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RESEARCH ARTICLE

Incremental prognostic value of biomarkers in PARADIGM-HF

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Aims It is uncertain how much candidate biomarkers improve risk prediction when added to comprehensive models including routinely collected clinical and laboratory variables in heart failure.

Methods and results Aldosterone, cystatin C, high-sensitivity troponin T (hs-TnT), galectin-3, growth differentiation factor-15 (GDF-15), kidney injury molecule-1, matrix metalloproteinase-2 and -9, soluble suppression of tumourigenicity-2, tissue inhibitor of metalloproteinase-1 (TIMP-1) and urinary albumin to creatinine ratio were measured in 1559 of PARADIGM-HF participants. We tested whether these biomarkers, individually or collectively, improved the performance of the PREDICT-HF prognostic model, which includes clinical, routine laboratory, and natriuretic peptide data, for the primary endpoint and cardiovascular and all-cause mortality. The mean age of participants was 67.3 ± 9.9 years, 1254 (80.4%) were men and 1103 (71%) were in New York Heart Association class II. During a mean follow-up of 30.7 months, 300 patients experienced the primary outcome and 197 died. Added individually, only four biomarkers were independently associated with all outcomes: hs-TnT, GDF-15, cystatin C and TIMP-1. When all biomarkers were added simultaneously to the PREDICT-HF models, only hs-TnT remained an independent predictor of all three endpoints. GDF-15 also remained predictive of the primary endpoint; TIMP-1 was the only other predictor of both cardiovascular and all-cause mortality. Individually or in combination, these biomarkers did not lead to significant improvements in discrimination or reclassification.

Conclusions None of the biomarkers studied individually or collectively led to a meaningful improvement in the prediction of outcomes over what is provided by clinical, routine laboratory, and natriuretic peptide variables.

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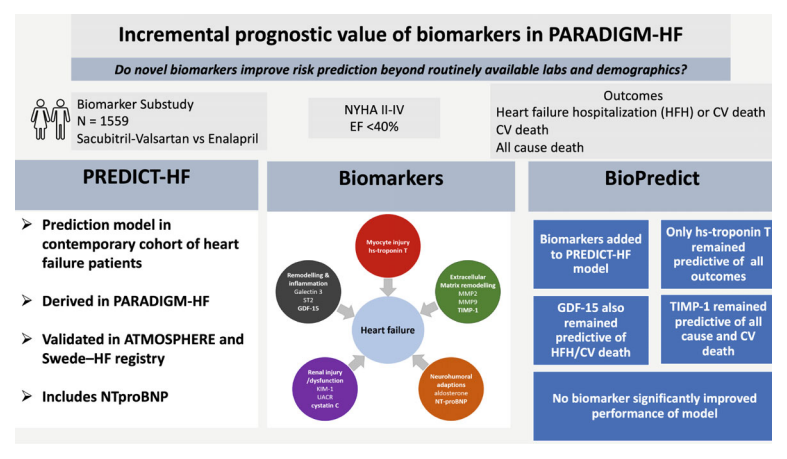
Graphical Abstract



Design and results of the BioPREDICT study of the incremental predictive value of an array of biomarkers added to the PREDICT-HF prognostic model. CV, cardiovascular; EF, ejection fraction; GDF-15, growth differentiation factor-15; HFH, heart failure hospitalization; hs, high-sensitivity; KIM-1, kidney injury molecule-1; MMP2, matrix metalloproteinase-2; MMP9, matrix metalloproteinase-9; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; ST2, soluble suppression of tumorigenicity-2; TIMP-1, tissue inhibitor of metalloproteinase-1; UACR, urinary albumin to creatinine ratio.

Keywords Biomarkers • Heart failure • Prediction

Introduction

Over the past two decades, prognostic models for heart failure with reduced ejection fraction (HFrEF) have evolved with a better understanding of which clinical variables are predictive, improved statistical approaches and, in particular, the incorporation of natriuretic peptides.[1–7] Risk models help clinicians to have informed discussions with their patients about prognosis which may aid decisions about adding new pharmacological treatments, other device and surgical interventions (including transplantation), frequency and intensity of monitoring, and the timing of end-of-life care.

