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RESEARCH ARTICLE

Association of baseline and longitudinal changes in insulin-like growth factor-binding protein-7 with the risk of incident heart failure: Data from the PREVEND study

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Aim

Senescence is a major risk factor for heart failure (HF), and insulin-like growth factor-binding protein-7 (IGFBP7) has been identified as an important senescence-inducing factor. The aim of this study was to examine the value of baseline and repeat IGFBP7 measurements in predicting future HF among community-dwelling Dutch adults from the Prevention of Renal and Vascular End-stage Disease (PREVEND) study.

Methods and results

Individuals without prevalent HF who attended PREVEND visits 2 and 4 median of 5.1 years apart (25th–75th percentile, 4.9–5.2) with measurements of IGFBP7 were included. We used Cox proportional hazards models to investigate the association between IGFBP7 and HF incidence. A total of 6125 participants attending visit 2 (mean ± standard deviation [SD] age 53.1 ± 12.2 years; 3151 [51.4%] men) were followed for a median of 8.4 (7.8–8.9) years, and 194 participants (3.2%) developed incident HF. Median baseline IGFBP7 concentration was 87.0 (75.1–97.3) ng/ml, and baseline IGFBP7 levels were significantly associated with risk for incident HF (HF risk factors adjusted hazard ratio [HR] per 1 SD change in log-transformed IGFBP7: 1.22, 95% confidence interval [CI] 1.03–1.46). Baseline IGFBP7 was also significantly associated with incident HF in individuals with N-terminal pro-B-type natriuretic peptide <125 ng/L. Among 3879 participants attending both visits 2 and 4 (mean ± SD age 57.5 ± 11.3 years; 1952 [50.3%] men), 93 individuals developed HF (after visit 4) during a median follow-up of 3.2 (2.8–3.9) years. Median increase in IGFBP7 concentration between visits was 0.68 (−7.09 to 8.36) ng/ml, and changes in IGFBP7 levels were significantly associated with risk for incident HF (HF risk factors adjusted HR per 1 SD change in log-transformed IGFBP7: 1.68, 95% CI 1.19–2.36).

Conclusions

Both baseline as well as repeat IGFBP7 measurements provide information about the risk of developing HF.

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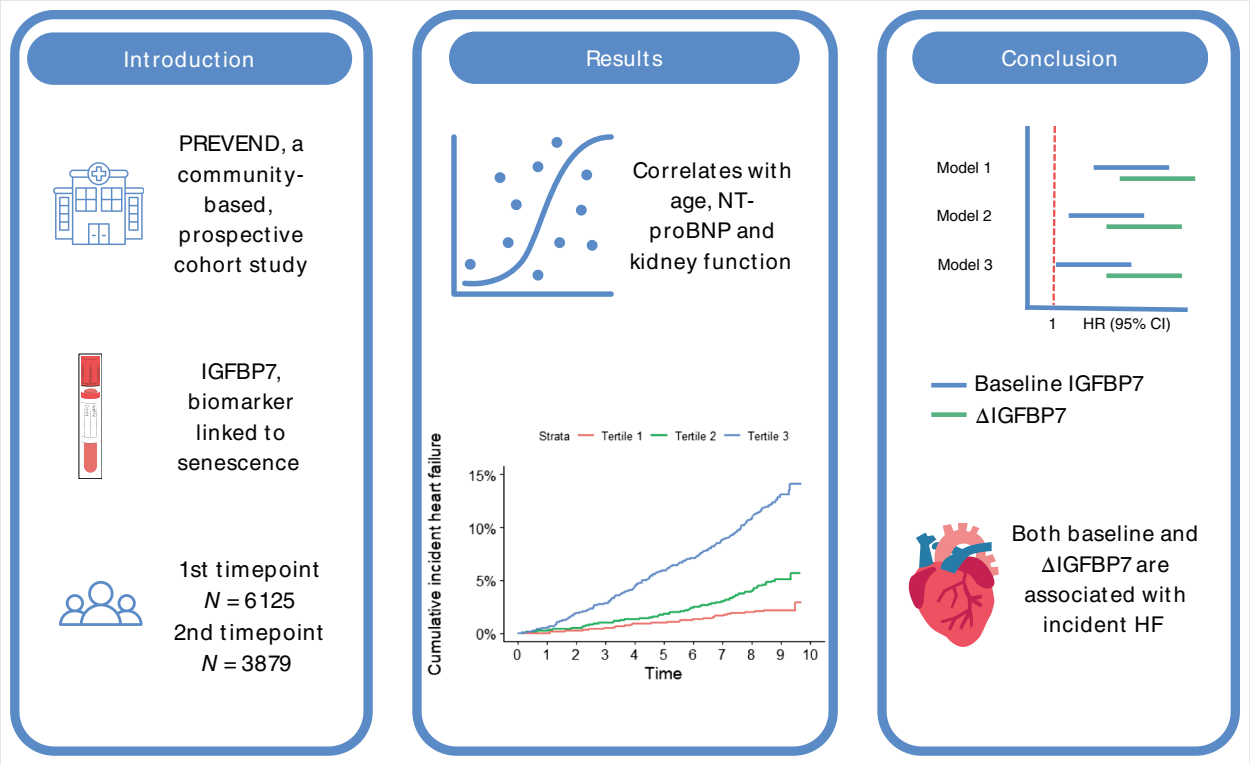
Graphical Abstract



Insulin-like growth factor-binding protein-7 (IGFBP7) and heart failure (HF) risk: the PREVEND study. CI, confidence interval; HR, hazard ratio.

