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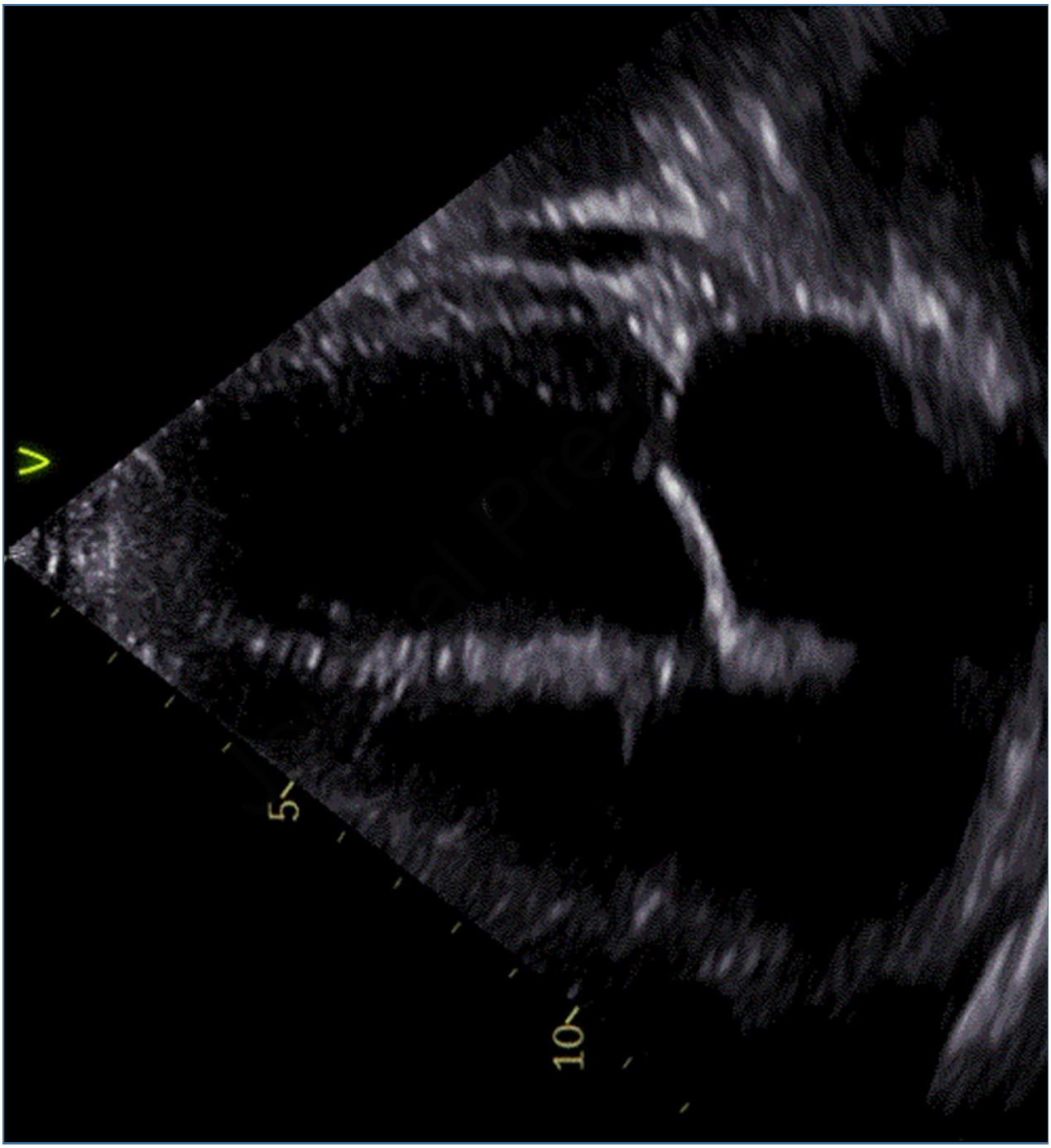
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Insulin-Like Growth Factor-Binding Protein-7 and risk of congestive heart failure hospitalization in patients with atrial fibrillation

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Abstract

Background: The occurrence of congestive heart failure (CHF) hospitalization among patients with atrial fibrillation (AF) is a poor prognostic marker.

Objective: To assess whether Insulin-Like Growth Factor-Binding Protein-7 (IGFBP-7), a marker of myocardial damage, identifies AF patients at high risk for this complication.