The PARADIGM Risk of Events and Death in the Contemporary Treatment of Heart Failure model (PREDICT-HF) is one of the most recent and comprehensive models, built in a trial population receiving contemporary treatment (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure, PARADIGM-HF) and validated in a second large trial (Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure, ATMOSPHERE) as well as in a 'real-world' registry (Swedish Heart Failure Registry, SwedeHF).[8] Uniquely, PREDICT-HF provides a prediction using either B-type natriuretic peptide (BNP) or N-terminal proBNP (NT-proBNP) which are now routine laboratory investigations.

It follows that the prognostic value of any new biomarker should be tested by adding it to a contemporary comprehensive risk model that incorporates a natriuretic peptide.[9–11] We have done this using 11 biomarkers, each potentially reflecting different underlying pathological pathways, to determine whether individually or collectively they improved the prognostic performance of PREDICT-HF. The 11 biomarkers examined were measured in a subset of patients enrolled in PARADIGM-HF.

Methods

The PARADIGM-HF trial

The design and results of the PARADIGM-HF trial are published.[12,13] Briefly, patients were eligible if they were in New York Heart Association (NYHA) functional class II–IV, had a left ventricular ejection fraction (LVEF) of ≤40%, had an elevated natriuretic peptide level, and were receiving an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) along with a beta-blocker (unless contraindicated or not tolerated) and a mineralocorticoid receptor antagonist (MRA) if indicated. After a run-in period, patients were randomly assigned to double-blind therapy with sacubitril/valsartan or enalapril. Patients with systolic blood pressure <95 mmHg, estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 or potassium >5.4 mmol/L were excluded. The primary outcome was the composite of time-to-first hospitalization for worsening heart failure or cardiovascular death.

PREDICT-HF derivation and validation

The derivation and validation of the PREDICT-HF models have been described elsewhere.[8,14,15] The models were validated using data from

the ATMOSPHERE study and the SwedeHF registry, which included an unselected nationwide cohort of patients with HFrEF.[8,14,15] Separate predictive models were built for the primary composite endpoint, cardiovascular death and all-cause mortality. Thirty-five variables were required for all three scores. The extent of missing data for each variable is shown in online supplementary *Table S1*. Data were complete for 20 of 35 variables. The proportion of missing data for the other 15 variables ranged from 0.1% to 6.5%. For missing values, the medians from the PARADIGM-HF cohort were used.

Biomarkers and laboratory measurements

Eleven candidate biomarkers were available at baseline as part of the PARADIGM-HF biomarker substudy: aldosterone, cystatin C, high-sensitivity troponin T (hs-TnT), galectin-3, growth differentiation factor-15 (GDF-15), kidney injury molecule-1 (KIM-1), matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), soluble suppression of tumourigenicity 2 (ST2), tissue inhibitor of metalloproteinase-1 (TIMP-1) and urinary albumin to creatinine ratio (UACR).

Whole blood taken by venipuncture was placed in serum and plasma vacutainers. Samples were processed by centrifugation at 3000 *g* for 15 min and the serum and plasma fractions were divided into aliquots for storage at −80° until assay. Spot urine samples, transferred at ambient temperature to central laboratory for immediate analysis were taken for UACR. Details of the measurement of biomarkers in the sacubitril/valsartan heart failure trial programme have been published elsewhere.[16–24] The assays used, the coefficient of variance, lower limit of detection, or lower limit of quantification, and measuring range for each biomarker are presented in online supplementary *Table S2*.

Statistical analysis

The incremental value of the candidate biomarkers in predicting the outcomes of interest was assessed. The logarithmic transformation of each biomarker was included to normalize the distribution. Univariable Cox regression was performed for all biomarkers for each of the three outcomes of interest: the primary composite endpoint (cardiovascular death or heart failure hospitalization), cardiovascular death and all-cause mortality. For the multivariable analyses, Cox proportional hazard models adjusted for the PREDICT-HF score were used to assess the incremental prognostic value of each biomarker in turn. The PREDICT-HF score was calculated using the sum of the multiplication of each variable in the model by the beta coefficient published previously. Single imputation of the median value was used for any missing data (online supplementary *Table S1*).