Keywords IGFBP7 • Senescence • Incident heart failure • General population

Introduction

Heart failure (HF), a condition characterized by its progressive nature and associated with significant morbidity and mortality, continues to pose a substantial challenge despite recent advancements in its treatment.[1,2] As our population continues to age, there is a looming expectation of a substantial rise in global public health burden of HF in the coming decade.[2,3] Specifically, the residual risk for adverse outcomes in all stages of HF remains high, as well as the residual risk for developing new-onset HF.[4] Therefore, identifying markers reflecting unique HF-related pathophysiologic processes that are known to predict outcomes in HF patients, and examining whether they also carry a predictive value for incident HF remains a clinically relevant question.

Emerging evidence has linked cellular senescence to HF, due to its role in cell cycle arrest and subsequently cardiac tissue senescence.[5–7] Insulin-like growth factor-binding protein-7 (IGFBP7) has been positioned as a marker of cellular senescence.[8]

Increased circulating levels of IGFBP7 have been strongly linked to adverse clinical outcomes in HF patients with preserved as well as reduced ejection fraction.[9–11] However, to our knowledge, there are no studies examining the prognostic value of circulating IGFBP7 levels with incident HF in the general population. Therefore, the aim of our study was to examine associations of baseline and longitudinal changes in IGFBP7 levels with incident HF in a well-characterized, community-based cohort. As IGFBP7 reflects premature tissue/cardiovascular ageing, a pathophysiologic pathway fundamentally different from that reflected by natriuretic peptides (myocardial stretch), we hypothesized that both baseline and repeat IGFBP7 will provide additional information on the risk of developing HF in the general population.

Methods

Study population

This study was performed in the context of the PREVEND (Prevention of Renal and Vascular End-stage Disease) study, a prospective observational community-based cohort study. Details of the original study design have been described previously[12,13]. In summary, residents of Groningen, the Netherlands, were enrolled in this study and followed-up for several years, with blood samples at various visits.

IGFBP7 was available at PREVEND visit 2 and 4, and thus included in the analyses. At visit 2, which was considered as baseline for the current analysis, 6125 participants were available. Regarding the analysis for incident HF, we excluded participants with missing IGFBP7 ($n = 2$) and prevalent HF at visit 2 ($n = 61$), leaving us with 6062 participants for analyses (online supplementary *Figure S1*). At visit 4, 4574 were available. However, 694 participants had no IGFBP7 measurements and 106 participants had prevalent HF at visit 4, leaving us with 3774 participants for the analysis of change in IGFBP7 in relation to incident HF (online supplementary *Figure S1*). Ethical approval was obtained from the local medical ethics committee of the University Medical Center Groningen (approval number: MEC96/01/022), all participants signed informed consent and the study was carried out in accordance with the Declaration of Helsinki.

Baseline assessment

The study participants underwent a comprehensive assessment that included a detailed medical history review, physical examination, and blood sample collection.

Standard methods were used to measure total cholesterol and plasma glucose. Serum creatinine was assessed using dry chemistry (Eastman Kodak, Rochester, NY, USA). Measurement of urinary albumin was conducted through nephelometry with a threshold of 2.3 mg/L. The mean of two 24 h urine collections was used to determine urinary albumin excretion. The estimated glomerular filtration rate (eGFR) was calculated using the serum creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation. Smoking status was defined as either current smoking or having quit smoking within the past year or never smokers. Body mass index was calculated by dividing an individual's weight by the square of their height (in kg/m^2). Blood pressure (BP) was determined by averaging two separate seated measurements. Relative fat mass (RFM) was calculated using the height and waist circumference (WC) with the following equation: $64 - (20 \times \text{height}/\text{WC}) + (12 \times \text{sex})$, with sex = 0 (men), and sex = 1 (women).[14] WC was measured midway between the lowest rib and the iliac crest at the end of expiration. Prevalent cardiovascular disease (i.e. myocardial infarction or stroke) was gathered from a structured questionnaire, which included criteria such as hospitalization lasting 3 days or more due to the specified condition. This data collection was supplemented by an examination of medical records.[14,15]

IGFBP7 measurements

Fasting samples were obtained at each examination and stored at −80°C until testing. IGFBP7 was measured by the Roche Elecsys assay on a Cobas E 411 analyser in plasma samples. The detection method used was a sandwich immunoassay developed on the Elecsys® platform, utilizing electro-chemiluminescence detection by Roche Diagnostics GmbH (Mannheim, Germany).[10] Mouse monoclonal antibodies were produced and tested to specifically identify IGFBP7.[10] The precision within-run coefficient of variation for IGFBP7 was 2%, and the limit of detection was 0.01 ng/ml. Baseline IGFBP7 was defined as IGFBP7 measurements at visit 2. Change in IGFBP7 was defined as the difference between IGFBP7 at visit 4 and visit 2. During visit 2, some participants ($n = 446$) exhibited double measurements of IGFBP7. In our analysis, we decided to exclude these duplicates after verifying that their presence had no influence on the overall outcome (sensitivity analysis). This was confirmed by performing the analysis for both of the duplicates.

