, Janssen, Novartis, and Roche Diagnostics; and participates in clinical endpoint committees/data safety monitoring boards for AbbVie, Siemens, Takeda, and Vifor. The rest of the authors have no disclosures.

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Supporting information

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

Table S1. Universal Definition of Heart Failure criteria.
Table S2. Baseline characteristics of the study population by primary outcome event.
Table S3. Association of clinical and biomarker variables with heart failure hospitalization/cardiovascular mortality A) Stage A/B or B) Stage C/D.
Table S4. Performance of each biomarker model.
Table S5. Performance of prognostic models.
Table S6. Fine Gray model results for predictors of heart failure hospitalization or CV death among individuals based on Universal Definition of Heart Failure A) Stage A/B or B) C/D.
Figure S1A. Cubic spline curve showing the shape of associa-

tion between each biomarker and incident heart failure hospitalization/cardiovascular mortality among stage A/B UDHF. **Figure S1B**. Cubic spline curve showing the shape of association between each biomarker and incident heart failure hospitalization/cardiovascular mortality among stage C/D UDHF.

References

1. Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Cheng S, Delling FN, Elkind MSV, Evenson KR, Ferguson JF, Gupta DK, Khan SS, Kissela BM, Knutson KL, Lee CD, Lewis TT, Liu J, Loop MS, Lutsey PL, Ma J, Mackey J, Martin SS, Matchar DB, Mussolino ME, Navaneethan SD, Perak AM, Roth GA, Samad Z, Satou GM, Schroeder EB, Shah SH, Shay CM, Stokes A, VanWagner L, Wang NY, Tsao CW, American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2021 update: A report from the American Heart Association. *Circulation* 2021; **143**: e254–e743.
2. Butler J, Yang M, Manzi MA, Hess GP, Patel MJ, Rhodes T, Givertz MM. Clinical course of patients with worsening heart failure with reduced ejection fraction. *J Am Coll Cardiol* 2019; **73**: 935–944.
3. Folsom AR, Shah AM, Lutsey PL, Roetker NS, Alonso A, Avery CL, Miedema MD, Konety S, Chang PP, Solomon SD. American Heart Association's life's simple 7: Avoiding heart failure and preserving cardiac structure and function. *Am J Med* 2015; **128**: 970–6 e2.
4. Ibrahim NE, Lyass A, Gaggin HK, Liu Y, van Kimmenade RRJ, Motiwala SR, Kelly NP, Gandhi PU, Simon ML, Belcher AM, Harisiades JE, Massaro JM, D'Agostino RB, Januzzi JL Jr. Predicting new-onset HF in patients undergoing coronary or peripheral angiography: Results from the catheter sampled blood archive in cardiovascular diseases (CASABLANCA) study. *ESC Heart Fail* 2018; **5**: 240–248.
5. Ibrahim NE, Januzzi JL Jr. Established and emerging roles of biomarkers in heart failure. *Circ Res* 2018; **123**: 614–629.
6. Choi EY, Bahrami H, Wu CO, Greenland P, Cushman M, Daniels LB, Almeida ALC, Yoneyama K, Opdahl A, Jain A, Criqui MH, Siscovick D, Darwin C, Maisel A, Bluemke DA, Lima JAC. N-terminal pro-B-type natriuretic peptide, left ventricular mass, and incident heart failure: Multi-ethnic study of atherosclerosis. *Circ Heart Fail* 2012; **5**: 727–734.
7. Ahmad T, Fiuzat M, Pencina MJ, Geller NL, Zannad F, Cleland JG, Snider JV, Blankenberg S, Adams KF, Redberg RF, Kim JB, Mascette A, Mentz RJ, O'Connor CM, Felker GM, Januzzi JL. Charting a roadmap for heart failure biomarker studies. *JACC Heart Fail* 2014; **2**: 477–488.
8. Gaggin HK, Liu Y, Lyass A, van Kimmenade RR, Motiwala SR, Kelly NP, Mallick A, Gandhi PU, Ibrahim NE, Simon ML, Bhardwaj A, Belcher AM, Harisiades JE, Massaro JM, D'Agostino RB Sr, Januzzi JL Jr. Incident type 2 myocardial infarction in a cohort of patients undergoing coronary or peripheral arterial angiography. *Circulation* 2017; **135**: 116–127.
9. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, Anker SD, Atherton J, Böhm M, Butler J, Drazner MH, Felker GM, Filippatos G, Fonarow GC, Fiuzat M, Gomez-Mesa JE, Heidenreich P, Imamura T, Januzzi J, Jankowska EA, Khazanie P, Kinugawa K, Lam CSP, Matsue Y, Metra M, Ohtani T, Francesco Piepoli M, Ponikowski P, Rosano GMC, Sakata Y, Seferović P, Starling RC, Teerlink JR, Vardeny O, Yamamoto K, Yancy C, Zhang J, Zieroth S. Universal definition and classification of heart failure: A report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *J Card Fail* 2021.
10. Dong H, Robison LL, Leisenring WM, Martin LJ, Armstrong GT, Yasui Y. Estimating the burden of recurrent events in the presence of competing risks: The method of mean cumulative count. *Am J Epidemiol* 2015; **181**: 532–540.
11. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999; **94**: 496–509.
12. Aimo A, Vergaro G, Passino C, Ripoli A, Ky B, Miller WL, Bayes-Genis A, Anand I, Januzzi JL, Emdin M. Prognostic value of soluble suppression of Tumorigenicity-2 in chronic heart failure: A meta-analysis. *JACC Heart Fail* 2017; **5**: 280–286.
13. Jackson SL, Tong X, King RJ, Loustalot F, Hong Y, Ritchey MD. National burden of heart failure events in the United States, 2006 to 2014. *Circ Heart Fail* 2018; **11**: e004873.
14. Nadar SK, Shaikh MM. Biomarkers in routine heart failure clinical care. *Card Fail Rev* 2019; **5**: 50–56.
15. Mann DL, Bristow MR. Mechanisms and models in heart failure: The biomechanical model and beyond. *Circulation* 2005; **111**: 2837–2849.
16. Ashrafian H, Frenneaux MP, Opie LH. Metabolic mechanisms in heart failure. *Circulation* 2007; **116**: 434–448.
17. Giaid A, Yanagisawa M, Langleben D, Michel RP, Levy R, Shennib H, Kimura S, Masaki T, Duguid WP, Stewart DJ. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N Engl J Med* 1993; **328**: 1732–1739.
18. Jankowich MD, Wu WC, Choudhary G. Association of elevated plasma endothelin-1 levels with pulmonary hypertension, mortality, and heart failure in African American individuals: The Jackson heart study. *JAMA Cardiol* 2016; **1**: 461–469.
19. Leary PJ, Jenny NS, Bluemke DA, Kawut SM, Kronmal RA, Lima JA, Maron BA, Ralph DD, Rayner SG, Ryan JJ, Steinberg ZL, Hinckley Stukovsky KD, Tedford RJ. Endothelin-1, cardiac morphology, and heart failure: The MESA angiogenesis study. *J Heart Lung Transplant* 2020; **39**: 45–52.
20. Li LC, Li J, Gao J. Functions of galectin-3 and its role in fibrotic diseases. *J Pharmacol Exp Ther* 2014; **351**: 336–343.
21. Fu H, Nie S, Luo P, Ruan Y, Zhang Z, Miao H, Li X, Wen S, Bai R. Galectin-3 and acute heart failure: Genetic polymorphisms, plasma level, myocardial fibrosis and 1-year outcomes. *Biomark Med* 2020; **14**: 943–954.
22. Edelmann F, Holzendorf V, Wachter R, Nolte K, Schmidt AG, Kraigher-Krainer E, Duvinage A, Unkelbach I, Düngen HD, Tschöpe C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Stough WG, Pieske BM. Galectin-3 in patients with heart failure with preserved ejection fraction: Results from the Aldo-DHF trial. *Eur J Heart Fail* 2015; **17**: 214–223.
23. Lau ES, Liu E, Paniagua SM, Sarma AA, Zampierollo G, López B, Díez J, Wang TJ, Ho JE. Galectin-3 inhibition with modified citrus pectin in hypertension. *JACC Basic Transl Sci* 2021; **6**: 12–21.
24. Daubert MA, Adams K, Yow E, Barnhart HX, Douglas PS, Rimmer S, Norris C, Cooper L, Leifer E, Desvigne-Nickens P, Anstrom K, Fiuzat M, Ezekowitz J, Mark DB, O'Connor CM, Januzzi J, Felker GM. NT-proBNP goal achievement is associated with significant reverse remodeling and improved clinical outcomes in