We also assessed the prognostic importance of the 11 biomarkers collectively, i.e. a 'multi-marker' approach. To do this, all biomarkers were added to the existing PREDICT-HF score using a backward, stepwise, procedure for each outcome with $p < 0.01$ as a criterion for inclusion in the final model. The performance of the final models was reassessed using 2-year time-dependent area under the curve (AUC) with the inclusion of biomarkers (individually and in combination if more than one was predictive following stepwise regression). The integrated discrimination improvement (IDI) and net reclassification index (NRI) were reported to assess whether the addition of each biomarker or combination of biomarkers, improved the prediction of each outcome. Internal validation of the final models with inclusion of biomarkers was performed using bootstrapping (1000 replicates) to assess predictive performance of these models.

The biomarkers included in the final models were also dichotomized at or above/below an optimal cutpoint using the Liu method to maximise the product of the sensitivity and specificity of the cutpoint related to each outcome.[25] Kaplan–Meier survival curves were constructed to illustrate the likelihood of outcome according to the number of elevated biomarkers.

Only patients with complete data available for all biomarkers were included in the multivariable analyses.

Analyses were conducted using Stata version 16.1 (College Station, TX, USA).

Results

Of the 8399 patients randomized in PARADIGM-HF, 1559 had a complete set of all candidate biomarkers. The baseline characteristics of patients with biomarker results available are shown in *Table 1*. The mean ± standard deviation age of those with biomarkers measured was 67.3 ± 9.9 years and 1254 (80.4%) were male. The mean LVEF was 30.7 ± 6%. A comparison of patients with complete biomarker data and those in the trial overall is shown in online supplementary *Table S3*.

The median value (and interquartile range) for each candidate biomarker in the study population is shown in *Table 1*. Of the 1559 patients with a measurement of all the candidate biomarkers, 300 experienced the primary composite endpoint, 135 patients died from a cardiovascular cause and 197 patients died from any cause.

Addition of biomarkers individually to the PREDICT-HF model

Univariable and multivariable risk related to a log unit change in each biomarker added individually

The unadjusted risks related to each biomarker for all three outcomes are shown in online supplementary *Table S4*. The results of the multivariable analyses in which each of the candidate biomarkers was added, individually, to the PREDICT-HF score are shown in *Table 2*.

Primary composite endpoint

Added individually, GDF-15, KIM-1, ST2, TIMP-1, cystatin C, hs-TnT and UACR were independent predictors of the primary composite endpoint. Cystatin C and TIMP-1 were associated with the greatest relative risk, with a hazard ratio of 1.74 (1.13, 2.69) and 1.80 (1.22, 2.66) per log unit increase ($p = 0.013$, $p = 0.003$), respectively.

Cardiovascular and all-cause mortality

GDF-15, TIMP1, cystatin C and hs-TnT were independent predictors of cardiovascular and all-cause mortality (*Table 2*). ST2, KIM-1 and UACR were also independent predictors of all-cause mortality, but not cardiovascular mortality (*Table 2*). In both types of mortality, the highest relative risks were seen with cystatin C and, especially, TIMP-1.