Study endpoints

Participants in the study were monitored prospectively to observe the first instance of HF or death. Information on HF occurrence, including the dates, was obtained from clinical records. Individuals suspected of having HF were identified based on the guidelines outlined by the European Society of Cardiology (ESC) in 2012,[16] by recording signs, symptoms, and objective evidence of HF. To ensure accuracy, a committee of seven independent HF experts further assessed the selected individuals, with each case being validated by two different experts, by reviewing anonymized clinical charts, hospitalization, and physician office records in order to ascertain the incidence of HF. In the event of any discrepancies, a consensus decision was reached within the committee.[15]

Statistical analyses

Distributions of continuous variables were tested for normality using the Shapiro–Wilk test. Normally distributed continuous variables are presented as mean ± standard deviation (SD), and non-normally distributed variables as median and 25th–75th percentile. Categorical variables are presented as numbers and percentages. The study population was divided into three IGFBP7 tertiles, tertile 1: 14–78 ng/ml; tertile 2: 78–92 ng/ml; tertile 3: 92–347 ng/ml. Differences in baseline characteristics between participants in the different IGFBP7 tertiles were tested using ANOVA and the Kruskal–Wallis test, for continuous variables, depending on normality of their distributions. For categorical variables, χ^2 tests and Fisher's exact tests were used.

First, we examined the associations of baseline IGFBP7 with clinical characteristics using linear regression. The assumptions of the linear regression were tested using Q–Q plots of the residuals in R. We used IGFBP7 as the dependent variable and clinical characteristics consecutively as the independent variables, and we adjusted for age and sex. Thereafter we further adjusted the model for relevant cardiovascular risk factors.[17] Moreover, we used hierarchical cluster analysis on variables, using Spearman correlations, to map the correlation-based distance of the clinical characteristics with IGFBP7. While examining associations of change in IGFBP7 (dependent variable) with clinical characteristics (independent variables) with linear regression, we first adjusted for age, sex and baseline IGFBP7, and thereafter we further adjusted the model for relevant cardiovascular risk factors.

To evaluate the association between IGFBP7 and incident HF, Cox proportional hazards regression was performed (after checking the proportional hazard assumption). First, we studied the association between baseline IGFBP7 and incident HF, adjusted for age and sex. In the analysis for change in IGFBP7, we also adjusted for baseline IGFBP7 (model 1). Next, we used multivariable models and added smoking, systolic blood pressure, antihypertensive treatment, glucose, cholesterol, lipid-lowering medication, body mass index, prevalent cardiovascular disease and eGFR (model 2). Lastly, we added N-terminal pro-B-type natriuretic peptide (NT-proBNP) to the model (model 3). We also tested for potential interactions with age, sex and NT-proBNP. In secondary analysis, we examined associations of baseline IGFBP7 and change in IGFBP7 treating all-cause mortality as a competing event for incident HF.

We log-transformed and standardized the variables when needed (to satisfy the assumptions of all used statistical models). We report our findings as hazard ratios (HRs) and the corresponding 95% confidence intervals (CI). All analyses were performed with R statistical software

using package survival. All tests were two-tailed, and *p*-values <0.05 were considered statistically significant.

Results

Baseline characteristics

At PREVEND visit 2, there were 6125 participants available for analysis. The mean age ± SD of the study population was 53 ± 12 years and 51.4% were women. Median IGFBP7 was 87.0 (75.1–97.3) ng/ml.

All baseline characteristics were significantly different across all tertiles of IGFBP7, with age and NT-proBNP increasing stepwise. While tertile 1 consisted of mostly women (71.5%), tertile 3 mostly comprised men (63.0%) (*Table 1*). Women had lower IGFBP7 values across the entire age spectrum (*Figure 1*). Baseline characteristics stratified by sex are presented in online supplementary *Table S1*.

Associations of baseline and serially measured IGFBP7 levels with clinical characteristics

In linear regression models, IGFBP7 was associated with several baseline characteristics and biomarkers (*Table 2*). Age, systolic BP and RFM were significantly associated with IGFBP7, with a standardized β (95% CI) of 0.48 (0.46–0.50) per SD increase in age, 0.08 (0.05–0.10) per SD change in BP, and −0.06 (−0.10 to −0.03) per SD increase in RFM. Moreover, women had lower IGFBP7 levels compared to men (β [95% CI]: −0.59 [−0.64 to −0.55]). Elevated NT-proBNP was also associated with higher IGFBP7 levels, whereas elevated eGFR levels were associated with lower IGFBP7 levels. In a multivariable model including age, sex, RFM, systolic BP, NT-proBNP and eGFR, all variables remained statistically significant (*Table 2*). IGFBP7 had the highest correlation with age and eGFR (online supplementary *Figure S2*).