Methods: We analyzed two prospective multicenter observational cohort studies including 3,691 AF patients. Levels of IGFBP-7 and N-terminal pro-brain natriuretic peptide (NT-proBNP) were measured from frozen plasma samples at baseline. The primary endpoint was hospitalization for CHF. Multivariable adjusted Cox-regression analyses were constructed.

Results: Mean age was 69±12 years, 1,028 (28%) were females and 879 (24%) had a history of CHF. The incidence per 1,000 patient-years across increasing IGFBP-7 quartiles was 7, 10, 32 and 85. The corresponding multivariable adjusted hazard ratios (aHRs) [95%CI] were 1.0, 1.05 [0.63;1.77], 2.38 [1.50;3.79], and 4.37 [2.72;7.04] (p for trend <0.001). In a subgroup of 2,812 patients without pre-existing CHF at baseline, the aHRs were 1.0, 0.90 [0.47;1.72], 1.69 [0.94;3.04], and 3.48 [1.94;6.24] (p for trend <0.001). Patients with IGFBP-7 and NT-proBNP levels above the biomarker-specific median had a higher risk of incident CHF hospitalization (aHR 5.20 [3.35; 8.09]) compared to those with only one elevated marker (elevated IGFBP-7 aHR 2.17[1.30;3.60]; elevated NT-proBNP aHR 1.97[1.17;3.33]) or no elevated marker (reference).

Conclusion: Higher plasma levels of IGFBP-7 were strongly and independently associated with CHF hospitalization in AF-patients. The prognostic information provided by IGFBP-7 was additive to that of NT-proBNP.

Keywords: Atrial fibrillation;Heart failure;IGFBP-7;Biomarkers;epidemiology

Introduction

In patients with atrial fibrillation (AF), most studies have focused on predicting and preventing stroke. Much less information is available with regard to congestive heart failure (CHF), despite a tight link between AF and CHF[1-3]. CHF hospitalizations put a substantial economic burden on health care systems and are associated with a worse prognosis among AF patients[4-6]. In contemporary, anticoagulated AF patients, CHF is much more common than stroke, and progressive CHF accounts for many deaths.[7] Therapy options for AF patients with concomitant CHF are limited[8], and established therapies may not have the same impact as in patients without AF[9]. Accurately identifying AF patients at increased risk for CHF hospitalization is an important first step towards the development of effective prevention strategies.

Insulin-like growth factor-binding protein 7 (IGFBP-7) plays a role in cell cycle arrest during early phases of cell injury[10], and may therefore be involved in the development of myocardial damage. It has been identified as a potential biomarker for CHF and cardiac hypertrophy[11]. Previous studies suggested that IGFBP-7 may be related to worsening CHF and hospitalization for CHF, and lower IGFBP-7 levels were associated with fewer cardiovascular events among CHF patients[12]. Higher IGFBP-7 levels predicted adverse outcome events in CHF patients with preserved but not those with reduced ejection fraction (EF).[13] However, all these prior studies on IGFBP-7 were small, included selected patient populations, and had short follow-up. In addition, there are no data available in patients with AF.

We therefore investigated the associations of IGFBP-7 levels with incident CHF hospitalization in a large cohort of patients with established AF, taking into account a large number of covariates and potential confounders.

Methods

Study Design and Participants

We combined datasets from two ongoing prospective, observational, multicenter cohort studies of AF patients in Switzerland. Both cohorts used similar eligibility criteria, outcome definitions and case report forms (CRFs). The study complies with the Declaration of Helsinki. The study protocols were approved by the local ethics committees, and informed written consent was obtained from each participant.

Between 2010 and 2014, the Basel Atrial Fibrillation (BEAT-AF) cohort study recruited 1,553 patients with documented AF across 7 centers in Switzerland. The Swiss Atrial Fibrillation (Swiss-AF) study enrolled 2,415 AF patients between 2014 and 2017 across 14 centers in Switzerland. Details about the methodology for BEAT-AF and Swiss-AF have been described previously.[14, 15] In both cohorts all patients were required to have previously documented AF. Main exclusion criteria for both cohorts were the inability to sign informed consent and the presence of potentially reversible forms of AF (e.g. AF after cardiac surgery). Patients with an acute illness within the last 4 weeks could be enrolled once their health status had stabilized. Patients enrolled in BEAT-AF were not eligible for participation in Swiss-AF.