Table 1 Baseline characteristics of participants with the full biomarker panel

Demographics	
Age, years	67.3 ± 9.9
Male sex	1254 (80.4)
Race	
White	1495 (95.9)
Black	37 (2.4)
Asian	4 (0.3)
Other	23(1.5)
Region	
North America	232 (14.9)
Latin America	0 (0.0)
Western Europe	700 (44.9)
Central Europe	627 (40.2)
Asia/Pacific	0 (0.0)
Body mass index, kg/m^2	29.6 ± 5.5
Current smoker	199 (12.8)
Heart rate, bpm	71.3 ± 12.2
Systolic blood pressure, mmHg	131.7 ± 17.4
eGFR, ml/min/1.73 m^2	64.8 ± 18.4
HF characteristics	
Left ventricular ejection fraction, %	30.7 ± 6.0
NYHA functional class	
I	2 (0.1)
II	1103 (70.8)
III	443 (28.4)
IV	10 (0.6)
Time since diagnosis of HF	
<1 year	345 (22.1)
1–5 years	549 (35.2)
>5 years	665 (42.7)
Ischaemic aetiology	999 (64.1)
Prior HF hospitalization	920 (59.0)
KCCQ-CSS	79.2 [62.5–91.1]
NT-pro-BNP, pg/ml	1467 [833–2830]
Medical and surgical history	
COPD	271 (17.4)
Hypertension	1211 (77.7)
Diabetes	635 (40.7)
Myocardial infarction	760 (48.7)
Percutaneous coronary intervention	458 (29.4)
Coronary artery bypass graft	369 (23.7)
Atrial fibrillation	761 (48.8)
Cerebrovascular disease	211 (13.5)
Baseline treatment	
Mineralocorticoid receptor antagonist	722 (46.3)
Beta-blocker	1485 (95.3)
Diuretic	1274 (81.7)
Digoxin	350 (22.5)
Implantable cardioverter-defibrillator	299 (19.2)
Cardiac resynchronization therapy	171 (11.0)
Baseline biomarker levels	
Aldosterone, pmol/L	273.3 [174.2–457.8]
Cystatin C, mg/L	1.13 [0.96–1.37]
Galectin-3, ng/ml	16.9[13.9–20.8]
GDF-15, ng/ml	1650 [1161–2398]
KIM-1, pg/ml	129 [87.9–192]
MMP-2, ng/ml	135 [116.3–157.6]
MMP-9, ng/ml	63.6[38.3–124.5]
ST2, ng/ml	32.1 [25.3–40.9]
TIMP-1, ng/ml	125.6 [105.4–152.6]
hs-TnT, ng/ml	0.02 [0.01–0.02]
UACR, mg/mmol	0.9 [0.4–3.2]

Data are given as mean ± standard deviation, *n* (%), or median [interquartile range]. Percentages may not total 100 due to rounding.
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; GDF-15, growth differentiation factor-15; HF heart failure; hs-TnT, high-sensitivity troponin T; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score; KIM-1, kidney injury molecule-1; NYHA, New York Heart Association; MMP, matrix metalloproteinase; ST2, suppression of tumourigenicity 2; TIMP-1, tissue inhibitor of metalloproteinase-1; UACR, urinary albumin to creatinine ratio.

Therefore, four biomarkers (GDF-15, TIMP-1, cystatin C and hs-TnT) were, individually, associated with a higher risk of all three outcomes (*Table 2*). Spline analysis revealed a linear association between each and risk (online supplementary *Figure S1*).

Simultaneous addition of all biomarkers to the PREDICT-HF model ('multi-marker' approach)

After stepwise variable selection and adding all biomarkers simultaneously to the PREDICT-HF base models for each outcome, only hs-TnT remained an independent predictor of all three outcomes. GDF-15 also remained predictive of the primary composite endpoint. TIMP-1 was the only other biomarker that remained a predictor of both cardiovascular and all-cause mortality. The optimal cutpoints for GDF-15, hs-TnT and TIMP-1 were 1939.9 ng/ml, 0.021 ng/ml, and 137.65 ng/ml, respectively. The number of participants found to have a biomarker level above these cutpoints were 593 (38.0%), 571 (36.6%), and 589 (38.0%), respectively. Those with both hs-TnT and GDF-15 elevated above the optimal cutpoints were at higher risk of the primary composite endpoint than patients with one or neither biomarker elevated (*Figure 1*). Those with both hs-TnT and TIMP-1 elevated were at highest risk of cardiovascular and all-cause death (*Figure 2*).

Model performance and improvement

Primary composite endpoint

As single biomarkers, hs-TnT and GDF-15 added the most prognostic information to the model, increasing the 2-year time-dependent AUC from 0.736 to 0.741 and 0.749, respectively. When both were added to the PREDICT-HF model, there was a non-significant improvement in the 2-year time-dependent AUC from 0.736 (0.702–0.771) to 0.748 (0.713–0.783) ($p = 0.34$; *Figure 3*). NRI improved by 0.66 (0.133–0.743; $p = 0.04$), but IDI did not.