The associations with change in IGFBP7 were different than with baseline IGFBP7; women had a larger change in IGFBP7 levels compared to men and the correlation disappeared for systolic BP, NT-proBNP and RFM. Moreover, the association with eGFR became positive (*Table 2*).

Associations of baseline IGFBP7 with incident heart failure

During a median follow-up of 8.4 years, 194 participants developed incident HF. The median (95% CI) IGFBP7 in participants who developed HF was 101 (64.7–215.2) ng/ml and 84.2 (55.9–127.3) ng/ml in participants who did not experience the event.

The cumulative incidence was also significantly different across the IGFBP7 tertiles, with participants with higher IGFBP7 levels having the highest cumulative incidence of HF (*Figure 2*). The absolute risks of incident HF after 8.4 years of follow-up in the three tertiles were 1.27%, 2.84% and 8.92%, respectively.

In Cox regression models adjusted for age and sex, baseline IGFBP7 was significantly associated with incident HF (HR per

Table 1 Baseline characteristics

Characteristic	All (*n* = 6125)	IGFBP7 tertile 1 (14–78 ng/ml) (*n* = 2041)	IGFBP7 tertile 2 (78–92 ng/ml) (*n* = 2041)	IGFBP7 tertile 3 (92–347 ng/ml) (*n* = 2041)	*p*-value
Clinical characteristics					
Women	3151 (51.4)	1460 (71.5)	934 (45.8)	755 (37.0)	<0.001
Age, years	53.65 (12.12)	47.10 (9.24)	52.80 (10.82)	61.07 (11.83)	<0.001
Body mass index, kg/m^2	26.7 (4.3)	26.1 (4.2)	26.6 (4.2)	27.3 (4.5)	<0.001
Relative fat mass, %	32.01 (7.28)	33.19 (6.78)	31.24 (7.53)	31.59 (7.36)	<0.001
Systolic blood pressure, mmHg	126.0 (18.9)	119.0 (14.9)	125.3 (17.4)	133.71 (21.0)	<0.001
Diastolic blood pressure, mmHg	73.1 (9.0)	70.6 (8.3)	73.2 (8.7)	75.4 (9.4)	<0.001
Prevalent CVD	386 (6.6)	72 (3.6)	117 (5.9)	197 (10.1)	<0.001
Smoking or quit <1 year	2155 (35.3)	833 (40.9)	739 (36.3)	582 (28.7)	<0.001
Biomarkers					
IGFBP7, ng/ml	87.0 [75.1–97.3]	70.8 [64.4–75.1]	84.8 [81.5–88.2]	101.8 [96.0–110.9]	<0.001
Glucose, mmol/L	5.1 (1.2)	4.8 (0.9)	5.0 (1.2)	5.3 (1.4)	<0.001
Total cholesterol, mmol/L	5.36 [4.69–6.10]	5.20 [4.58–5.94]	5.43 [4.70–6.18]	5.47 [4.82–6.18]	<0.001
eGFR, mL/min/1.73m^2	93.7 [81.2–104.0]	101.2 [92.5–109.5]	94.7 [84.3–103.6]	81.5[69.5–93.3]	<0.001
NT-proBNP, ng/L	43.01 [22.65–82.15]	38.36 [21.21–67.10]	38.13 [19.75–69.46]	60.08 [28.50–125.78]	<0.001
Urinary albumin excretion, mg/L	8.24 [5.95–13.93]	7.32 [5.63–10.89]	8.15 [5.99–12.82]	10.01 [6.51–22.66]	<0.001
Medications					
Antihypertensive	1382 (22.6)	237 (11.6)	400 (19.6)	745 (36.6)	<0.001
Antidiabetic	206 (3.4)	30 (1.5)	63 (3.1)	113 (5.5)	<0.001
Lipid-lowering	655 (10.7)	113 (5.5)	211 (10.4)	331 (16.2)	<0.001

Continuous variables are as presented as mean (standard deviation) or as median [interquartile range], and categorical variables as *n* (%).
CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; IGFBP7, insulin-like growth factor-binding protein-7; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

