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Biomarkers and low risk in heart failure. Data from COACH and TRIUMPH

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Aim Traditionally, risk stratification in heart failure (HF) emphasizes assessment of high risk. We aimed to determine if biomarkers could identify patients with HF at low risk for death or HF rehospitalization.

Methods and results This analysis was a substudy of The Coordinating Study Evaluating Outcomes of Advising and Counselling in Heart Failure (COACH) trial. Enrolment of HF patients occurred before discharge. We defined low risk as the absence of death and/or HF rehospitalizations at 180 days. We tested a diverse group of 29 biomarkers on top of a clinical risk model, with and without N-terminal pro-B-type natriuretic peptide (NT-proBNP), and defined the low risk biomarker cut-off at the 10th percentile associated with high positive predictive value. The best performing biomarkers together with NT-proBNP and cardiac troponin I (cTnI) were re-evaluated in a validation cohort of 285 HF patients. Of 592 eligible COACH patients, the mean (±SD) age was 71 (±11) years and median (IQR) NT-proBNP was 2521 (1301–5634) pg/mL. Logistic regression analysis showed that only galectin-3, fully adjusted, was significantly associated with the absence of events at 180 days (OR 8.1, 95% confidence interval 1.06–50.0, $P = 0.039$). Galectin-3, showed incremental value when added to the clinical risk model without NT-proBNP (increase in area under the curve from 0.712 to 0.745, $P = 0.04$). However, no biomarker showed significant improvement by net reclassification improvement on top of the clinical risk model, with or without NT-proBNP. We confirmed our results regarding galectin-3, NT-proBNP, and cTnI in the independent validation cohort.

Conclusion We describe the value of various biomarkers to define low risk, and demonstrate that galectin-3 identifies HF patients at (very) low risk for 30-day and 180-day mortality and HF rehospitalizations after an episode of acute HF. Such patients might be safely discharged.

Keywords Heart failure • Prognosis • Biomarker • N-terminal pro-B-type natriuretic peptide • Galectin-3 • Risk stratification

Introduction

Heart failure (HF) has significant clinical impact and leads to considerable costs; in the United Kingdom, estimated hospitalization costs exceed £716 million per year.[1] While the overall mortality rate after acute heart failure (AHF) has decreased in the past two decades, the number of survivors requiring rehospitalization owing to HF after an initial admission have risen steadily.[2,3] Not only are readmissions associated with higher costs, they imply an overall worse prognosis. Patients with four or more AHF readmissions

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have a mortality risk exceeding 40% in the subsequent 6 months, and a median survival of 0.6 months after the fourth readmission.[4] The extent of this problem is apparent from a recent analysis of nearly 12 million Medicare beneficiaries,[3] where HF was the number one cause of 30-day rehospitalization, occurring in 25% of all HF cases and representing 7.6% of all 30-day rehospitalizations.

Consequently, the ability to identify a population of HF patients at low risk of early revisits and mortality could be beneficial, allowing early and safe discharge of a selected group with such low risk. In addition, the remaining population could be targeted for more aggressive therapy, thus decreasing their probability of short-term HF rehospitalization as well.

Multiple clinical predictions models with a wide variety of variables have been developed[5–7] to adequately predict either mortality, HF rehospitalization or a composite of mortality and HF rehospitalization. However, most prediction models identify high-risk patients. The absence of high risk is not sufficient to predict patients who are at low-risk for these endpoints. Biomarkers are commonly used in HF,[8,9] but biomarkers that identify patients at high risk, such as troponin,[10] B-type natriuretic peptide (BNP),[11] blood urea nitrogen (BUN), and creatinine[12] do not—when present at low levels—necessarily identify a cohort at low risk. Therefore, for this analysis, our purpose was to evaluate a large panel of diverse biomarkers to identify a cohort at low short-term risk for mortality and/or HF rehospitalization after hospital discharge for HF.

Methods

Derivation cohort

The Coordinating Study Evaluating Outcomes of Advising and Counselling in Heart Failure (COACH)[13] trial was a multicentre, randomized, controlled study in which 1023 patients were enrolled after hospitalization because of acutely decompensated HF. Patients were assigned to one of three groups: a control group (follow-up by a cardiologist) and two intervention groups with additional basic or intensive support by a nurse specializing in management of patients with HF. Patients were studied for 18 months.[14,15] From this data set, we analysed the mortality and HF rehospitalization rates of 592 patients after hospital discharge for low-risk predictors of death or rehospitalization. Of these 592 patients plasma was available, as previously published,[16] and baseline characteristics were fully comparable to the complete COACH cohort (data not shown). Blood samples were collected at study enrolment, this was for the COACH study at discharge. Patients were hospitalized for 13 days (± 10) after admission with AHF.

Validation cohort

The Translational Initiative on Unique and novel strategies for Management of Patients with Heart Failure (TRIUMPH; NTR1893; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC = 1893, $N = 478$) trial was a multicentre, observational trial, which aimed to identify and validate potentially clinically important biomarkers in patients admitted to the hospital with a diagnosis of AHF. Inclusion criteria of the TRIUMPH trial were age ≥18 years, admitted with the diagnosis of AHF increased N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, treated with diuretics and evidence of left ventricular dysfunction. Patients were excluded when HF was caused by a non-cardiac condition, severe valvular dysfunction, or an acute cardiac syndrome, had a planned coronary intervention, were on the cardiac transplantation list, received haemodialysis, or had a non-cardiac condition associated with a life expectancy of less than 1 year. The primary endpoint was the composite of cardiovascular death, left ventricular assist device implantation, heart transplantation or rehospitalization for the management of acute HF. From this data set, we analysed the mortality and HF rehospitalization rates of 285 patients after hospital discharge from whom only galectin-3, NT-proBNP, and cTnI levels were available. Blood sampling in both studies was performed at hospital discharge, providing the best prognostic value for NT-proBNP. These studies and the current analyses have been performed conform the Declaration of Helsinki; both study protocols, were reviewed and approved by the local Institutional Review Board, and all study subjects provided written informed consent.