Table 2 Biomarkers remaining independent predictors of risk when added individually to the PREDICT-HF base model score

	Hazard ratio (95% CI)[a]	*p*- value	Time-dependent AUC (2 years)
Primary composite outcome			
Base model[b]			0.736
Cystatin C	1.74 (1.13,2.69)	0.013	0.732
GDF-15	1.66 (1.33,2.06)	<0.001	0.749
TIMP-1	1.80 (1.22,2.66)	0.003	0.737
hs-TnT	1.55 (1.29,1.86)	<0.001	0.741
ST2	1.50 (1.14,1.98)	0.004	0.740
KIM-1	1.24 (1.04,1.47)	0.015	0.736
UACR	1.11 (1.04,1.19)	0.001	0.731
Cardiovascular mortality			
Base model[b]			0.672
Cystatin C	2.70 (1.38, 5.26)	0.004	0.663
GDF-15	1.69 (1.21,2.29)	0.002	0.685
TIMP-1	3.59 (1.99,6.47)	<0.001	0.679
hs-TnT	1.65 (1.26,2.16)	<0.001	0.670
All-cause mortality			
Base model[b]			0.663
Cystatin C	2.74 (1.59, 4.72)	<0.001	0.656
GDF-15	1.94 (1.49, 2.52)	<0.001	0.684
TIMP-1	3.36 (2.06,5.48)	<0.001	0.672
hs-TnT	1.63 (1.31,2.03)	<0.001	0.664
ST2	1.73 (1.23,2.45)	0.002	0.661
KIM-1	1.30 (1.06,1.60)	0.013	0.664
UACR	1.13 (1.05,1.26)	0.002	0.668

AUC, area under the curve; CI, confidence interval; GDF-15, growth differentiation factor-15; hs-TnT, high-sensitivity troponin T; KIM-1, kidney injury molecule-1; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ST2, suppression of tumourigenicity 2; TIMP-1, tissue inhibitor of metalloproteinase-1; UACR, urinary albumin to creatinine ratio.
[a]Hazard ratios are per log unit increase.
[b]Base model: PREDICT-HF model including NT-proBNP.

Cardiovascular and all-cause mortality

Adding hs-TnT and TIMP-1 to the model improved performance for all-cause mortality only slightly and non-significantly as reflected by the 2-year time-dependent AUC increasing from 0.663 (0.609–0.716) to 0.675 (0.619–0.730) ($p = 0.48$; *Figure 3*) and did not improve IDI or NRI. Adding both biomarkers to the model for cardiovascular death did not improve the 2 year time dependent AUC significantly—it increased from 0.672 (0.611–0.732) to 0.681 (0.617–0.746) ($p = 0.23$; *Figure 3*) – and did not improve IDI or NRI.

These findings were confirmed on internal validation by bootstrapping (1000 replicates) with no significant change in the AUCs for the final model compared to the main analysis of the overall dataset (online supplementary *Table S5*).

Discussion

While many individual biomarkers are associated with adverse clinical outcomes in heart failure, their additional predictive benefit is rarely rigorously tested by adding them to a comprehensive prognostic model (including clinical, routine laboratory, and natriuretic peptide data).[8–11] We believe that the present report is one of the largest studies to test emerging biomarkers in this way in patients with chronic HFrEF. We found that 4 of 11 biomarkers tested were 'independent' predictors of all three outcomes assessed when added, individually, to the PREDICT-HF model; these biomarkers were hs-TnT, GDF-15, TIMP-1, and cystatin C. However, adding the candidate biomarkers to the PREDICT-HF model did not lead to a clinically or statistically significant improvement in discrimination or net reclassification (*Graphical Abstract*). These results suggest that these additional biomarkers, though strongly associated with outcomes, may not add useful prognostic value beyond routinely collected information.