HFrEF. *JACC Heart Fail* 2019; **7**: 158–168.
25. Januzzi JL Jr, Ahmad T, Mulder H, Coles A, Anstrom KJ, Adams KF, Ezekowitz JA, Fiuzat M, Houston-Miller N, Mark DB, Piña IL, Passmore G, Whellan DJ, Cooper LS, Leifer ES, Desvigne-Nickens P, Felker GM, O'Connor CM. Natriuretic peptide response and outcomes in chronic heart failure with reduced ejection fraction. *J Am Coll Cardiol* 2019; **74**: 1205–1217.
26. Murphy SP, Kakkar R, McCarthy CP, Januzzi JL Jr. Inflammation in heart failure: JACC state-of-the-art review. *J Am Coll Cardiol* 2020; **75**: 1324–1340.
27. Thuno M, Macho B, Eugen-Olsen J. suPAR: The molecular crystal ball. *Dis Markers* 2009; **27**: 157–172.
28. Koller L, Stojkovic S, Richter B, Sulzgruber P, Potolidis C, Liebhart F, Mörtl D, Berger R, Goliasch G, Wojta J, Hülsmann M, Niessner A. Soluble urokinase-type plasminogen activator receptor improves risk prediction in patients with chronic heart failure. *JACC Heart Fail* 2017; **5**: 268–277.
29. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, Jamal W, Kimura K, Schnee J, Zeller C, Cotton D, Bocchi E, Böhm M, Choi DJ, Chopra V, Chuquiure E, Giannetti N, Janssens S, Zhang J, Gonzalez Juanatey JR, Kaul S, Brunner-la Rocca HP, Merkely B, Nicholls SJ, Perrone S, Pina I, Ponikowski P, Sattar N, Senni M, Seronde MF, Spinar J, Squire I, Taddei S, Wanner C, Zannad F. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020; **383**: 1413–1424.
30. Latouche A, Allignol A, Beyersmann J, Labopin M, Fine JP. A competing risks analysis should report results on all cause-specific hazards and cumulative incidence functions. *J Clin Epidemiol* 2013; **66**: 648–653.
31. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation* 2016; **133**: 601–609.
32. McCaw ZR, Claggett BL, Tian L, Solomon SD, Berwanger O, Pfeffer MA, Wei LJ. Practical recommendations on quantifying and interpreting treatment effects in the presence of terminal competing risks: A review. *JAMA Cardiol* 2022; **7**: 450–456.
33. Yamamoto K, Matsumura-Nakano Y, Shiomi H, Natsuaki M, Morimoto T, Kadota K, Tada T, Takeji Y, Yoshikawa Y, Imada K, Domei T, Kaneda K, Taniguchi R, Ehara N, Nawada R, Yamaji K, Kato E, Toyofuku M, Kanemitsu N, Shinoda E, Suwa S, Iwakura A, Tamura T, Soga Y, Inada T, Matsuda M, Koyama T, Aoyama T, Sato Y, Furukawa Y, Ando K, Yamazaki F, Komiya T, Minatoya K, Nakagawa Y, Kimura T, CREDO-Kyoto PCI/CABG Registry Cohort-3 Investigators. Effect of heart failure on long-term clinical outcomes after percutaneous coronary intervention versus coronary artery bypass grafting in patients with severe coronary artery disease. *J Am Heart Assoc* 2021; **10**: e021257.
34. Verbrugge FH, Dupont M, Vercammen J, Jacobs L, Verhaert D, Vandervoort P, Tang WHW, Mullens W. Time from emerging heart failure symptoms to cardiac resynchronisation therapy: Impact on clinical response. *Heart* 2013; **99**: 314–319.
35. Peterson PN, Rumsfeld JS, Liang L, Albert NM, Hernandez AF, Peterson ED, Fonarow GC, Masoudi FA, American Heart Association Get With the Guidelines-Heart Failure Program. A validated risk score for in-hospital mortality in patients with heart failure from the American Heart Association get with the guidelines program. *Circ Cardiovasc Qual Outcomes* 2010; **3**: 25–32.