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Atrial Fibrillation and the Prognostic Performance of Biomarkers in Heart Failure

Eugene S.J. Tan,[a,b] Siew-Pang Chan,[a,b] Oi-Wah Liew,[b] Jenny P.C. Chong,[b] Gerard K.T. Leong,[c] Daniel P.S. Yeo,[d] Hean-Yee Ong,[e] Fazlur Jaufeerally,[f,g] Jonathan Yap,[h] David Sim,[g,h] Tze-Pin Ng,[b] Lieng-Hsi Ling,[a,b] Carolyn S.P. Lam,[g,h,i] and Arthur M. Richards[a,j,k,*]

BACKGROUND: Consideration of circulating biomarkers for risk stratification in heart failure (HF) is recommended, but the influence of atrial fibrillation (AF) on prognostic performance of many markers is unclear. We investigated the influence of AF on the prognostic performance of circulating biomarkers in HF.

METHODS: N-terminal pro-B-type natriuretic peptide (NT-proBNP), mid-regional-pro-atrial natriuretic peptide, C-type natriuretic peptide (CNP), NT-proCNP, high-sensitivity troponin-T, high-sensitivity troponin-I, mid-regional-propeptide adrenomedullin, co-peptin, growth differentiation factor-15, soluble Suppressor of Tumorigenicitiy (sST2), galectin-3, and procalcitonin plasma concentrations were measured in a prospective, multicenter study of adults with HF. AF was defined as a previous history of AF, and/or presence of AF/flutter on baseline 12-lead electrocardiogram. The primary outcome was the composite of HF-hospitalization or all-cause mortality at 2 years.

RESULTS: Among 1099 patients (age 62 ± 12years, 28% female), 261(24%) patients had AF. Above-median concentrations of all biomarkers were independently associated with increased risk of the primary outcome. Significant interactions with AF were detected for galectin-3 and sST2. In considering NT-proBNP for additive risk stratification, sST2 (adjusted hazard ratio [AHR]1.85, 95%confidence interval [C.I.] 1.17-2.91) and galectin-3 (AHR1.85, 95%C.I. 1.09-2.45) were independently associated with increased primary outcome only in the presence of AF. The prognostic performance of sST2 was also stronger in AF for all-cause mortality (AF: AHR2.82, 95%C.I. 1.26-6.21; non-AF: AHR1.78, 95% C.I. 1.14-2.76 without AF), while galectin-3 predicted HF-hospitalization only in AF (AHR1.64, 95%C.I. 1.03-2.62).

CONCLUSIONS: AF modified the prognostic utility of selected guideline-endorsed HF-biomarkers. Application of markers for prognostic purposes in HF requires consideration of the presence or absence of AF.

CLINICAL TRIAL REGISTRATION: ACTRN12610000374066

Introduction

Circulating biomarkers have established roles in diagnosis and risk stratification in heart failure (HF) (1). Beyond troponin and the cardiac B-type cardiac natriuretic peptides (NT-proBNP and BNP), the emergence of soluble Suppressor of Tumorigenicitiy 2 (sST2) and galectin-3 as prognostic markers (2–6) has led to their inclusion in the American College of Cardiology HF guidelines for additive risk stratification (7). Other non-cardiac specific biomarkers such as mid-regional propeptide adrenomedullin (MR-proADM), arginine vasopressin (AVP), growth differentiation factor-15 (GDF-15) and C-type natriuretic peptide (CNP) (8–11) while prognostic, have not been integrated into routine clinical practice.

Atrial fibrillation (AF) is the most common arrhythmia in HF and perturbs a wide variety of circulating biomarkers also associated with HF. Although the prognostic value of natriuretic peptides has not been reported to differ by AF status in acute and chronic HF (12, 13), the influence of AF on the prognostic significance of other novel biomarkers in HF has not been studied. Identification of biomarkers that may be

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affected by the presence of AF may help in the selection of biomarkers during additive risk stratification. The aim of our study was therefore to evaluate the influence of AF on the prognostic performance of novel biomarkers in HF.

Methods

STUDY POPULATION

Participants were from the prospectively designed, longitudinal study of adults with HF across 6 centers from the Singapore Heart Failure Outcomes and Phenotypes (SHOP) study (trial registration: ACTRN12610000374066). The study design and outcomes have previously been reported (14). In short, patients presenting to hospital with a primary diagnosis of HF or attending hospital-clinics for HF management within 6 months of decompensated HF were enrolled and followed according to identical protocols. All patients were above 21 years of age and provided informed consent. Ethics approval was obtained from the National Healthcare Group Domain Specific Review Board (reference number 2010/00114), and the study complies with the Declaration of Helsinki.