Our results for hs-TnT support and extend the findings of an individual patient data analysis in which hs-TnT was predictive of non-fatal and fatal outcomes, independently of proven risk markers including sex, age, LVEF, eGFR, ischaemic aetiology, and, importantly, NT-proBNP in 9289 patients with heart failure.[26] The list of prognostic variables included in the PREDICT-HF base model was even more extensive, yet hs-cTnT remained a significant predictor of outcomes when added as an individual biomarker. More recently, hs-TnT was found to provide incremental prognostic information in the EMPEROR-Reduced trial (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction), a finding confirmed by a validation analysis of the BIOSTAT-CHF study (a systems BIOlogy Study to TAilored

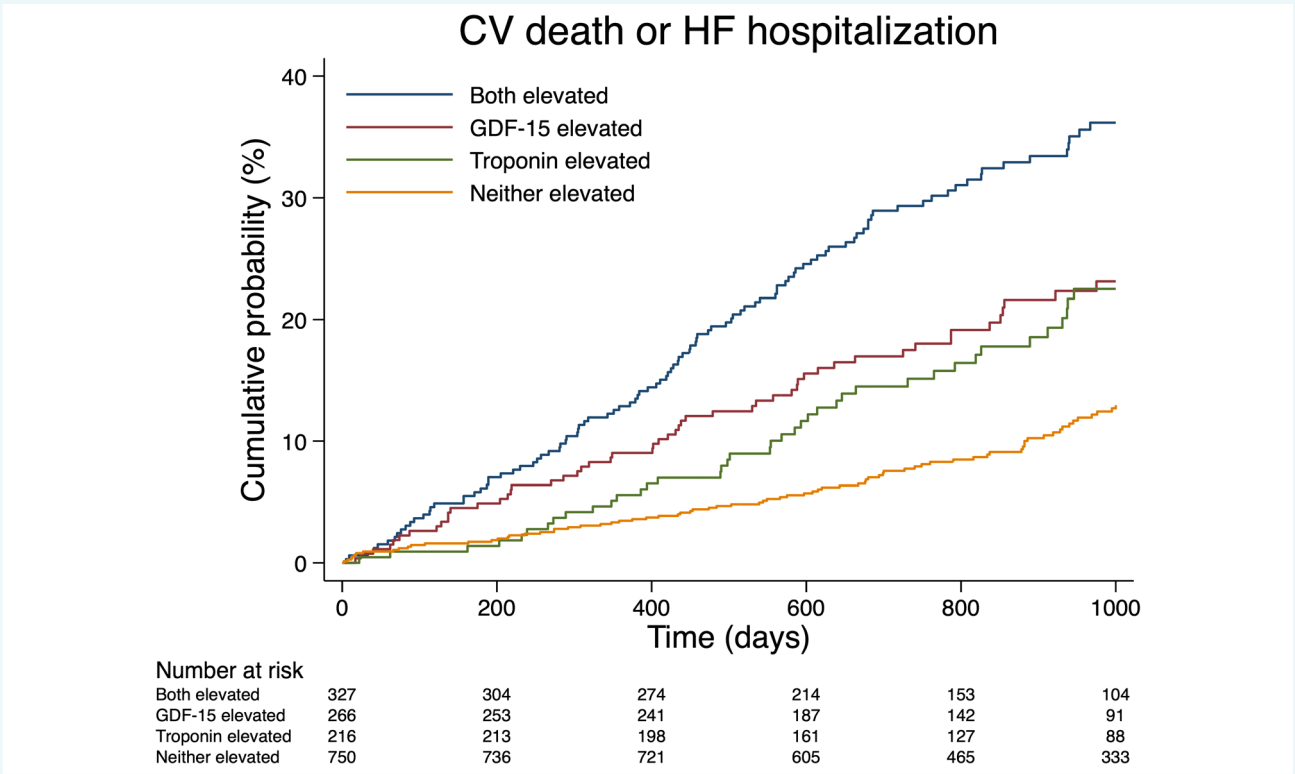


Figure 1 Cumulative incidence of the primary composite endpoint according to high-sensitivity troponin T or growth differentiation factor-15 (GDF-15) elevation. Elevated GDF-15 was defined as a level above an optimal cutpoint of 1939.9 ng/ml. Elevated troponin was defined as a level above an optimal cutpoint of 0.021 ng/ml. CV, cardiovascular; HF, heart failure.