End points

The primary outcome for the present analyses was the absence of all-cause mortality and/or HF rehospitalization after 180 days. Secondary outcomes were the absence of all-cause mortality and/or HF rehospitalization at 30, 90 and 365 days. An independent end-point committee adjudicated all endpoints.[13,17]

Biochemical measurements

Biomarker analyses were performed using the following commercial assays: C-reactive protein (CRP), pentraxin-3, growth differentiation factor 15 (GDF-15), myeloperoxidase (MPO), syndecan-1, periostin, tumour necrosis factor alpha receptor 1a (TNFαR1a), osteopontin, receptor of advanced glycation end-products (RAGE), angiogenin, endothelial cell-selective adhesion molecule (ESAM), D-dimer, prosaposin B (PSAP-B), BNP, Troy, supression of tumorigenicity 2 ST-2, neuropilin, mesothelin, polymeric immunoglobulin receptor 1 (PIGR-1), cystatin C, and neutrophil gelatinase-associated lipocalin (NGAL) were measured by Alere San Diego, Inc. (San Diego, CA, USA) using competitive enzyme-linked immunosorbent assays (ELISAs) on a Luminex® platform. Galectin-3 plasma levels were measured using a commercial enzyme-linked immunosorbent assay (BG Medicine, Waltham, MA, USA).[18,19] Transforming growth factor-beta (TGF-β) and vascular endothelial growth factor (VEGF) were analysed by SearchLight® proteome arrays (Aushon BioSystems, Billerica, MA, USA) using a quantitative multiplexed sandwich ELISA system. The NT-proBNP concentration was measured by using the Elecsys proBNP ELISA (Roche Diagnostics, Mannheim, Germany). Erythropoietin alpha (EPO) was measured using the immulite® EPO ELISA (Diagnostic Products Corporation, Los Angeles, CA, USA). Cardiac troponin I (cTnI) and interleukin-6 (IL-6) were measured using highly sensitive single molecule counting (SMC™) technology (RUO, Erenna Immunoassay System; Singulex Inc., Alameda, CA, USA). The intra- and inter-assay coefficients of variation of each biomarker is presented in the Supplementary material online, *Table S1*. The Modification of Diet in Renal Disease (MDRD) formula was used to estimate glomerular filtration rate (eGFR).

Statistical analyses

Baseline characteristics are presented as means and standard deviations (SDs), or medians and interquartile ranges (IQRs), as appropriate.

To determine the optimal biomarker cut point for predicting low risk, we performed a sensitivity analysis, exploring different values of various biomarkers. We used the 10th, 20th, and 30th decile values of all biomarkers studied in COACH, a cut point at the 10th percentile was found to provide most optimal sensitivity and still selected enough patients to be clinically relevant. We expanded our sensitivity analysis with the best-performing biomarkers over the complete range of percentiles (5th−95th). In the primary analysis, all biomarkers were ranked based upon positive predictive value (PPV). Logistic regression analysis (univariable, and multivariable analyses) was used to generate estimates of odds ratios and 95% CIs associated with the four best-performing biomarkers, and commonly used biomarkers (NT-proBNP and cTnI), as dichotomized values. Consistent with previous studies,[20,21] we adjusted in a multivariable analysis first for age and sex, then second for a clinical model that has been published (the COACH risk engine),[22] with the further addition of the duration of hospitalization. The COACH risk engine consists of the following parameters: age, sex, diastolic blood pressure, pulse pressure, stroke, myocardial infarction, atrial fibrillation, peripheral arterial disease, diabetes, left ventricle ejection fraction, previous HF hospitalization, serum sodium, serum creatinine, and the biomarker plasma NT-proBNP. As this analysis aimed to describe the value of biomarkers, and as NT-proBNP is a biomarker, we present the results for the various biomarkers on top of the clinical risk model (COACH risk engine), both excluding NT-proBNP (−) and including NT-proBNP (+). To confirm our ranking, we performed multiple (×1000) bootstrap runs in which all the biomarkers and the clinical risk model variables were entered in a stepwise logistic regression analysis for the absence of an event, and performed ranking based upon the frequency a variable was added to the model. Cox proportional hazards regression analyses were performed to adjust for the time to event, using the same model and biomarkers. Areas under receiver operating characteristic curves (AUROCs) were derived from the clinical risk model excluding or including NT-proBNP, and these models plus biomarker (<10th percentile and continuously) were compared using the method of deLong *et al.*,[23] which accounts for the correlated nature of the curves. We calculated odds ratios for each patient using the clinical risk model with NT-proBNP, and we divided the population in tertiles (odds ratio <4.3, 4.4−8.4, >8.5). Notably, a low odds ratio is associated with a high event rate, while a high odds ratio is associated with a low event rate. We then we assessed the distribution and event rates of patients with biomarker levels <10th percentile.

Reclassification indices were assessed using the continuous net reclassification improvement (NRI) metric and integrated discrimination improvement (IDI).[24]

Finally, galectin-3, NT-proBNP, and cTnI were validated using the TRIUMPH data set. Both PPV and logistic regression analysis were repeated with the 10th percentile found in TRIUMPH for both biomarkers. For both analyses, *P*-values below <0.05 were considered to denote significant differences. Analyses were performed with STATA software (version 13.0; Stata Corp, College Station, TX, USA).

Results

Derivation cohort (COACH)

Data from 592 patients were available for the current analyses. This subset of patients had baseline characteristics that were comparable to the entire COACH cohort as reported ($N = 1023$, data not shown).[16] The mean (SD) age was 71 (±11) years, and 227 (38%) patients were female. Median [IQR] NT-proBNP was 2521 [1301−5634] pg/mL and mean ejection fraction was 33% (±14%). *Table 1* displays the baseline characteristics of this population, and whether or not they endured an event after 180 days.