Patients were assessed at baseline (recruitment), follow-up clinic visits at 6 weeks and 6 months, and via phone-calls at 1 and 2 years. Baseline demographics, comorbidities, standard 12-lead electrocardiogram (ECG), and samples for circulating biomarkers were obtained at recruitment. Comprehensive transthoracic echocardiography was performed and interpreted in accordance with American Society of Echocardiography guidelines.

Atrial fibrillation was defined as either a previous history of AF or presence of AF/atrial flutter on ECG at time of recruitment. Paroxysmal AF was defined as positive history of AF but without AF on baseline ECG, and permanent AF was defined as positive history of AF with AF on baseline ECG. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m^2.

BIOMARKERS

Samples for assay of circulating biomarkers including NT-proBNP, high-sensitivity troponin-T (hs-cTnT), high-sensitivity troponin-I (hs-cTnI), GDF-15, sST2, galectin-3, procalcitonin (PCT), co-peptin (PAVP), MR-proADM, mid-regional-pro-atrial natriuretic peptide (MR-proANP), CNP and N-terminal pro C-type natriuretic peptide (NT-proCNP) were obtained at baseline. Venous samples were taken into EDTA tubes, kept on ice during transport, with separation of plasma within an hour of sampling and storage at -80 °C prior to assay. Samples obtained at each center were stored at the National University Heart Centre Singapore for further analyses. Plasma NT-proBNP and hs-cTnT were measured by electrochemiluminescence immunoassays on the Elecsys cobas e411 immunoanalyzer (Roche Diagnostics). hs-cTnI was measured by chemiluminescent microparticle immunoassay on an Architect i2000SR platform (Abbott Ireland Diagnostic Division). The precision of these 3 assays has been previously described (2). GDF-15 and Galectin-3 (Quantikine®, R&D Systems, Inc.), sST2 (Presage ST2 assay, Critical Diagnostics), CNP (Cloud Clone Corp), and NT-proCNP (Biomedica Medizinprodukte GmbH & Co KG) were measured by ELISA.

Laboratory inter-assay coefficients of variation of quality control samples derived from over 170 independent assays were 13.1% at 144 ng/L, 11.8% at 398 ng/L and 10.1% at 793 ng/L for GDF-15, 7.29% at 860 ng/L, 8.59% at 2.47 μg/L and 8.33% at 4.83 μg/L for galectin-3, and 14.9% at 31.7 μg/L and 15.7% at 67.8 μg/L for sST2. Inter-assay coefficients of variation for CNP and NT-proCNP over 30 independent assays were 8.25% at 259 ng/L and 9.08% at 5.18 pmol/L, respectively. Plasma concentrations of PCT, PAVP, MR-proADM and MR-proANP were obtained by immunoluminometric assays on the B·R·A·H·M·S KRYPTOR analyzer (Thermo Scientific GmbH). Inter-assay coefficient of variation established over 42 independent runs were 4.83% at 0.28 μg/L and 2.55% at 11.0 μg/L for PCT, 8.06% at 4.56 pmol/L and 2.24% at 102 pmol/L for PAVP, 4.44% at 0.71 nmol/L and 3.86% at 4.39 nmol/L for MR-proADM, and 5.68% at 102 pmol/L and 5.69% at 507 pmol/L for MR-proANP.

OUTCOME

The primary outcome of this study was the composite of HF-hospitalization or all-cause mortality over 2 years. As participants of this study were patients followed-up at public healthcare institutions with electronic health records, clinical outcomes could be reliably ascertained, according to protocol, over the course of follow-up in clinic or by phone calls, nationally linked public-hospital database and the National Death Registry within Singapore.