From the combined dataset (n=3,968), we excluded 206 (5.2%) patients with missing IGFBP-7 or N-terminal pro-natriuretic peptide (NT-proBNP) measurements, and 64 (1.6%) without follow-up information. Seven (0.2%) patients with accidental inclusion in both cohorts were only counted once, leaving 3,691 (93.0%) patients for these analyses. We used all available data up to April 17th 2019.

Blood samples

Non-fasting venous blood samples were collected from each patient at the initial study visit. All study samples were taken during study visits and outside of any procedure. Plasma samples were centrifuged, aliquoted and stored at -80°C in a central biobank. IGFBP-7 and NT-proBNP levels were

measured from frozen samples using an automated cobas Elecsys electrochemiluminescence immunoassay analyzer (Roche Diagnostics, Mannheim, Germany) by laboratory personnel blinded to clinical information. The method of detection for IGFBP-7 was an immunoassay developed for electrochemiluminescent detection applying monoclonal antibodies that were specifically generated against IGFBP-7 and screened for specific detection. For IGFBP-7 the limit of detection was 0.01 ng/mL and within-run precision coefficient of variation 2%.

Assessment of study variables

Both cohorts collected information about personal, medical and lifestyle factors through very similar study CRFs.. Weight and height were directly measured using calibrated devices. Body mass index (BMI) was calculated as weight in kg divided by height in meters squared. AF was classified into paroxysmal AF, persistent AF or permanent AF[16].

After a face-to-face baseline examination, all yearly follow-up examinations were performed by mail and telephone interviews in BEAT-AF, and by yearly in-person visits in Swiss-AF. During these follow-up visits, we collected detailed information on adverse outcome events.

Definitions and Outcomes

The outcome for this analysis was hospitalization for CHF, defined in both cohorts as a hospitalization for CHF that was associated with at least one overnight stay, or a CHF exacerbation that led to an extension of an existing hospitalization. Source documentation for these events included symptoms and signs of CHF (e.g. weight gain, shortness of breath, rales), imaging evidence of pulmonary congestion, BNP or NT-proBNP levels and information on left ventricular function in some cases. We used cases with available information on left ventricular function to assess the associations of IGFBP-7 with CHF hospitalization with reduced EF (i.e. left ventricular EF <50%) versus CHF hospitalization with preserved EF (i.e. left ventricular EF ≥50%). Based on all available source data each event was independently validated by two physicians. In case of discrepancy, a third physician was consulted for a final decision.

Statistical Analysis

Baseline characteristics were stratified by quartiles of IGFBP-7. Categorical variables were presented as numbers (percentages) and compared using χ^2-tests. The distribution of continuous variables was checked using kurtosis, skewness and visual inspection of the histogram. They were then presented as means ± standard deviation (SD) or median (interquartile range [IQR]), and compared using analysis of variance or Wilcoxon-Rank-Sum tests, as appropriate.

Incidence rates were calculated as number of events per 1,000 patient years of follow-up. To assess the association between baseline IGFBP-7 levels and incident CHF hospitalization, we obtained hazard ratios and 95% confidence intervals (CI) from Cox proportional-hazards models. Multivariable models were adjusted for a pre-defined set of covariates, including age, sex, BMI, heart rate, systolic blood pressure, glomerular filtration rate, AF type at baseline (paroxysmal vs. non-paroxysmal), current smoking, cohort (BEAT-AF vs. Swiss-AF), and history of diabetes, coronary artery disease, hypertension, stroke/transient ischemic attack, or CHF. The variable selection for the multivariable models was predefined and mainly included known risk-factors and comorbidities associated with CHF and its pathophysiology. Potential collinearity between covariates in the Cox models was assessed using Pearson correlation coefficients. With one exception, all correlation coefficients were <0.25 (data not shown).