Biomarkers and prediction

All available biomarkers are displayed in *Table 2* ordered by performance (PPV for composite endpoint). For each biomarker, we report the 10th percentile cut-off value, the sensitivity, 1-specificity, the PPV, and the exact number of events, occurring within 180 days for patients <10th percentile. For clarity, we present the exact number of events within 30 days, 90 days, and 1 year in the Supplementary material online, *Table S2*. Of all biomarkers evaluated, galectin-3 had the highest PPV to rule out events (0.983), corresponding with rank 1, while periostin had the lowest PPV (0.733), resulting in rank 29. The top four biomarkers were selected (galectin-3, EPO, TNFαR1a, and TGF-β) and considered for additional analyses. We also evaluated NT-proBNP and cTnI because these are commonly used in daily clinical practice. We have also performed all analyses with BNP; this yielded inferior results compared with NT-proBNP and these data are therefore not shown. Logistic regression analyses were performed with these biomarkers as dichotomized values for the absence of an event within 180 days. After adjustment for age and sex, galectin-3, EPO and TNFαR1a remained significant predictors of low risk. After adjusting for the clinical risk model with NT-proBNP, only galectin-3 remained significant (OR 8.1 [1.06−50], $P = 0.039$). No other biomarkers were (univariably) predictive for low risk (*Table 3*). Additional sensitivity analyses were performed. First, consecutive percentile cut-offs for the selected biomarkers were assessed (*Figure 1*), and it was observed that galectin-3 has particular value in the low end with adjusted ORs ranging between 4 and 8. Second, we considered the 10th, 20th, and 30th percentile but this did not substantially alter the ranking (see the Supplementary material online, *Table S3*). Finally, after a 1000 bootstrap runs, EPO and galectin-3 consistently emerged as top ranked biomarkers for the 10th and 20th and 30th percentiles (see the Supplementary material online, Table S4). In the Cox proportional hazard analysis, which relates to the time that passes before an event occurs using the same biomarkers and clinical risk model with NT-proBNP, we observed that only galectin-3 remained significant after full adjustment (HR 7.69 IQR 1.04−50, $P = 0.045$; Supplementary material online, *Table S5*).

The AUROCs are presented in the Supplementary material online (*Table S6*) and no biomarker by itself had a significant addition to the clinical risk model with NT-proBNP. We observed that galectin-3 showed incremental value ($P = 0.04$) on top of the clinical risk model without NT-proBNP, while the others did not (including NT-proBNP <10th percentile); the combination of the top four biomarkers also showed incremental value ($P = 0.02$). In addition to the 10th percentile cut-off we also show the AUROCs for biomarkers when added continuously (see the Supplementary material online, *Table S6*).

When considering the tertiles in ORs based upon the clinical risk model with NT-proBNP, we observed that 30−57% of the patients

Table 1 Baseline characteristics of the Coordinating Study Evaluating Outcomes of Advising and Counselling in Heart Failure (COACH) study and stratified by events at 180 days

Characteristics	Total ($N = 592$)	No event at 180 days ($n = 452$)	Event at 180 days ($n = 140$)	*P*-value
Age (years), mean (SD)	71 (11)	70 (11)	73 (11)	0.003
Female, *n* (%)	227 (38)	182 (40)	45 (32)	0.084
SBP (mmHg), mean (SD)	118 (21)	119 (21)	115 (20)	0.10
DBP (mmHg), mean (SD)	69 (12)	69 (12)	66 (12)	0.005
Hypertension, *n* (%)	256 (43)	194 (43)	62 (44)	0.78
BMI (kg/m^2), mean (SD)	27 (6)	27 (5)	27 (6)	0.52
Diabetes, *n* (%)	176 (30)	117 (26)	59 (42)	<0.001
Current smoker, *n* (%)	101 (17)	78 (18)	23 (17)	0.76
Atrial fibrillation, *n* (%)	270 (46)	197 (44)	73 (52)	0.076
Myocardial infarction, *n* (%)	239 (40)	170 (38)	69 (49)	0.014
HF history				
NYHA				
Class I/II, *n* (%)	279 (47)	232 (51)	47 (34)	0.002
Class III, *n* (%)	293 (50)	208 (46)	85 (61)	
Class IV, *n* (%)	20 (3)	13 (3)	7 (5)	
LVEF (%), mean (SD)	33 (14)	34 (14)	32 (14)	0.22
Treatment				
ACEi/ARB, *n* (%)	486 (82)	376 (83)	110 (79)	0.21
β-Blocker, *n* (%)	398 (67)	317 (70)	81 (58)	0.007
Loop diuretic, *n* (%)	567 (96)	431 (95)	136 (97)	0.36
Digoxin, *n* (%)	190 (32)	142 (31)	48 (34)	0.53
MRA, *n* (%)	328 (55)	248 (55)	80 (57)	0.64
Laboratory measurements				
eGFR (mL/min.1.73 m^2), mean (SD)	54 (20)	56 (20)	46 (18)	<0.001
NT-proBNP (pg/mL), median [IQR]	2521 [1301–5634]	2239 [1170–4576]	4480 [2131–11318]	<0.001
Creatinine (μmol/L), mean (SD)	127 (54)	120 (49)	148 (62)	<0.001
Sodium (mmol/L), mean (SD)	139 (4)	139 (4)	138 (5)	0.002
Duration of admission, mean (SD)	13 (10)	13 (9)	15 (11)	0.030

SD, standard deviation; SBP, systolic blood pressure, DBP, diastolic blood pressure; BMI, body mass index; NYHA, New York Heart Association Class; LVEF, left ventricle ejection fraction; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; IQR, interquartile range.

with the selected biomarker (galectin-3, EPO, TNF-αR1a, TGF-β) levels <10th percentile could be classified as 'high likelihood' for the absence of an event, whereas the clinical risk model with NT-proBNP predicted a low likelihood for the absence of an event in these patients; in other words, we could potentially and adequately reclassify these patients by considering the low value of the biomarker (*Table 4*). To follow up on this reclassification, we calculated continuous NRI and IDI, which, however, showed insignificant NRIs for single selected biomarkers, likely due in part to the very low numbers of reclassified patients (Supplemental Table S7).