STATISTICAL ANALYSIS

Baseline characteristics of patients were reported as mean ± standard deviation or percentages, and median (interquartile range) for biomarkers by AF status. Comparisons of baseline characteristics were performed by independent *t*-test (parametric) or Mann-Whitney U test (nonparametric) for continuous and chi-square test for categorical variables. Multivariable Cox-proportional hazards models were performed for the association of

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each biomarker (above vs below median concentration of total cohort) with primary outcome and its individual components in the absence of other biomarkers. Each biomarker was tested for interaction with AF, with respect to its association with outcomes. In the presence of an interaction, the association of the biomarker with primary outcome and its individual components was then compared separately in multivariable models stratified by AF status. Kaplan-Meier survival curves were performed individually for each biomarker with primary outcome and individual components. Sensitivity analyses were performed for interactions between AF and biomarkers among those with paroxysmal AF and AF on baseline ECG (permanent AF). Linear regression analyses were performed for biomarkers demonstrating interactions with AF to determine its association with clinical correlates. Absolute *t*-statistic scores were compared for the ranking of clinical predictors of biomarkers with and without AF. A *P* value of <0.05 was considered to be statistically significant.

Results

Among 1,099 patients (mean age 62 ± 12 years, 28% female, mean left ventricular ejection fraction [LVEF] $35 \pm 16\%$), 261 (24%) patients had a history of AF. Of these, 85 (8%) patients had paroxysmal AF and 176 (16%) patients had AF on baseline ECG (permanent AF).

BASELINE CHARACTERISTICS

Patients with AF were older, had worse New York Heart Association (NYHA) functional status, and were more likely to have a history of stroke, non-ischemic HF, but less likely to have diabetes (Table 1). Median concentrations of NT-proBNP, GDF-15, sST2, MR-proADM, MR-proANP, and CNP were higher among patients with AF (Table 1).

OUTCOMES

During 2-years of follow-up, 456 (42%) patients either died from any cause or were hospitalized for HF (48% AF vs 39% non-AF, $P = 0.01$). There were 357 (33%) HF-hospitalizations (37% AF vs 31% non-AF, $P = 0.09$), and 171 (16%) all-cause deaths (20% AF vs 14% non-AF, $P = 0.03$). Adjusting for age, sex, diabetes, CKD, left bundle branch block (LBBB), and NYHA class, AF was significantly associated with increased rates of the primary outcome (adjusted hazard ratio [AHR] 1.28, 95% confidence interval [C.I.] 1.03-1.59) (Supplemental Fig. 1).

ASSOCIATION OF BIOMARKERS WITH PRIMARY OUTCOME AND INTERACTIONS WITH AF

In multivariable analyses adjusting for clinical risk factors and AF, above median concentrations of NT-proBNP, hs-cTnT, GDF-15, sST2, galectin-3, hs-cTnI, PCT, PAVP, MR-proADM, MR-proANP, CNP, and NT-proCNP were all independently associated with greater incidence of the primary outcome at 2 years (Table 2). Kaplan-Meier survival curves for the nominated clinical endpoints for biomarker concentrations above compared with below median values are shown in Supplemental Fig. 2(A–K). Optimum cut-off points, sensitivity, and specificity of biomarkers by AF status for primary composite outcome are given in Supplemental Table 1.

Unlike conventionally measured biomarkers NT-proBNP and hs-cTnT (Supplemental Fig. 3), galectin-3 and sST2 curves indicated that the prognostic performance for the primary outcome was confined to, or stronger in, AF than in normal sinus rhythm (Fig. 1). With respect to sST2, interaction with AF was found for the primary endpoint ($P_{interaction} = 0.01$) and HF-hospitalization ($P_{interaction} = 0.04$). For galectin-3, similar interactions were present for HF-hospitalization and all-cause mortality ($P_{interaction} = 0.04$ and $= 0.048$, respectively) (Figs. 2 and 3). In adjusted multivariable models, sST-2 above median ($>35.6\,\mu g/L$) carried stronger prognostic effect among patients with AF for primary composite outcome and HF-hospitalization compared to non-AF, while independent prognostic associations of galectin-3 ($>7.7\,\mu g/L$) with HF-hospitalization and all-cause death were confined to patients with AF (Table 3). More strikingly, when NT-proBNP and LVEF was added to the multivariable model for additive risk stratification, the prognostic performance of galectin-3 and sST2 with respect to primary outcome, and galectin-3 for HF-hospitalization were limited only to patients with AF, while sST2 showed a stronger prognostic performance in all-cause mortality in the presence of AF (Table 3). Interactions between AF and the other biomarkers with respect to prognostic outcomes were not significant (Supplemental Table 2). Despite greater separation between Kaplan-Meier curves, in AF compared to normal rhythm, for PAVP, MR-proADM and MR-proANP (Supplemental Fig. 4), statistical significance was not attained. The association of galectin-3 with the composite outcome was not modified by HF-type (HF with preserved EF [HFpEF] vs reduced EF [HFrEF]; *P* for 3-way interaction $= 0.61$) except for sST2 (*P* for 3-way interaction $= 0.018$), where the association appeared stronger in patients with HFpEF and AF (HR 3.12, 95% C.I. 1.26-7.78) compared to those with HFrEF and AF (HR 1.83, 95% C.I. 1.01-3.33) although numbers of events in each subgroup were small.