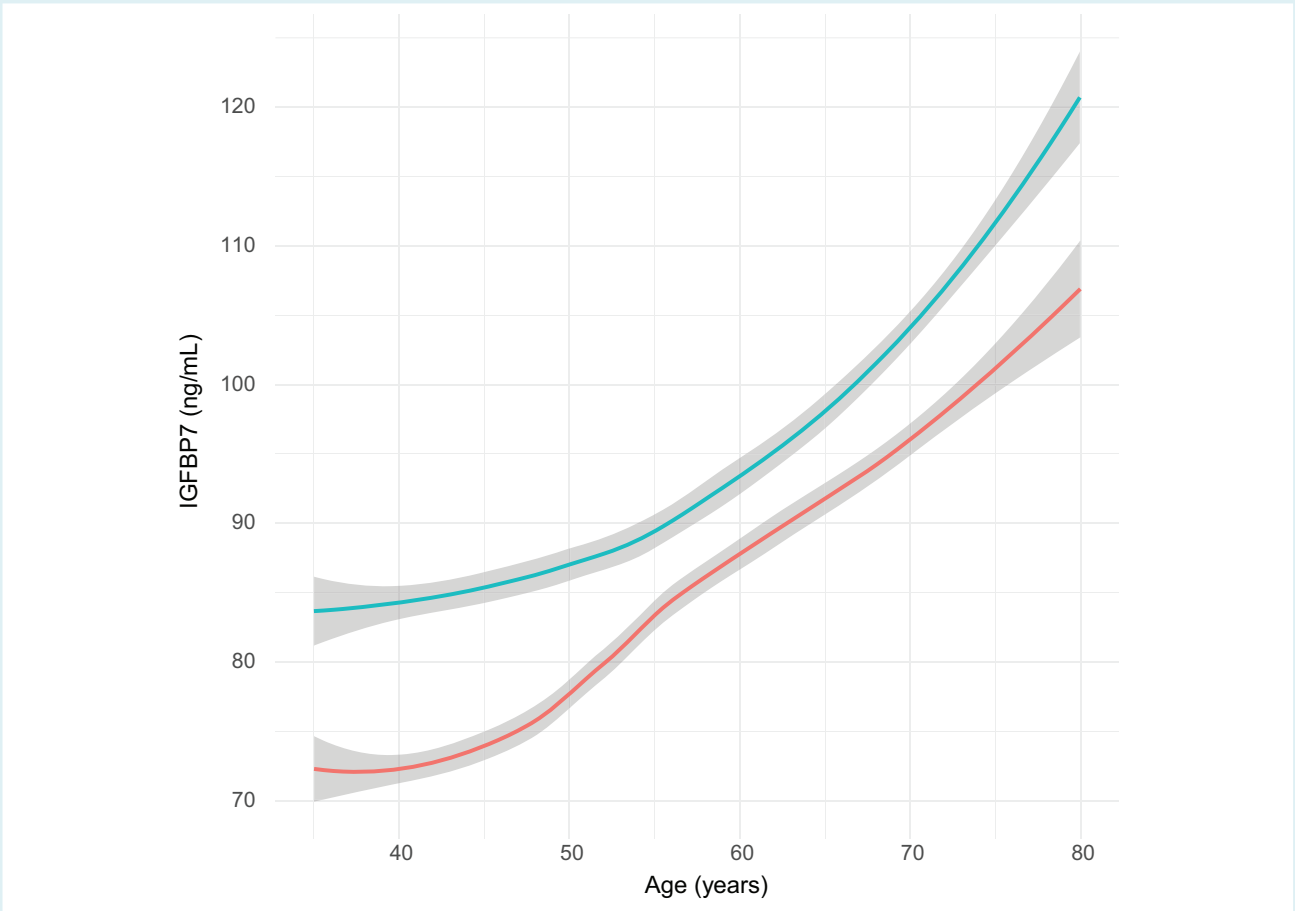


Figure 1 Associations between age and insulin-like growth factor-binding protein-7 (IGFBP7) levels in men and women. Red lines represent median IGFBP7 (ng/ml) levels in women; blue lines represent median IGFBP7 (ng/ml) levels in men; grey bands represent prediction intervals of median IGFBP7.

Table 2 Associations of baseline and longitudinal changes in IGFBP7 levels with clinical characteristics

Characteristic	Baseline IGFBP7				Change in IGFBP7[a]			
	Age- and sex-adjusted		Multivariate		Age- and sex-adjusted		Multivariate	
	Std. β (95% CI)	*p*-value	Std. β (95% CI)	*p*-value	Std. β (95% CI)	*p*-value	Std. β (95% CI)	*p*-value
Age	0.48 (0.46– 0.50)	<0.001	0.18 (0.15–0.21)	<0.001	0.50 (0.42–0.58)	<0.001	0.08 (0.06–0.13)	<0.001
Women	−0.59 (−0.64 to −0.55)	<0.001	−0.36 (−43 to −0.29)	<0.001	0.12 (0.06–0.17)	<0.001	0.13 (0.08–0.19)	<0.001
Relative fat mass	−0.06 (−0.10 to −0.03)	<0.001	−0.12 (−0.16 to −0.09)	<0.001	0.02 (−0.02 to 0.06)	0.3		
Systolic BP	0.08 (0.05–0.10)	<0.001	0.08 (0.07–0.11)	<0.001	−0.01 (−0.01 to 0.01)	0.5		
NT-proBNP	0.14 (0.12–0.16)	<0.001	0.05 (0.03–0.07)	<0.001	0.01 (0.01–0.02)	0.2		
eGFR	−0.42 (−0.44 to −0.39)	<0.001	−0.41 (−0.43 to −0.38)	<0.001	0.07 (0.03–0.10)	<0.001	0.06 (0.02–0.10)	0.001
Body mass index	0.09 (−2.40 to 2.20)	0.9			−0.21 (−3.11 to 2.69)	0.9		
Diastolic BP	0.01 (−0.01 to 0.03)	0.9			−0.01 (−0.01 to 0.01)	0.4		
Cholesterol	0.01 (−0.01 to 0.03)	0.4			−0.03 (−0.05 to −0.01)	0.02		
Glucose	0.01 (−0.01 to 0.03)	0.3			0.01 (−0.02 to 0.02)	0.8		

Results are displayed as standardized β coefficient, which represents the standard deviation (SD) change in dependent variable for 1 SD change in the independent (continuous) variable or for 1 unit change in the independent (categorical) variable. Multivariable model included age, sex, relative fat mass, systolic BP, NT-proBNP, cystatin C, eGFR and serum creatinine.

BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; IGFBP7, insulin-like growth factor-binding protein-7; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

[a]Also adjusted for baseline IGFBP7.

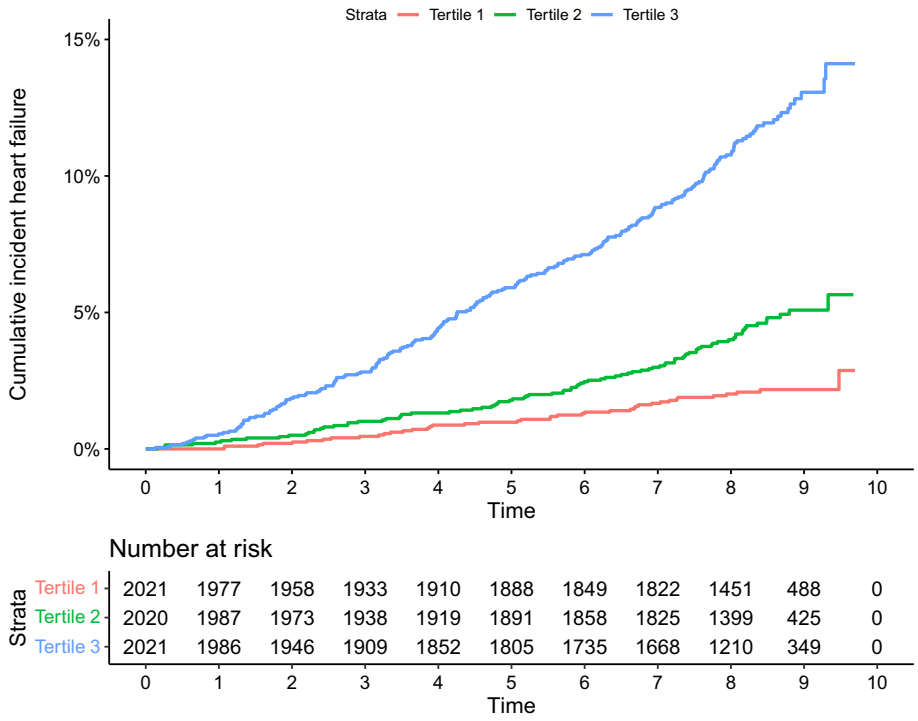


Figure 2 Cumulative incidence of heart failure (HF) according to insulin-like growth factor-binding protein-7 (IGFBP7) tertiles. The cumulative HF event rates are visualized on the *y*-axis, and time from inclusion in the study till the event or censoring on the *x*-axis. The table below shows the number of participants at risk per IGFBP7 tertile.

Table 3 Associations of baseline and longitudinal changes in IGFBP7 with incident heart failure

	Baseline IGFBP7[a]		Change in IGFBP7[a]	
	HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**
Incident HF	*n* = 6062, 194 events		*n* = 3774, 58 events	
Model 1	1.42 (1.25–1.62)	<0.001	1.66 (1.23–2.24)	<0.001
Model 2	1.29 (1.10–1.52)	0.002	1.69 (1.19–2.38)	0.003
Model 3	1.22 (1.03–1.46)	0.04	1.68 (1.19–2.36)	0.003

CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; IGFBP7, insulin-like growth factor-binding protein-7; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation.
Model 1: adjusted for age, sex (and baseline IGFBP7 in the model for change in IGFBP7).
Model 2: sdjusted for age, sex, smoking, systolic blood pressure, antihypertensive treatment, glucose, cholesterol, lipid-lowering medication, body mass index, eGFR and prevalent cardiovascular disease (and baseline IGFBP7 levels in the model for change in IGFBP7). Model 3: above-mentioned covariates and NT-proBNP.
[a]Log-transformed and standardized, so HR represents the hazard for 1 SD change in IGFBP7 (log-transformed).

1 SD change in log IGFBP7: 1.42 [95% CI 1.25–1.62]). After adjustment for cardiovascular risk factors, including NT-proBNP, baseline IGFBP7 was still associated with incident HF (HR per 1 SD change in IGFBP7 [log-transformed]: 1.22 [95% CI 1.03–1.46]) (*Table 3*). IGFBP7 did not significantly interact with NT-proBNP (*p*-value for interaction 0.6), as well as with age and sex (*p*-value for interaction 0.8 and 0.4, respectively) in relation to incident HF.