To assess whether the association between IGFBP-7 and CHF hospitalization provides independent information beyond that of natriuretic peptides, we adjusted the multivariable models for plasma levels of NT-proBNP. In a separate step we created four mutually exclusive groups, according to whether IGFBP-7 and NT-proBNP levels were above or below their respective median. We constructed Kaplan-Meier survival curves across these. We then calculated hazard ratios (95%CI) across these 4 groups in multivariable adjusted Cox regression models. Finally, we calculated receiver operating characteristic (ROC) curves for NT-proBNP, IGFBP-7 and both markers combined. We performed a sensitivity analysis where we additionally adjusted the multivariable model for AF

duration (years since first diagnosis of AF), history of pulmonary vein isolation; baseline rhythm (atrial fibrillation/flutter vs. all other rhyhtm), AF-related symptoms and baseline medical therapy (beta blocker, class Ic antiarrhythmic drugs, class III antiarrhythmic drugs). For this sensitivity analysis, we excluded 594 (16.1%) patients with missing information on one or more of these covariates.

We did not exclude patients with a history of CHF from our main analyses to increase the generalizability of our data. To investigate the potential influence of preexisting CHF on the observed associations, we repeated the main analyses separately in patients with and without a history of pre-existing CHF. Formal differences were evaluated using tests for interaction in the non-stratified model. Sensitivity analyses for incident CHF hospitalization with preserved versus reduced EF were also performed. For these analyses, we censored patients with unknown or the other EF type at the time of CHF hospitalization. To not overfit these models, they were adjusted for age, sex, heart rate, systolic blood pressure, glomerular filtration rate history of coronary artery disease, hypertension or CHF at baseline. All statistical analyses were performed using SAS 9.4 (SAS Corporation, Cary, North Carolina, USA) and SPSS Statistics for Windows, Version 25 (IBM Corp., Armonk, New York, USA). A two-sided p value < 0.05 was considered to indicate statistical significance.

Results

Baseline characteristics stratified by quartiles of IGFBP-7 are presented in **Table 1**. Quartile specific median (interquartile range) IGFBP-7 levels were 147 (138;153), 169 (164;176), 196 (188;206) and 249 (230;291) ng/l, respectively.

Association of IGFBP-7 with heart failure hospitalization

Of the 3,691 patients included in this analysis, 385 (10.4%) had a CHF hospitalization during a mean follow-up of 3.7 ± 1.8 years, corresponding to an incidence of 29.5 cases per 1,000 patient-years of follow-up. The incidence was 6.7, 10.0, 31.9 and 85.0 per 1,000 patient years across increasing IGFBP-7 quartiles (p<0.001) (**Figure 1**). Age and sex adjusted Cox regression models confirmed a steep increase in the risk of CHF hospitalization across quartiles of IGFBP-7 (**Table 2)**. The multivariable adjusted hazard ratio (aHR) for the highest compared with the lowest quartile was 4.37 (95%CI 2.72;7.04), with a p for trend across quartiles of <0.001. After additional adjustment for NT-proBNP, the association remained highly significant. In models stratified by history of CHF at baseline, the associations did not significantly differ between patients with and without a history of CHF **(Supplemental Table S-1 and S-2)**, even though the risk increase by IGFBP-7 seemed less pronounced among patients with a history of CHF (p for interaction 0.07).Additional adjustment for AF-related symptoms, history of pulmonary vein isolation, baseline rhythm, AF-duration and baseline medication did not significantly change the association of IGFBP-7 and CHF hospitalization (Supplemental Table S-3). Left ventricular EF at the time of the outcome event was available in 156 patients, 83 (53.2%) with reduced EF and 73 (46.8%) with preserved EF. The multivariable adjusted hazard ratios (95%CI) per unit increase of log transformed IGFBP-7 were 4.58 [1.98;10.59] and 6.99 [2.87;17.03] for CHF hospitalization with reduced and preserved EF, respectively **(Supplemental Table S-4 and S-5**).

Association of NT-proBNP with heart failure hospitalization

Table S-6 and Figure S-1 in the Supplemental Material show the association of baseline NT-proBNP values with hospitalization for CHF. The incidence of CHF per 1,000 patient-years across increasing quartiles of baseline NT-proBNP was 3.1, 15.4, 34.0 and 81.3, respectively. In the highest NT-proBNP quartile, the multivariable aHR was (95%CI 4.93;17.59) compared to the lowest quartile (p for trend <0.001). Further adjustment for IGFBP-7 attenuated this association (aHR 7.09 [95%CI 3.72;13.50).