Further evaluation of the events: death

Of the 22 (3.7%) patients who died within 30 days, median biomarker levels of the composite endpoint are displayed in the Supplementary material online (*Table S8*). None of these had a galectin-3, NT-proBNP, TNFα-R1a, or EPO level below the 10th percentile after discharge. At 180 days 91 (15.4%) patients died; no patient below the 10th percentile cut-off of galectin-3 died, while other biomarkers failed to identify several patients who endured an event. After 1 year of follow-up, only two patients with a galectin-3 < 10th percentile died out of a total of 131 deaths.

Further evaluation of the events: rehospitalization owing to heart failure

Rehospitalization owing to HF occurred within 30 days in 32 patients (5.4%). None who were rehospitalized had a galectin-3 value below the 10th percentile cut-off. The composite endpoint of death and HF rehospitalization occurred 202 times within 1 year after discharge, and only four endpoints occurred in patients with a galectin-3 < 10th percentile. The rate of HF rehospitalizations and death occurring in both studies, at 30, 90, and 180 days are displayed in the Supplementary material online (*Table S9*).

Validation cohort

Data from 285 patients from the TRIUMPH study was available for use in the current analyses. This subset of patients had baseline characteristics, which were comparable to the entire TRIUMPH cohort ($N = 478$, data not shown). The mean (SD) age was 72

Table 2 Biomarkers stratified by rank, displays the cut-off value, the sensitivity and specificity for the cut-off value and the exact number of endpoints at 180 days in Coordinating Study Evaluating Outcomes of Advising and Counselling in Heart Failure [COACH; complete list; ranked based upon positive predictive value PPV)]

Biomarker	Cut-off value	Sensitivity	1 – Specificity	PPV	HF rehospitalization	Death	Composite	Rank
Galectin-3, ng/mL	<11.8	0.872	0.993	0.983	1	0	1	1
EPO, IU/L	<2.7	0.879	0.957	0.900	4	2	6	2
TNFαR1a, ng/mL	<1.6	0.888	0.957	0.900	5	2	6	3
TGF-β,* ng/mL	>104.75	0.886	0.948	0.883	4	3	7	4
PSAP-B, ng/mL	<37.0	0.885	0.949	0.883	4	4	7	5
GDF-15, ng/mL	<1.5	0.874	0.949	0.883	4	4	7	6
Interleukin 6, ng/mL	<3.6	0.889	0.940	0.867	7	1	8	7
Neuropilin ng/mL	<5.3	0.89	0.942	0.867	6	3	8	8
cTnI, pg/mL	<2.0	0.889	0.944	0.867	4	5	8	9
Mesothelin, ng/mL	<19.2	0.885	0.949	0.867	5	5	8	10
Troy, ng/mL	<0.5	0.89	0.942	0.867	7	5	8	11
ST-2, ng/mL	<0.86	0.887	0.948	0.850	7	5	9	12
ESAM, ng/mL	<38.9	0.888	0.935	0.850	7	5	9	13
PIGR-1, ng/mL	<297.7	0.852	0.935	0.850	6	6	9	14
Osteopontin, ng/mL	<76.1	0.892	0.928	0.833	8	3	10	15
VEGF, ng/mL	<13.5	0.892	0.922	0.833	6	4	10	16
Syndecan-1, ng/mL	<9.5	0.89	0.928	0.833	9	4	10	17
D-Dimer, µg/mL	<0.1	0.927	0.928	0.833	6	5	10	18
RAGE, ng/mL	<1.4	0.878	0.920	0.833	6	6	10	19
CRP, µg/mL	<1.8	0.895	0.920	0.817	7	5	11	20
Angiogenin,* µg/mL	>12013.9	0.895	0.913	0.817	10	5	11	21
NT-proBNP, pg/mL	<626.8	0.895	0.915	0.817	6	6	11	22
Pentraxin-3, ng/mL	<1.8	0.895	0.899	0.800	8	8	12	23
NRP-1, ng/mL	<656.4	0.899	0.906	0.783	5	8	13	24
BNP, pg/mL	<95.7	0.904	0.893	0.767	8	7	14	25
Cystatin C, µg/mL	<5387.9	0.902	0.899	0.767	7	9	14	26
NGAL, ng/mL	<62.8	0.904	0.899	0.767	6	10	14	27
MPO, ng/mL	<12.1	0.899	0.899	0.750	10	9	15	28
Periostin, ng/mL	<2.6	0.878	0.884	0.733	13	11	16	29

HF, heart failure; CRP, C-reactive protein; cTnI, cardiac troponin I; GDF-15, growth differentiation factor 15; RAGE, receptor for advanced glycation end-products; TNF-αR1a, tumour necrosis factor alpha receptor 1a; MPO, myeloperoxidase; PIGR-1, polymeric immunoglobulin receptor 1; TGF-β, transforming growth factor-beta; NRP-1, neutropilin 1; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ST-2, suppression of tumorigenicity 2; VEGF, vascular endothelial growth factor; EPO, erythropoietin ; ESAM, endothelial cell-selective adhesion molecule; NGAL, neutrophil gelatinase-associated lipocalin; BNP, B-type natriuretic peptide; PSAP-B, prosaposin B.
*High levels of these markers are associated with less severe HF, and low levels with severe HF.

(±12) years, and 96 (34%) were female. Median [IQR] NT-proBNP was 2305 [1205–4871] pg/mL and ejection fraction was 32% .[14] The Supplementary material online (*Table S10*) displays the characteristics of this population. Both derivation and validation HF cohorts had similar composite event rates with an overall 365-day event rate of 35%. The distribution of plasma galectin-3 levels in both trials was also similar (see the Supplementary material online, *Figure S1*) and measurements were performed with the same validated assay. The baseline characteristics of COACH and TRIUMPH are presented in the Supplementary material online (*Table S11*). For both studies we stratified patients regarding their galectin-3 levels (10th percentile), as displayed in the Supplementary material online (*Table S12*).