When the same analysis was conducted with all-cause mortality as a competing risk, a small decrease in the HR for baseline IGFBP7 was observed, but the association was still statistically significant in model 1 and 2 (HR per 1 SD change in IGFBP7 [log-transformed]: 1.36 [1.19–1.56] and 1.24 [1.02–1.50], respectively) (*Table 4*). After additional adjustment for NT-proBNP, the association was no longer significant.

Lastly, we performed a sensitivity analysis with the duplicates that were available at visit 2. When using the second duplicated measurement of IGFBP7 for the participants who had duplicates, the results were essentially the same as with the first set of duplicates (*n* = 466, online supplementary *Table S2*).

Table 4 Associations of baseline and longitudinal changes in IGFBP7 with incident heart failure with all-cause mortality as competing event

	Baseline IGFBP7[a]		Change in IGFBP7[a]	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Incident HF	*n* = 6062, 194 events		*n* = 3774, 58 events	
Model 1	1.36 (1.19–1.56)	<0.001	1.25 (1.02–1.54)	0.003
Model 2	1.24 (1.02–1.50)	0.002	1.38 (1.07–1.78)	0.014
Model 3	1.15 (0.94–1.42)	0.1	1.39 (1.06–1.81)	0.018

CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; IGFBP7, insulin-like growth factor-binding protein-7; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation.
Model 1: adjusted for age, sex (and baseline IGFBP7 in the model for change in IGFBP7).
Model 2: adjusted for age, sex, smoking, systolic blood pressure, antihypertensive treatment, glucose, cholesterol, lipid-lowering medication, body mass index, eGFR and prevalent cardiovascular disease (and baseline IGFBP7 in the model for change in IGFBP7).
Model 3: above-mentioned covariates and NT-proBNP.

Additional subgroup analysis revealed that the associations IGFBP7 for incident HF remained statistically significant in participants with NT-proBNP <125 ng/L (HR per 1 SD change in IGFBP7 [log-transformed]: 1.32 [1.04–1.66]) and NT-proBNP ≥125 ng/L (HR per 1 SD change in IGFBP7 [log-transformed]: 1.26 [1.06–1.49]). After accounting for mortality as a competing event, the results remained essentially the same (*Table 5*).

Associations of changes in IGFBP7 levels with incident heart failure

Among 3879 participants attending both visits 2 and 4, a total of 93 participants developed HF (after visit 4) during a median follow up of 3.2 years. Median increase in IGFBP7 concentration between visits was 0.68 ng/ml (25th–75th percentile: −7.09 to 8.36), and was statistically significant ($p = 0.01$). In Cox regression models adjusted for age, sex, and baseline IGFBP7, change in IGFBP7 was significantly associated with incident HF (HR per 1 SD change in IGFBP7 [log-transformed]: 1.66 [1.23–2.24]). After adjustment for cardiovascular risk factors, including NT-proBNP, change in IGFBP7 was still associated with incident HF (HR per 1 SD change in IGFBP7 [log-transformed]: 1.68 [1.19–2.36]) (*Table 3*).

For the abovementioned participants, we also calculated the relative change of IGFBP7 and conducted the analysis. The association of the relative change was significant in all models (online supplementary *Table S3*). Accordingly, a 10% relative increase in IGFBP7 levels corresponded to a 15% (95% CI 9–19%) increase in the risk of incident HF.

Additionally, we performed the same analysis with all-cause mortality as a competing risk. The latter also resulted in a decreased effect size, but the association was still statistically significant in all models, even after adjusting for NT-proBNP (HR per 1 SD change in IGFBP7 [log-transformed]: 1.25 [1.02–1.54], 1.38 [1.07–1.78] and 1.39 [1.06–1.81], respectively) (*Table 4*).

Table 5 Associations of IGFBP7 with incident heart failure according to NT-proBNP subclasses

Subgroup analysis	Baseline IGFBP7[a]	
	HR (95% CI)	*p*-value
	n = 5238, 91 events	
NT-proBNP <125 ng/L		
Age- and sex-adjusted	1.32 (1.04–1.66)	0.02
With all-cause mortality as a competing risk	1.31 (1.03–1.69)	0.03
	n = 775, 102 events	
NT-proBNP ≥125 ng/L		
Age- and sex-adjusted	1.26 (1.06–1.49)	0.007
With all-cause mortality as a competing risk	1.20 (1.02–1.43)	0.04

CI, confidence interval; HR, hazard ratio; IGFBP7, insulin-like growth factor-binding protein-7; NT-proBNP, N-terminal pro-B-type natriuretic peptide.
[a]Log-transformed and standardized.

Discussion

In this community-based study consisting of 6125 participants with 8.4 years of follow-up (resulting in 514 500 participant-years), we found that both baseline IGFBP7 levels as well as change in IGFBP7 levels were associated with incident HF independent of major cardiovascular risk factors and NT-proBNP (*Graphical Abstract*). Additionally, IGFBP7 was also significantly associated with incident HF in participants with low NT-proBNP levels (<125 ng/L), a category in which HF generally is not expected, further suggesting the potential clinical usefulness of IGFBP7. To our knowledge, we are the first to examine the predictive value of baseline IGFBP7 levels and longitudinal change in IGFBP7 levels for incident HF in the general population.