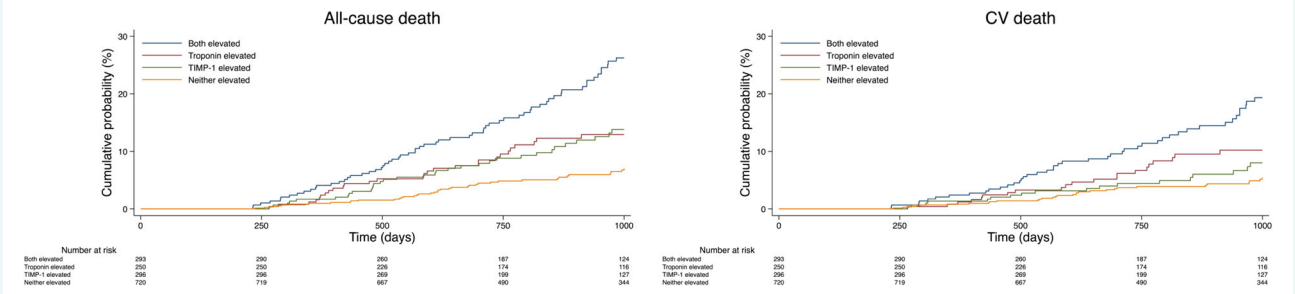


Figure 2 Cumulative incidence of all-cause death and cardiovascular (CV) death according to high-sensitivity troponin T or tissue inhibitor of metalloproteinase-1 (TIMP-1) elevation. Elevated TIMP-1 was defined as a level above 137.65 ng/ml. Elevated troponin was defined as a level above an optimal cutpoint of 0.021 ng/ml.

Treatment in Chronic Heart Failure).[27] It was therefore not surprising that when all biomarkers were added simultaneously to the PREDICT-HF base models for each outcome of interest, hs-TnT remained a predictor of death (cardiovascular and all-cause) and of the primary composite outcome.

GDF-15 has been predictive of outcomes in several studies which used models adjusted to some extent for other prognostic variables.[28–30] Conversely, while several studies have evaluated cystatin C in patients with acute heart failure, and a few have examined TIMP-1 mainly in patients with heart failure and preserved ejection fraction, none of these was large or extensively adjusted for recognized prognostic variables.[31–36] Yet, when all 11 candidate biomarkers were added simultaneously to the PREDICT-HF base models, beyond hs-TnT, TIMP-1 was the only biomarker that remained a predictor of both cardiovascular and all-cause mortality and GDF-15 was the only other independent predictor of the primary composite endpoint.

The explanation for these findings is uncertain. TIMP-1 levels, reflecting extracellular matrix remodelling, may represent a pathophysiological pathway that other clinical or biomarker variables