Heart failure hospitalization according to levels of IGFBP-7 and NT-proBNP

Compared to patients with IGFBP-7 and NT-proBNP levels below the median, the multivariable aHRs (95%CI) were 1.97 (95%CI 1.77;3.33) in patients with high NT-proBNP (but low IGFBP-7) levels, and 2.17 (95% CI 1.30;3.60) in patients with high IGFBP-7 (but low NT-proBNP) levels, and 5.20 (95%CI 3.35; 8.09) in patients where both IGFBP-7 and NT-proBNP levels were high **(Table 3, Figure 2)**. The corresponding incidence rates per 1,000 patient-years were 5.3, 17.3, 19.4 and 73.3, respectively. The area under the curve was 0.75 (Ref.) for NT-proBNP, 0.76 (p=0.60) for IGFBP-7, and 0.78 for both markers combined (p<0.001) (**Figure 3**).

Discussion

To the best of our knowledge, this is the first large study to assess the association between IGFBP-7 and CHF hospitalization, and the first study to show the prognostic value of IGFBP-7 in patients with AF. We observed several new and clinically important findings. First, the risk of CHF hospitalization was high with an overall incidence of 29.5 cases per 1,000 patient-years. Second, increasing levels of IGFBP-7 and NT-proBNP were strongly and independently associated with incident CHF hospitalization. Third, both markers provided additive information that was independent of each other. Patients with elevated IGFBP-7 and elevated NT-proBNP had a more than 5-fold increase in risk of CHF hospitalization after multivariable adjustment. The corresponding incidence was 73 cases per 1,000 patient-years. Thus, a combination of both markers may be useful to identify AF patients at very high risk of CHF hospitalization. Finally, these associations were observed among patients with and without pre-existing CHF at baseline.

Patients with both AF and CHF have a higher risk for AF progression[17], a lower quality of life[18], an increased risk for recurrent hospitalizations[19] and a higher risk of death[7]. CHF is one of the main drivers for mortality among AF patients receiving anticoagulation for stroke prevention[20]. AF patients with a recent CHF decompensation have a particularly high risk for serious complications[21]. CHF remains a main driver of health-care costs[22] and a substantial number of patients are readmitted within the first year after a hospitalization for CHF[23, 24]. Therefore, the concomitant occurrence of AF and CHF has important implications. Early identification of AF patients at increased risk of a CHF hospitalization may therefore have an important impact not only on the individual patient, but also on a socio-economical level.

Our study showed an 8-fold higher incidence of CHF hospitalization among patients in the highest compared to the lowest IGFBP-7 quartile. These relationships remained highly significant after multivariable adjustment. While this association seemed stronger among patients with a history of CHF (p for interaction 0.07), the risk increase was still highly significant among patients without a

history of CHF at baseline (adjusted HR for quartile IV versus I 3.48 [1.94; 6.24]). The risk seemed comparable for CHF admissions with preserved versus CHF admissions with reduced EF (Supplemental Tables S-3 and S-4). The prognostic information was additive and independent to the gold-standard marker NT-proBNP. Patients with both markers above the biomarker specific median had a nearly 6-fold increased risk for a CHF hospitalization compared to patients with both biomarkers below the median. These markers might therefore be very helpful in risk assessment and early identification of patients who may need closer follow-up to prevent recurrent CHF admissions. Based on our findings, future studies should assess whether AF patients with elevated levels of both IGFBP-7 and NT-proBNP benefit from more advanced evaluations, such as echocardiography or other imaging modalities, whether they need closer follow-up, more intense risk factor management or more frequent referrals for advanced treatment modalities such as catheter ablation, and whether these intervention can prevent costly CHF hospital admissions and other outcomes in this high-risk population. . From a clinical practice perspective, our data therefore suggest that IGFBP-7 may have a place in the assessment and management of AF patients at risk of CHF hospitalizations.

IGFBP-7 has been found through proteomic searches to be associated with cardiac hypertrophy[11]. The IGF axis was associated with New York Heart Association functional class and predicted adverse outcomes among 142 CHF patients[25]. Higher IGFBP-7 levels were related to diastolic function and exercise capacity among patients with CHF with preserved EF[26]. A retrospective analysis of 151 CHF patients with reduced EF showed that serial IGFBP-7 measurements predicted cardiovascular death, CHF hospitalization and worsening CHF[12]. Another small study showed that levels of IGFBP-7 decreased among CHF patients after implantation of a left ventricular assist device, suggesting that a lower IGFBP-7 level reflects less severe CHF[13]. In this context, our study is by far the largest and we were able to exactly quantify the impact of IGFBP-7 in AF patients.