Correlations of IGFBP7 with clinical characteristics

In our study, IGFBP7 was linked to various patient characteristics, such as age, sex, NT-proBNP and eGFR. Multiple studies have shown that higher IGFBP7 levels correlate with an older age and

elevated NT-proBNP levels,[11,18-20] which we confirm in our study as well. Moreover, several studies have also shown an inverse relation between IGFBP7 and kidney function. For example, in the DAPA-HF trial, both HF with reduced and preserved ejection fraction HFrEF and HFpEF patients with a lower eGFR had higher IGFBP7 levels.[11]

Associations of IGFBP7 with heart failure

The prognostic value of IGFBP7 has been studied in various patient populations, specifically in patients with established cardiovascular disease and HF. In individuals with chronic HF from the RELAX trial, IGFBP7 was indicative of diastolic dysfunction and functional capacity.[21] In another HF population, IGFBP7 levels were associated with diastolic filling and the enlargement of the left atrium, and treatment with sacubitril/valsartan reduced IGFBP7 levels.[9] Furthermore, in a large cohort of worsening HF, IGFBP7 pathways were found to be involved in different stages of immune system regulation, linking HF to senescence.[10] Moreover, in a community aging study comprised of patients 65 years or older, IGFBP7 levels independently predicted left ventricular hypertrophy and cardiac remodelling and predicted all-cause mortality.[22]

In the current study conducted on community-dwelling individuals, we report for the first time that baseline IGFBP7 was strongly associated with future HF risk in the total population, and this association persisted after also accounting for NT-proBNP. In sub-analysis, we specifically examined whether IGFBP7 had a predictive value for incident HF in individuals with low NT-proBNP (i.e. <125 ng/L). This is because NT-proBNP is the most widely utilized biomarker in HF, and when used as a rule-out test for left ventricular dysfunction, the current ESC guidelines recommend a cutpoint of 125 ng/L.[23] Moreover, NT-proBNP levels are known to be affected by several factors, such as male sex and obesity, which results in 'pseudo-low' NT-proBNP levels, even in individuals prone to developing HF.[24–26] Again, we found that baseline IGFBP7 remained associated with future HF risk in individuals with low NT-proBNP, adding to the potential clinical relevance of this biomarker. Lastly, we found that change in IGFBP7 was also strongly associated with incident HF in this community-based cohort, suggesting that not only baseline IGFBP7 measurements but also repeat IGFBP7 measurements provide independent information on the risk of future HF in the general population.

Pathophysiological pathways related to IGFBP7

IGFBP7 is a senescence-related protein belonging to the insulin-like growth factor family, and is expressed in several tissues over the entire body.[27] Although organs with the highest IGFBP7 expression include the brain and the renal tubules,[27,28] IGFBP7 is also abundantly expressed in the cardiovascular system (online supplementary *Figure S3*).[29,30]

IGFBP7 is related to cellular senescence, and thus may also reflect cardiac tissue senescence. Moreover, IGFBP7 is directly implicated in pathways relevant to HF, and influences pathological cardiac remodelling and fibrosis by blocking the FOXO3a-mediated pro-longevity pathway.[8,31] FOXO3a is a transcription factor involved in the regulation of DNA repair, and in removal of reactive oxygen species from multiple tissues including the heart.[32,33] These functions inhibit adverse ventricular remodelling, leading to reduced cardiac inflammation and tissue fibrosis. Targeting these pathways could therefore offer a novel therapeutic approach for HF patients, aiming to mitigate cellular/cardiovascular senescence and lessen myocardial damage caused by fibrosis and inflammation. Further research is warranted to explore the potential therapeutic application of inhibiting IGFBP7-regulated senescence pathways for HF.

Strengths and limitations

Our study benefits from a well-characterized cohort with long-term follow-up and rigorous incident HF diagnosis validation by an adjudication committee. Moreover, a 1:1 distribution of males and females strengthens our study. However, individuals enrolled in the PREVEND study were predominantly White, limiting the generalizability of our findings to other racial or ethnic groups. Additionally, given the observational nature of our study, the potential for residual confounding cannot be ruled out. Furthermore, The PREVEND study, by design, included a larger number of individuals with mildly elevated urinary albumin excretion.[13] However, this is unlikely to affect the interpretation of results, as previous research has demonstrated that findings from the PREVEND study align well with those from broader population cohorts like the Framingham Heart Study.[34] Lastly, we did not distinguish between HF with preserved and reduced ejection fraction, due to limited statistical power.

Conclusion

Both baseline IGFBP7 levels and changes in IGFBP7 levels are associated with an increased risk for incident HF in the general population, highlighting the potential value of IGFBP7 measurement in informing HF risk. Studies focusing on IGFBP7 as a novel therapeutic target for HF, particularly investigating inhibition of IGFBP7 or its upstream pathways, are needed.

Supplementary Information

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

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