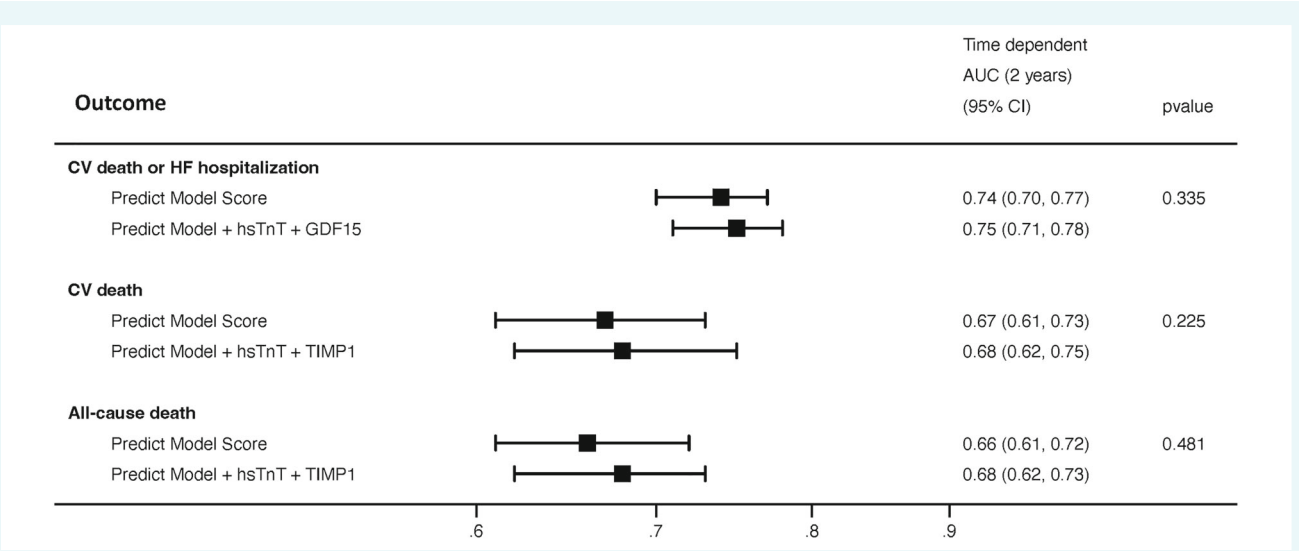


Figure 3 Discrimination of the PREDICT-HF model before and after the addition of biomarkers which remained independently predictive of outcomes when all biomarkers were added simultaneously. AUC, area under the curve; CI, confidence interval; CV, cardiovascular; GDF-15, growth differentiation factor-15; HF, heart failure; hsTnT, high-sensitivity troponin T.

do not account for, and that pathway may be a more powerful predictor of death. We know of no other study where the prognostic value of TIMP-1 (or any other marker of extracellular matrix remodelling) has been tested in addition to multiple biomarkers, including hs-TnT.[34–36] Clearly, this is a question worthy of further investigation. If our finding is validated, it may, potentially, alter thinking about the pathophysiological mechanisms driving progression and therapeutic approaches to in HFrEF. Likewise, the strong performance of GDF-15 as an independent predictor of the primary composite endpoint is unexplained. Although GDF-15 is often described as a stress-responsive cytokine belonging to the transforming growth factor-β superfamily which is thought to be increased by several stimuli, including inflammation, oxidative stress, tissue injury and hypoxia, its actual mechanistic role in heart failure is unclear.[28–30] As with TIMP-1, it would appear that GDF-15 reflects a pathophysiological pathway that is distinct from those reflected by the other biomarkers measured (and the prognostic clinical variables included in the PREDICT-HF model).

Our findings are important for other reasons. Only 4 of the 11 candidate biomarkers tested provided incremental prognostic information when added to a comprehensive model containing routinely collected clinical variables and laboratory measures, plus NT-proBNP. In other words, most of the prognostic information could be obtained without the expense of measuring new biomarkers and such models can be simplified as a score or prognosis estimated using a simple online calculator. Furthermore, the present findings question the recent interest in a multi-marker approach to risk prediction in heart failure.[37–39] Our study suggests that the prognostic information provided by many biomarkers is redundant because, beyond hs-TnT, only one of the 11 evaluated was independently predictive of death and only one other predictive of the primary composite endpoint. These findings challenge the potentially very expensive multi-marker approach using conventional assays, although new multiplex and other proteomic approaches may change this calculation in the future.[36–39]

An alternative use of novel biomarkers might be to replace existing prognostic variables, thereby simplifying predictive models. Here again, there is interesting information about hs-TnT. A recent report from the EMPEROR-Reduced trial suggested that the addition of hs-TnT to NT-proBNP allows the creation of prognostic models with only 4–9 variables that perform as well as models including up to 30 or more conventional variables.[40] The question about this alternative approach to prognostication is whether the advantage of simplification of predictive models outweighs the cost of a new biomarker or biomarkers.

Finally, we only investigated one use of biomarkers (i.e. to predict outcomes) and they have other roles including diagnosis, assessing response to treatment, suggesting new pathophysiological pathways, and potentially identifying treatment targets.

Limitations

Our study has several limitations. This analysis was not pre-specified and retrospective analysis of this type may be subject to residual/unmeasured confounding. Only single baseline biomarker values were included in this study. Longitudinal monitoring of biomarkers may be more useful for risk stratification. While we studied 1559 patients, a larger sample size may have led to different findings. Although we evaluated 11 biomarkers, many other candidate biomarkers are available and may be more predictive.

Conclusions

When added to a comprehensive prognostic model (including clinical, routine laboratory, and natriuretic peptide data), only 4 of

11 biomarkers tested individually were independently associated with non-fatal and fatal heart failure outcomes. However, none meaningfully enhanced the prediction of outcomes. The association of GDF-15 and TIMP-1 with outcomes may point to pathophysiological pathways and therapeutic targets worthy of further exploration.

Supplementary Information

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

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