The mechanisms of the association between IGFBP-7 and CHF are not well understood. Being associated with cell cycle arrest[10], higher levels of IGFBP-7 might accelerate the senescence of

myocardial cells[27]. IGFBP-7 was associated with hepatic fibrogenesis[28]. Therefore, promoting myocardial fibrosis might be another pathophysiological pathway explaining the association with CHF. IGFBP-7 seems to be up-regulated in inflammatory states like exacerbations of chronic obstructive pulmonary disease[29] or inflammatory breast cancer[30], suggesting that inflammation may be a potential link.

The key strengths of this analysis are the availability of two large cohorts of well-characterized AF patients with a very low rate of missing values and central adjudication of all outcome events. Our study therefore has adequate power to thoroughly assess the value of IGFBP-7 in this context. As in any observational design, our study is unable to prove causality and residual confounding may persist despite multivariable adjustment. Echocardiography was not systematically performed and AF burden was not available, and we were unable to take into account the potential importance of these factors. Future studies are needed to assess whether interventions that favorably address/treat AF correlate with a reduced level of IGFB-7 to potentially assess causality versus association.

Conclusions

This study found that increasing levels of IGFBP-7 are strongly and independently associated with CHF hospitalization in patients with established AF and provide prognostic information over and beyond the use of natriuretic peptides. The combination of IGFBP-7 and NT-proBNP may help to better identify patients at high risk of CHF hospitalization in the future, and therefore become an important tool in the management of patients with AF.

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Figure Legends

Figure 1:Risk of congestive heart failure hospitalization stratified by baseline IGFBP-7 quartiles in all patients

p<0.001 (log rank); IGFBP-7=Insulin-Like Growth Factor-Binding Protein-7

y-axis:congestive heart failure hospitalization free survival

x-axis:follow-up in years.

Figure 2:Risk of congestive heart failure hospitalization stratified by baseline IGFBP-7 and NT-proBNP values in all patients

p<0.001 (log rank); CHF=congestive heart failure; low= <biomarker specific median; high= ≥ biomarker specific median; IGFBP-7=Insulin-Like Growth Factor-Binding Protein-7; NT-proBNP=N-terminal pro brain natriuretic peptide

y-axis:congestive heart failure hospitalization free survival

x-axis:follow-up in years.

Figure 3: Receiver operating characteristic curves according to baseline IGFBP-7 and NT-proBNP values

IGFBP-7=Insulin-Like Growth Factor-Binding Protein-7; NT-proBNP=N-terminal pro brain natriuretic peptide

1 Table 1: Baseline characteristics stratified by IGFBP-7 quartiles

Characteristic	**Quartile I**	**Quartile II**	**Quartile III**	**Quartile IV**	**p-value**
n	922	923	923	923	
IGFBP-7 range [ng/ml]	85-159	159-182	182-216	216-986	
Age[years]	64±11	70±9	74±7	77±8	<0.001
Female sex	277 (30.0)	265 (28.7)	234 (25.4)	252 (27.3)	0.14
Body mass index[kg/m^2]	27.3±4.5	27.6±4.8	27.6±4.7	27.2±4.9	0.15
Heart rate[beats/min]	68±16	68±16	70±17	72±18	<0.001
Current Smoker	97 (10.6)	64 (7.0)	74 (8.0)	54 (5.9)	0.002
Systolic blood pressure [mmHg]	133±17	135±18	135±19	133±21	0.003
NT-proBNP level[pg/ml]	184[74;448]	347[130;806]	747[302;1341]	1654[888;2910]	<0.001
Atrial Fibrillation Type					
Paroxysmal	574(62.3)	503(54.6)	420(45.5)	315(34.1)	
Persistent	262(28.5)	263(28.5)	258(28.0)	224(24.3)	<0.001
Permanent	85(9.2)	156(16.9)	245(26.5)	384(41.6)	
Rhythm					
Sinus	669(72.6)	556(60.2)	442(47.9)	235(25.5)	<0.001
Atrial Fibrillation	213(23.1)	304(32.9)	417(45.2)	611(66.2)	
Atrial Flutter	11(1.2)	18(2.0)	19(2.1)	26(2.8)	
Other	25(2.7)	42(4.6)	33(3.6)	44(4.8)	
Medication					
Beta Blocker	566(61.4)	626(67.8)	661(71.6)	692(75.0)	<0.001
Class Ic AAD	90(9.8)	72(7.8)	23(2.5)	10(1.1)	<0.001
Class III AAD	200(21.7)	193(20.9)	154(16.7)	132(14.3)	<0.001
AF-related symptoms	699(77.0)	628(69.2)	568(62.6)	498(54.5)	<0.001
History of PVI	343(37.2)	219(23.8)	144(15.6)	70(7.6)	<0.001
History of atrial flutter	188(20.4)	191(20.7)	212(23.0)	162(17.6)	0.04
History of coronary artery disease	141(15.3)	206(22.3)	277(30.0)	353(38.2)	<0.001
History of stroke/TIA	129(14.0)	146(15.8)	164(17.8)	186(20.3)	0.003