Using the TRIUMPH data set, we further evaluated galectin-3, NT-proBNP, and cTnI. Galectin-3 < 10th percentile and NT-proBNP <10th percentile were, in both cohorts, associated with absence of 30-day mortality. Positive predictive value was calculated for galectin-3, NT-proBNP, and cTnI and were 0.888, 0.852, and 0.857, respectively (see the Supplementary material online, *Table S13*). Logistic regression analysis showed that galectin-3 adjusted for age and sex was significantly associated with the absence of an event after 180 days, whereas unadjusted NT-proBNP and cTnI were non-significant (see the Supplementary material online, *Table S14*). The composite endpoint at 180 days from the derivation and validation cohort are displayed in *Figure 2*; where we indicated a consistent cut-off point derived from COACH, namely 11.8 ng/mL. From both studies we calculated the event count for galectin-3, NT-proBNP and cTnI (see the Supplementary material online, Table S15).

Discussion

We set out to identify patients at low risk for death or HF rehospitalization, using a large set of biomarkers. We

Table 3 Logistic regression model for absence of death and/or heart failure (HF) rehospitalization at 180 days; biomarker values presented are the 10th percentile cut off in Coordinating Study Evaluating Outcomes of Advising and Counselling in Heart Failure (COACH)

Biomarker (<10th percentile) based upon rank	Odds ratio	95% CI	*P*-value
Galectin-3	20.9	2.86–100	0.003
+ Age and sex	19.7	2.70–100	0.003
+ Clinical risk model + NT-proBNP	8.1	1.06–50	0.039
EPO	3.0	1.27–7.14	0.013
+ Age and sex	2.7	1.14–6.67	0.025
+ Clinical risk model + NT-proBNP	1.8	0.95–6.67	0.237
TNFαR1a	2.9	1.19–6.67	0.018
+ Age and sex	2.5	1.03–5.88	0.042
+ Clinical risk model + NT-proBNP	1.1	0.50–3.23	0.819
TGF-β	2.3	1.04–5.26	0.041
+ Age and sex	2.2	0.96–5.00	0.063
Biomarkers (<10th percentile) commonly used in daily practice			
NT-proBNP	1.1	0.56–2.27	0.750
cTnI	1.7	0.77–3.69	0.188

CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide; EPO, erythropoietin alpha; TGF-β, transforming growth factor-beta; TNFαR1a, tumour necrosis factor alpha receptor 1a.
Clinical risk model: age, sex, diastolic blood pressure, pulse pressure, stroke, myocardial infarction, atrial fibrillation, peripheral arterial disease, diabetes, left ventricle ejection fraction, previous HF hospitalization, sodium, creatinine, duration of admission

demonstrated that out of 29 biomarkers, four biomarkers, namely galectin-3, EPO, TNFαR1a, and TGF-β had the best performance to identify patients at low risk for events, at their 10th percentile cut point. Galectin-3 identified patients that suffered no 30-day or 180-day mortality and no 30-day HF rehospitalizations, and only one 180-day HF rehospitalization. After correction for the clinical risk model including NT-proBNP, galectin-3 remained an independent predictor for the absence of events in the logistic regression and Cox proportional hazard models.

The primary aim was to compare different biomarkers with respect to their value to identify patients at low risk. Therefore, we show data for all biomarkers on top of the clinical risk model without NT-proBNP. As NT-proBNP is the golden standard of HF biomarkers, we also show additional data on top of the clinical risk model with NT-proBNP. Galectin-3 levels, not NT-proBNP levels (both <10th percentile), showed incremental value on top of the clinical risk model, and the same was observed when combining galectin-3, EPO, TNFαR1a and TGF-β (all <10th percentile). We performed area under the curve (AUC) analyses with and without NT-proBNP present in the clinical risk model to better position the role of biomarkers in assessing low risk. We believe this provides insights in the value of biomarkers predominantly in the low range. When we included NT-proBNP in the clinical risk model, no biomarker (galectin-3 included) was associated with a significant improvement when assessed by NRI.

Galectin-3, which is a surrogate marker of cardiac remodelling, demonstrates better prognostic value for short-term low risk compared with biomarkers that resemble haemodynamic loading conditions, such as natriuretic peptides. We hypothesize that in low-risk patients, cardiac remodelling may not (yet) have progressed to a state associated elevated biomarkers of remodeling, and these patients may therefore be identified by low galectin-3. *Figure 1* depicts how values of galectin-3 have particular power in the low-range.

As most risk engines or risk scores have been developed to identify high-risk patients, from a clinical perspective, there is a clear need to assess if low risk may be present. Such knowledge may help to safely discharge patients.

So while this may have obvious clinical utility, one should realize that when selecting a cut point for optimal biomarker decision making, the conflict between executing a safe discharge must be balanced with the predicted value of a longer hospital stay or additional intervention. Further, the challenge, when optimizing a cut point to sensitivity for adverse events is that, because of the consequent deterioration in specificity, the population of candidates may become so small as to be clinically useless. It is for this rationale that we selected the 10th percentile as optimal cut point, with a high specificity but with a reasonable number of patients with such low values. This implies that a subset of HF patients exists that can be prospectively identified for safe early discharge. Alternatively, a clinician could be less strict and allow an event rate of 5–10%, resulting in a higher percentile of patients who will be classified as low risk, but simultaneously accept a higher incidence of events. However, the consequence of optimizing safety at a predefined cost of low numbers of patients and subsequent events limits the power in statistical analyses (absolute number of reclassification events is low).

