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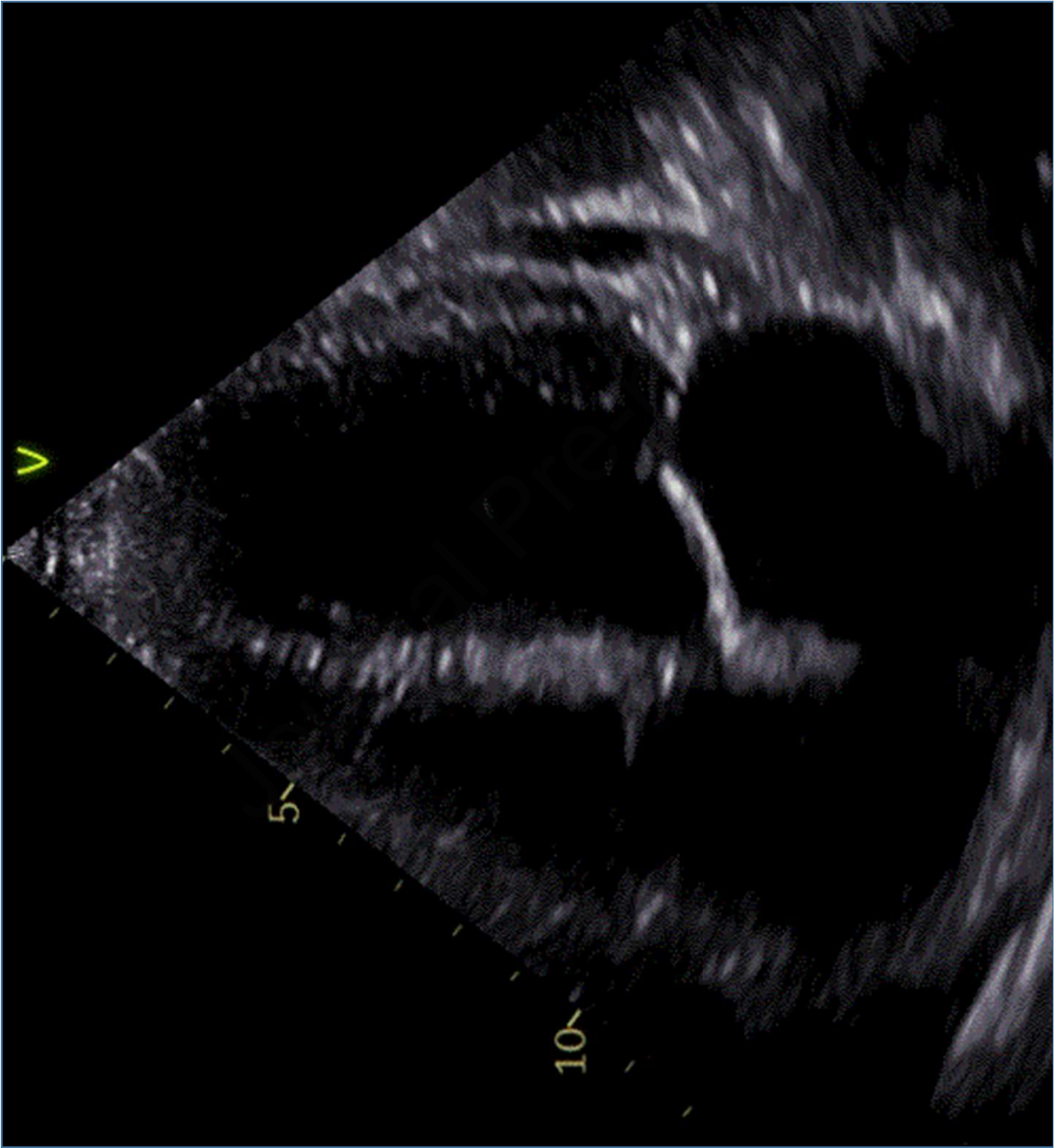
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1 **Insulin-Like Growth Factor-Binding Protein-7 and risk of congestive heart**
2 **failure hospitalization in patients with atrial fibrillation**

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16

1 **Abstract**

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

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

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

10 **Results:** Mean age was 69 ± 12 years, 1,028 (28%) were females and 879 (24%) had a history of CHF.
11 The incidence per 1,000 patient-years across increasing IGFBP-7 quartiles was 7, 10, 32 and 85. The
12 corresponding multivariable adjusted hazard ratios (aHRs) [95%CI] were 1.0, 1.05 [0.63;1.77], 2.38
13 [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-
14 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
15 for trend < 0.001). Patients with IGFBP-7 and NT-proBNP levels above the biomarker-specific median
16 had a higher risk of incident CHF hospitalization (aHR 5.20 [3.35; 8.09]) compared to those with only
17 one elevated marker (elevated IGFBP-7 aHR 2.17[1.30;3.60]; elevated NT-proBNP aHR
18 1.97[1.17;3.33]) or no elevated marker (reference).