History of hypertension	512(55.5)	589(63.8)	698(75.6)	746(80.8)	<0.001
History of heart failure	108(11.7)	149(16.1)	234(25.4)	388(42.0)	<0.001
History of diabetes mellitus	83(9.0)	106(11.5)	160(17.3)	240(26.0)	<0.001
GFR(ml/min/1.7m^2)	76±15	68±15	60±15	47±18	<0.001

1 IGFBP-7=Insulin-Like Growth Factor-Binding Protein-7; NT-proBNP=N-terminal pro-brain natriuretic

2 peptide; TIA=transient ischemic attack; GFR=glomerular filtration rate; AAD=antiarrhythmic drug

3 Data are means±standard deviation, medians[interquartile range] or counts (%) as appropriate.

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Table 2: Relationship between IGFBP-7 and congestive heart failure hospitalization

	Continuous*	**Quartile I**	**Quartile II**	**Quartile III**	**Quartile IV**	**p for trend**
	n=3691	**n=922**	**n=923**	**n=923**	**n=923**	
Incidence per 1,000 patient years	29.5	6.7	10.0	31.9	85.0	
Age/Sex adj.	11.74[8.56;16.10]§	Reference	1.25[0.75;2.10]	3.46[2.19;5.46]	8.27[5.30;12.90]	<0.001
Multivariable adjusted†	6.55[4.39;9.77]§	Reference	1.05[0.63;1.77]	2.38[1.50; 3.79]	4.37[2.72;7.04]	<0.001
Additionally adjusted for NT-proBNP	3.75[2.36;5.95]§	Reference	0.93[0.55;1.56]	1.89[1.19;2.99]	2.85[1.76;4.64]	<0.001

IGFBP-7=Insulin-Like Growth Factor-Binding Protein-7;NT-proBNP=N-terminal pro brain natriuretic peptide;*IGFBP-7 log transformed;†adjusted for age, sex, BMI, heart rate,systolic blood pressure,glomerular filtration rate,AF type at baseline (paroxysmal vs. non-paroxysmal),current smoking,cohort (BEAT-AF vs. Swiss-AF), and history of diabetes,coronary artery disease,hypertension,stroke/transient ischemic attack,or CHF;§p<0.001; Max.62 (1.7%) observations were deleted due to missing variables

Table 3: Relationship of IGFBP-7 and NT-proBNP categories with congestive heart failure hospitalization

	IGFBP-7 low, NT-proBNP low	**IGFBP-7 low, NT-proBNP high**	**IGFBP-7 high, NT-proBNP low**	**IGFBP-7 high, NT-proBNP high**
	n=1335	**n=511**	**n=511**	**n=1334**
Incidence per 1,000 patient years	5.3	17.3	19.4	73.3
Age/Sex adjusted	Reference	2.75[1.66;4.57]	2.89[1.75;4.77]	9.80[6.52;14.73]
Multivariable adjusted *	Reference	1.97[1.17;3.33]	2.17[1.30;3.60]	5.20[3.35;8.09]

Low= < biomarker specific median; High= >=biomarker specific median; IGFBP-7=Insulin-Like Growth Factor-Binding Protein-7;NT-proBNP=N-terminal pro brain natriuretic peptide;*adjusted for age,sex,BMI,heart rate,systolic blood pressure,glomerular filtration rate,AF type at baseline (paroxysmal vs. non-paroxysmal), current smoking,cohort (BEAT-AF vs. Swiss-AF),and history of diabetes,coronary artery disease,hypertension,stroke/transient ischemic attack,CHF;max.62 (1.7%) patients were removed from these models due to missing data.