We thus acknowledge the limitation that is intrinsic to the (small) number of patients in the 10th percentile. Therefore, we explored other cut points at the 20th and 30th percentiles, and noted that TNFαR1a, EPO and galectin-3 remained one of the best biomarkers in predicting low risk. The chosen cut point can

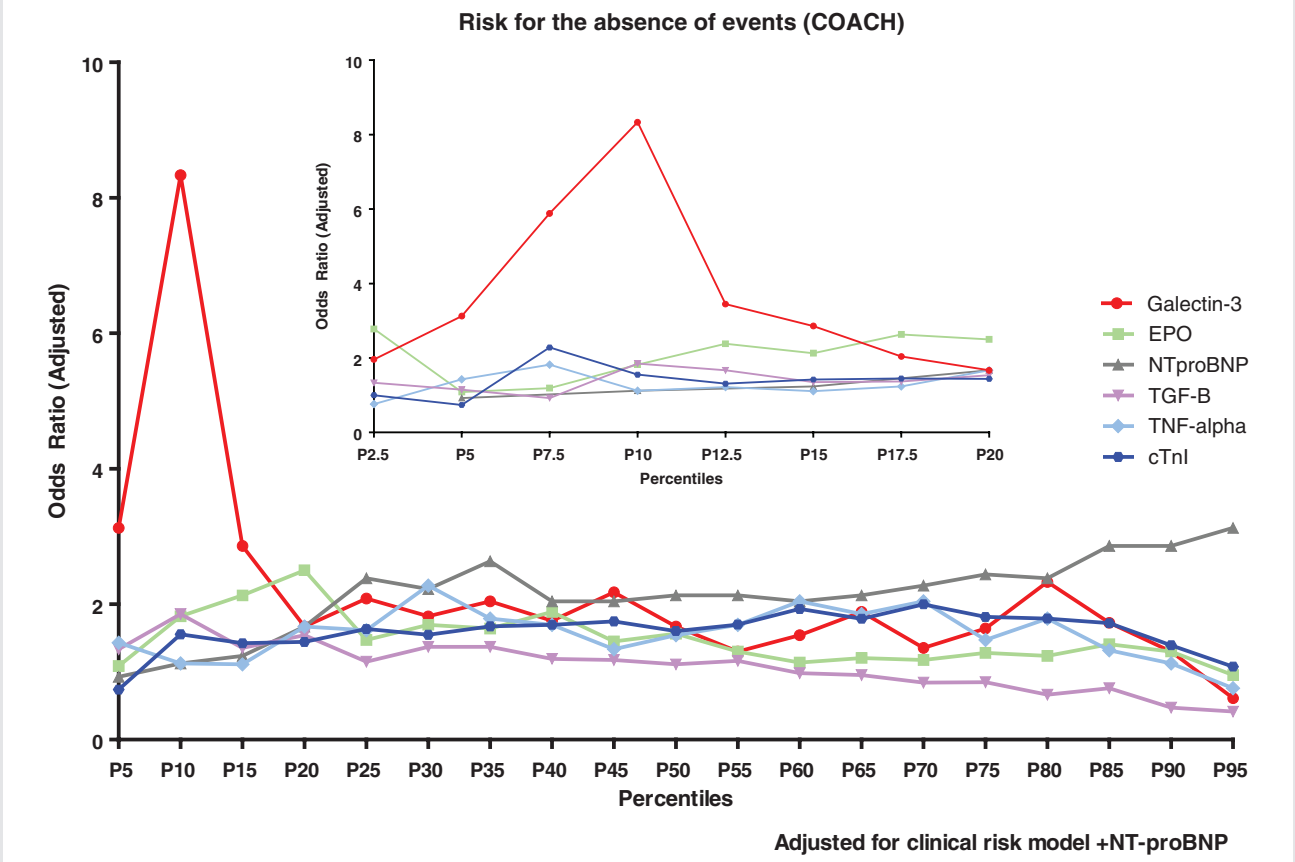

Figure 1 Adjusted logistic regression analysis for the absence of events in Coordinating Study Evaluating Outcomes of Advising and Counselling in Heart Failure (COACH) within 180 days for the selected biomarkers across the complete range of percentiles (5th–95th). cTnI, cardiac troponin I; EPO, erythropoietin alpha; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TGF-B, transforming growth factor-β; TNF, tumour necrosis factor

be increased depending on the event rate that is accepted by the caregiver.

We identified several markers that appear helpful in identifying patients at low risk, representing several pathophysiological domains of heart failure that include inflammation, fibrosis, and anaemia. For low-risk detection, a cut-off of 1.6 ng/mL of TNFαR1a was associated with no deaths and only one HF rehospitalization after 30 days. TNFαR1a is involved in cardiac inflammation, which is considered an important mechanism contributing to the symptoms and progression of HF. Clinically, plasma levels of TNFαR1a are correlated with the severity of congestive HF and are associated with increased risk for incident HF.[25] TGF-β is linked to fibrosis, and therefore not cardiac specific. This may imply that the fibrotic response—as a generic response to injury—might reflect accumulative tissue damage in the HF syndrome. The median TGF-β levels in acute HF patients are lower compared with healthy subjects and may thus reflect impaired repair mechanisms.[26] High (protective) levels of TGF-β were associated with three and seven deaths at, respectively, 30 days and 180 days follow-up. Galectin-3 is also related to tissue fibrosis.[27] It has been shown to predict short-term mortality and HF rehospitalization[17,28–31] and might be of potential value in patients with HF with preserved ejection fraction.[32,33] Galectin-3 recently received Class IIb American College of Cardiology/American Heart Association guideline recommendation as additive for risk stratification.[34]

Another symptom that is prevalent in HF is anaemia. Erythropoietin alpha, which is produced by the kidneys, promotes the proliferation and differentiation of erythroid progenitor cells and is highly expressed under stress and hypoxic[35] conditions, including HF.[36]. It also identified a low rate of HF readmissions throughout the complete follow-up, and no patients with an EPO below the 10th percentile died within 90 days of follow-up. Interestingly, both inflammatory and fibrotic biomarkers were present in the top four biomarkers that provided best prediction of low risk. This underscores a potential role for inflammation and fibrosis formation in the period after AHF.

We further validated the main results from galectin-3, NT-proBNP, and cTnI in an independent validation cohort, also of patients admitted to the hospital with AHF, and observed a similar pattern to that in the derivation cohort.