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

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

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1 Introduction

2 In patients with atrial fibrillation (AF), most studies have focused on predicting and
3 preventing stroke. Much less information is available with regard to congestive heart failure (CHF),
4 despite a tight link between AF and CHF¹⁻³. CHF hospitalizations put a substantial economic burden
5 on health care systems and are associated with a worse prognosis among AF patients⁴⁻⁶. In
6 contemporary, anticoagulated AF patients, CHF is much more common than stroke, and progressive
7 CHF accounts for many deaths.⁷ Therapy options for AF patients with concomitant CHF are limited⁸,
8 and established therapies may not have the same impact as in patients without AF⁹. Accurately
9 identifying AF patients at increased risk for CHF hospitalization is an important first step towards the
10 development of effective prevention strategies.

11 Insulin-like growth factor-binding protein 7 (IGFBP-7) plays a role in cell cycle arrest during
12 early phases of cell injury¹⁰, and may therefore be involved in the development of myocardial
13 damage. It has been identified as a potential biomarker for CHF and cardiac hypertrophy¹¹. Previous
14 studies suggested that IGFBP-7 may be related to worsening CHF and hospitalization for CHF, and
15 lower IGFBP-7 levels were associated with fewer cardiovascular events among CHF patients¹². Higher
16 IGFBP-7 levels predicted adverse outcome events in CHF patients with preserved but not those with
17 reduced ejection fraction (EF).¹³ However, all these prior studies on IGFBP-7 were small, included
18 selected patient populations, and had short follow-up. In addition, there are no data available in
19 patients with AF.

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

23

1 **Methods**

2 *Study Design and Participants*

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

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

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

21 *Blood samples*

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

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

7 *Assessment of study variables*

8 Both cohorts collected information about personal, medical and lifestyle factors through very
9 similar study CRFs.. Weight and height were directly measured using calibrated devices. Body mass
10 index (BMI) was calculated as weight in kg divided by height in meters squared. AF was classified into
11 paroxysmal AF, persistent AF or permanent AF¹⁶.

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

15 *Definitions and Outcomes*

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

1 *Statistical Analysis*

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

7 Incidence rates were calculated as number of events per 1,000 patient years of follow-up. To
8 assess the association between baseline IGFBP-7 levels and incident CHF hospitalization, we obtained
9 hazard ratios and 95% confidence intervals (CI) from Cox proportional-hazards models. Multivariable
10 models were adjusted for a pre-defined set of covariates, including age, sex, BMI, heart rate, systolic
11 blood pressure, glomerular filtration rate, AF type at baseline (paroxysmal vs. non-paroxysmal),
12 current smoking, cohort (BEAT-AF vs. Swiss-AF), and history of diabetes, coronary artery disease,
13 hypertension, stroke/transient ischemic attack, or CHF. The variable selection for the multivariable
14 models was predefined and mainly included known risk-factors and comorbidities associated with
15 CHF and its pathophysiology. Potential collinearity between covariates in the Cox models was
16 assessed using Pearson correlation coefficients. With one exception, all correlation coefficients were
17 <0.25 (data not shown).

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

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

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

1 Results

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

5 *Association of IGFBP-7 with heart failure hospitalization*

6 Of the 3,691 patients included in this analysis, 385 (10.4%) had a CHF hospitalization during a
7 mean follow-up of 3.7 ± 1.8 years, corresponding to an incidence of 29.5 cases per 1,000 patient-
8 years of follow-up. The incidence was 6.7, 10.0, 31.9 and 85.0 per 1,000 patient years across
9 increasing IGFBP-7 quartiles ($p < 0.001$) (**Figure 1**). Age and sex adjusted Cox regression models
10 confirmed a steep increase in the risk of CHF hospitalization across quartiles of IGFBP-7 (**Table 2**). The
11 multivariable adjusted hazard ratio (aHR) for the highest compared with the lowest quartile was 4.37
12 (95%CI 2.72;7.04), with a p for trend across quartiles of < 0.001 . After additional adjustment for NT-
13 proBNP, the association remained highly significant. In models stratified by history of CHF at
14 baseline, the associations did not significantly differ between patients with and without a history of
15 CHF (**Supplemental Table S-1 and S-2**), even though the risk increase by IGFBP-7 seemed less
16 pronounced among patients with a history of CHF (p for interaction 0.07). Additional adjustment for
17 AF-related symptoms, history of pulmonary vein isolation, baseline rhythm, AF-duration and baseline
18 medication did not significantly change the association of IGFBP-7 and CHF hospitalization
19 (Supplemental Table S-3). Left ventricular EF at the time of the outcome event was available in 156
20 patients, 83 (53.2%) with reduced EF and 73 (46.8%) with preserved EF. The multivariable adjusted
21 hazard ratios (95%CI) per unit increase of log transformed IGFBP-7 were 4.58 [1.98;10.59] and 6.99
22 [2.87;17.03] for CHF hospitalization with reduced and preserved EF, respectively (**Supplemental**
23 **Table S-4 and S-5**).