The prognostic importance of dynamics of (or change in) NT-proBNP during hospitalization have been studied in seven

Table 4 Patients were initially stratified by the clinical risk model+NT-proBNP into tertiles. The right columns depict the actual number of events of patients with low biomarker levels (<10th percentile), validating the clinical score

	Tertiles of odds ratios as calculated by the clinical risk model + NT-proBNP for the absence of an event			Number of events		
Biomarkers <10th percentile ($n = 60$/group)	OR <4.3, 'High risk'	OR 4.4–8.4, 'Intermediate risk'	OR >8.5 'Low risk'	OR <4.3	OR 4.4–8.4	OR >8.5
Galectin-3	12%	18%	70%	1	0	0
EPO	17%	33%	50%	2	2	1
TNFα-R1a	17%	17%	66%	2	1	3
TGF-β	30%	27%	43%	3	1	2

OR, odds ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; EPO, erythropoietin alpha; TGF-β, transforming growth factor-beta; TNFαR1a, tumour necrosis factor alpha receptor 1a.
Percentages indicate the proportion of patients with low biomarker level that are in each tertile of the clinical risk model: age, sex, diastolic blood pressure, pulse pressure, stroke, myocardial infarction, atrial fibrillation, peripheral arterial disease, diabetes, left ventricle ejection fraction, previous HF hospitalization, sodium, creatinine, duration of admission + NT-proBNP.

(acute) HF cohorts, together comprising 1301 patients, in the European collaboration on acute decompensated heart failure (ÉLAN-HF).[37] The study has shown that changes in NT-proBNP during hospitalization improve the prediction of future events. We only had discharge NT-proBNP values and, although discharge levels have better prognostic value than admission levels,[38,39] we thus could not look at changes in NT-proBNP. Further, our clinical risk model differed from ÉLAN-HF: both models included age, sodium, blood pressure, New York Heart Association (NYHA) functional class, but we used creatinine and ÉLAN-HF urea, and we entered sex, left ventricular ejection fraction (LVEF), diabetes, pulse pressure, stroke, myocardial infarction, atrial fibrillation, peripheral arterial disease, previous HF hospitalization, duration of admission, and NT-proBNP, while ÉLAN-HF entered peripheral oedema. But most importantly, ELAN-HF focused on high risk and did not specifically address low-risk assessment. In our analyses, we chose to base our clinical risk model on the published risk model, namely the COACH risk engine. Although it includes several established prognostic factors, this risk engine does not include all known prognostic factors, such as the presence of anaemia, left bundle branch block, and HF medication. Inclusion of these variables might potentially have altered the performance of the biomarkers within the multivariable analyses. From our data, we conclude that NT-proBNP might be a better predictor for high risk in acute HF than it is for low risk—an observation that has been made before.[40]

Our data might be of help in daily care for HF patients. In clinical practice, NT-proBNP is the gold standard for estimating the prognosis of HF patients. In our dataset however, as demonstrated by logistic regression analysis (*Table 3*), NT-proBNP (<10th percentile) was not significantly associated with the absence of death and/or HF rehospitalization. Our data therefore questions whether NT-proBNP is the ideal marker for assessing low risk in semi-acute HF patients, although at present the aggregate data for risk assessment in HF are clearly supporting a central role for natriuretic peptides. The use of biomarkers may help to decide whether to safely discharge hospitalized patients with low risk, as indicated by these markers. Knowledge of risk status may also allow personalization of their follow-up schedule. For example, whereas high-risk patients may benefit from more frequent and immediate post-discharge monitoring, low-risk patients could be identified as requiring lower intensity post-discharge resource utilization. Reclassification of patients based upon low biomarker levels may be helpful in reducing the burden of frequent hospital visits, but clinicians should always be aware of other signs and symptoms that could help avoid incorrect reclassification.

The advantage of our analysis is that by selecting an outcome by the lowest 10th percentage of a certain biomarker in the total HF population it is more plausible for clinical use. As the current national 30-day HF rehospitalization rate in the USA exceeds 25%, a strategy considering galectin-3 levels may represent a more precise and objective identification of discharge candidates than existing tools.

Strengths and limitations

Our analysis has several limitations. As a substudy of the original COACH and TRIUMPH trials, our conclusions should be limited to that of generating a hypothesis. Further, many of the assays we evaluated are only available as research tools, and additional assays could not be performed in COACH given the limited volume of sample per patient. In addition, most biomarkers were measured on a multiple platform. Importantly, in COACH, no clinical decision-making was based upon marker levels, such that our findings must be prospectively validated before being applied clinically.

Other limitations include that we cannot make statements about the dynamics of biomarkers, and it has been reported that changes of, for example galectin-3[41–44] and NT-proBNP[37,45] confer additional prognostic importance. Further, all patients studied were hospitalized and sample collection took place before discharge. Thus, these findings cannot be applied to emergency department disposition decision-making without further evaluation. Finally, in the validation cohort (TRIUMPH trial), only galectin-3, NT-proBNP, and cTnI were available.

The strengths of the study are the pre-specified adjudicated end point assessment, the pre-specified biomarker substudies,

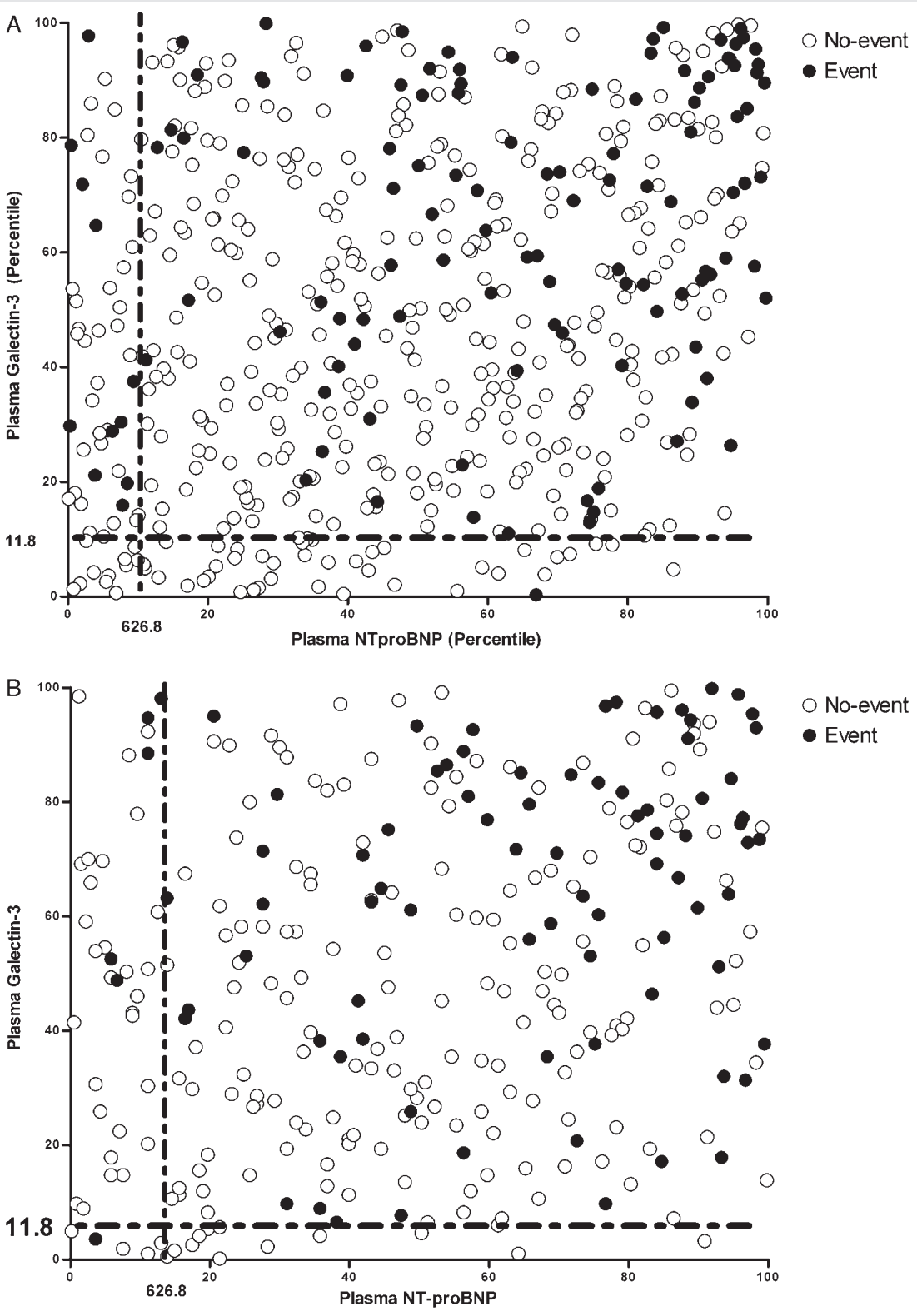

Figure 2 Galectin-3 and N-terminal pro-B-type natriuretic peptide (NT-proBNP) for composite endpoint at 180 days in the derivation and validation cohort. (a) Derivation cohort [Coordinating Study Evaluating Outcomes of Advising and Counselling in Heart Failure (COACH)]. (b) Validation cohort (Translational Initiative on Unique and novel strategies for Management of Patients with Heart Failure (TRIUMPH)).

and a very large set of biomarkers. Further, we could validate the results of our initial observations in a completely independent cohort, with almost identical outcomes. Thus, our results do suggest that biomarker testing may enable the identification of a cohort of potential candidates for early hospital discharge in selected low-risk HF patients. As the impact and timing of post-discharge is controversial,[46,47] an objective determinate (i.e. a biomarker level) may assist in the proper use of these resources. Our approach could help in identifying patients that would benefit from early follow-up visits or could be monitored less frequently.

Conclusion

Most clinically available biomarkers have been assessed for their ability to identify patients at high risk of adverse events. We show data that suggest that biomarkers can be used to assess low risk. Out of a large panel of 29 biomarkers, galectin-3, EPO, TNFαR1a, and TGF-β emerged as predictors for low risk, while the routine biomarkers NT-proBNP and cTnI did not. Galectin-3 remained significantly associated with low risk after adjustment for the clinical risk model with NT-proBNP. Future studies are needed to prospectively validate our findings, as biomarkers indicating low risk may be helpful to identify patients that can be safely discharged or do not need short-term revision in the outpatient clinic.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Distribution of galectin-3 in the derivation (COACH) and validation (TRIUMPH) cohort.

Table S1. The intra- and inter-assay coefficients of variation of the biomarkers.

Table S2. Counts of death, HF rehospitalization and composite end point based upon the 10th percentile for all biomarkers at 30 days, 90 days, 180 days, and 1 year.

Table S3. 'Top 4' biomarker rank (based upon number of events); shown for different Cut off values (10th, 20th, and 30th percentiles).

Table S4. Ranking of biomarkers based upon the frequency they were added to the model after multiple (×1000) bootstrap runs where all the biomarkers and variables of the clinical risk model were entered in a stepwise backward logistic regression analysis for the absence of an event.

Table S5. Cox regression model for death and/or HF rehospitalization at 180 days; biomarker values presented are the 10th percentile cut off in COACH.

Table S6. Receiver operating characteristic upon the addition of different biomarkers based upon the 10th percentile for HF rehospitalisation and fatal event at 180 days in COACH.

Table S7. The reclassification indices; NRI continuous and IDI at 180 days.

Table S8. Biomarker levels of patients who endured a composite event at 30 days and 180 days, or not (COACH).

Table S9. Count of HF rehospitalization and death occurring in both studies at 30, 90, 180, and 365 days.

Table S10. Baseline characteristics—validation cohort (TRIUMPH).

Table S11. Baseline characteristics of the COACH and TRIUMPH studies.

Table S12. Baseline characteristics stratified by galectin-3 level for COACH and TRIUMPH.

Table S14 Logistic regression model for absence of death and/or HF rehospitalization at 180 days; biomarker values presented are the 10th percentile cut off in TRIUMPH.

Table S15. Counts of HF rehospitalization and all-cause mortality across both studies at different time-points.

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