24 *Association of NT-proBNP with heart failure hospitalization*

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

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

8 Compared to patients with IGFBP-7 and NT-proBNP levels below the median, the
9 multivariable aHRs (95%CI) were 1.97 (95%CI 1.77;3.33) in patients with high NT-proBNP (but low
10 IGFBP-7) levels, and 2.17 (95% CI 1.30;3.60) in patients with high IGFBP-7 (but low NT-proBNP) levels,
11 and 5.20 (95%CI 3.35; 8.09) in patients where both IGFBP-7 and NT-proBNP levels were high (**Table 3,**
12 **Figure 2**). The corresponding incidence rates per 1,000 patient-years were 5.3, 17.3, 19.4 and 73.3,
13 respectively. The area under the curve was 0.75 (Ref.) for NT-proBNP, 0.76 ($p=0.60$) for IGFBP-7, and
14 0.78 for both markers combined ($p<0.001$) (**Figure 3**).

15

1 Discussion

2 To the best of our knowledge, this is the first large study to assess the association between
3 IGFBP-7 and CHF hospitalization, and the first study to show the prognostic value of IGFBP-7 in
4 patients with AF. We observed several new and clinically important findings. First, the risk of CHF
5 hospitalization was high with an overall incidence of 29.5 cases per 1,000 patient-years. Second,
6 increasing levels of IGFBP-7 and NT-proBNP were strongly and independently associated with
7 incident CHF hospitalization. Third, both markers provided additive information that was
8 independent of each other. Patients with elevated IGFBP-7 and elevated NT-proBNP had a more than
9 5-fold increase in risk of CHF hospitalization after multivariable adjustment. The corresponding
10 incidence was 73 cases per 1,000 patient-years. Thus, a combination of both markers may be useful
11 to identify AF patients at very high risk of CHF hospitalization. Finally, these associations were
12 observed among patients with and without pre-existing CHF at baseline.

13 Patients with both AF and CHF have a higher risk for AF progression¹⁷, a lower quality of life¹⁸,
14 an increased risk for recurrent hospitalizations¹⁹ and a higher risk of death⁷. CHF is one of the main
15 drivers for mortality among AF patients receiving anticoagulation for stroke prevention²⁰. AF patients
16 with a recent CHF decompensation have a particularly high risk for serious complications²¹. CHF
17 remains a main driver of health-care costs²² and a substantial number of patients are readmitted
18 within the first year after a hospitalization for CHF^{23, 24}. Therefore, the concomitant occurrence of AF
19 and CHF has important implications. Early identification of AF patients at increased risk of a CHF
20 hospitalization may therefore have an important impact not only on the individual patient, but also
21 on a socio-economical level.

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

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

15 IGFBP-7 has been found through proteomic searches to be associated with cardiac
16 hypertrophy¹¹. The IGF axis was associated with New York Heart Association functional class and
17 predicted adverse outcomes among 142 CHF patients²⁵. Higher IGFBP-7 levels were related to
18 diastolic function and exercise capacity among patients with CHF with preserved EF²⁶. A retrospective
19 analysis of 151 CHF patients with reduced EF showed that serial IGFBP-7 measurements predicted
20 cardiovascular death, CHF hospitalization and worsening CHF¹². Another small study showed that
21 levels of IGFBP-7 decreased among CHF patients after implantation of a left ventricular assist device,
22 suggesting that a lower IGFBP-7 level reflects less severe CHF¹³. In this context, our study is by far the
23 largest and we were able to exactly quantify the impact of IGFBP-7 in AF patients.

24 The mechanisms of the association between IGFBP-7 and CHF are not well understood. Being
25 associated with cell cycle arrest¹⁰, higher levels of IGFBP-7 might accelerate the senescence of

1 myocardial cells²⁷. IGFBP-7 was associated with hepatic fibrogenesis²⁸. Therefore, promoting
2 myocardial fibrosis might be another pathophysiological pathway explaining the association with
3 CHF. IGFBP-7 seems to be up-regulated in inflammatory states like exacerbations of chronic
4 obstructive pulmonary disease²⁹ or inflammatory breast cancer³⁰, suggesting that inflammation may
5 be a potential link.

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

15 **Conclusions**

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

21

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1 **Figure Legends**

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

4 $p < 0.001$ (log rank); IGFBP-7=Insulin-Like Growth Factor-Binding Protein-7

5 y-axis: congestive heart failure hospitalization free survival

6 x-axis: follow-up in years.

7

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

10 $p < 0.001$ (log rank); CHF=congestive heart failure; low= <biomarker specific median; high= \geq
11 biomarker specific median; IGFBP-7=Insulin-Like Growth Factor-Binding Protein-7; NT-proBNP=N-
12 terminal pro brain natriuretic peptide

13 y-axis: congestive heart failure hospitalization free survival

14 x-axis: follow-up in years.

15

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

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

20

21

22

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.

4

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 n=1335	IGFBP-7 low, NT-proBNP high n=511	IGFBP-7 high, NT-proBNP low n=511	IGFBP-7 high, NT-proBNP high 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.

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