In sensitivity analyses among only patients with AF on baseline ECG (permanent AF), interactions with AF were sustained for sST2 ($P_{interaction}$ for primary composite outcome $= 0.01$; $P_{interaction}$ for HF-hospitalization $= 0.02$) and became significant for MR-

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Table 1. SHOP baseline characteristics and biomarkers by AF

	Total n = 1099 (100%)	Non-AF n = 838 (76.2%)	AF n = 261 (23.8%)	*P*-value
Demographics				
Age (years)	62.1 ± 12.2	60.6 ± 12.1	66.7 ± 11.6	<0.001
Female (%)	271 (27.7)	198 (23.6)	73 (28.0)	0.155
Ethnicity (%)				<0.001
Chinese	667 (60.7)	480 (57.3)	187 (71.7)	
Malay	301 (27.4)	242 (28.9)	59 (22.6)	
Indian	121 (11.0)	107 (12.8)	14 (5.4)	
Other	10 (0.9)	9 (1.1)	1 (0.4)	
BMI (kg/m^2)	26.3 ± 5.4	26.3 ± 5.5	26.3 ± 5.1	0.693
NYHA status (%)				0.002
Class I	268 (24.4)	223 (26.6)	46 (17.6)	
Class II	633 (57.7)	483 (57.6)	150 (57.5)	
Class III	161 (14.7)	110 (13.1)	51 (19.5)	
Class IV	16 (1.5)	9 (1.1)	7 (2.7)	
Medical History				
Ischemic HF (%)	647 (58.9)	530 (63.3)	117 (44.8)	<0.001
Hypertension (%)	791 (72.0)	603 (72.0)	188 (72.0)	0.982
Diabetes (%)	625 (56.9)	497 (59.3)	128 (49.0)	0.003
Stroke (%)	120 (10.9)	80 (9.6)	40 (15.3)	0.009
COPD (%)	93 (8.5)	70 (8.4)	23 (8.8)	0.816
LBBB (%)	79 (7.2)	63 (7.5)	16 (6.1)	0.449
CKD (%)	93 (8.5)	70 (8.4)	23 (8.8)	0.896
Medications				
ACE-I/ARB (%)	770 (70.1)	596 (71.1)	174 (66.7)	0.146
Beta-Blocker (%)	956 (87.0)	731 (87.3)	225 (86.2)	0.667
Spironolactone (%)	479 (43.6)	387 (46.2)	92 (35.3)	0.002
Echocardiography				
LVEF categories				
<40%	731 (67)	589 (70)	152 (55)	<0.001
40-49%	121 (11)	81 (10)	40 (15)	
≥50%	244 (22)	166 (20)	78 (30)	
LAVI (mL/m^2)	43.1 ± 18.6	39.8 ± 16.0	53.9 ± 22.1	<0.001
Mitral E/e' (average)	17.3 ± 8.2	17.7 ± 8.1	16.2 ± 8.6	<0.001
Biomarkers				
NT-proBNP (ng/L)	2059 (841, 4464)	1887 (740, 4126)	2557 (1313, 6449)	<0.001*
hs-cTnT (ng/L)	28.5 (16.6, 50.3)	28.4 (16.4, 51.6)	28.5 (17.3, 47.8)	0.908
GDF-15 (ng/L)	2550 (1596, 4011)	2426 (1498, 3823)	3060 (1952, 4449)	<0.001*
sST-2 (μg/L)	35.6 (25.1, 53.2)	34.8 (24.7, 52.0)	40.0 (26.7, 59.5)	0.011*
Galectin-3 (μg/L)	7.7 (6.0, 9.5)	7.6 (6.0, 9.4)	8.1 (6.0, 10.0)	0.073
hs-cTnI (ng/L)	23.0 (11.5, 53.7)	23.0 (11.6, 53.7)	22.7 (11.2, 52.9)	0.972
PCT (μg/L)	0.09 (0.07, 0.14)	0.09 (0.07, 0.13)	1.0 (0.07, 0.16)	0.241
PAVP (pmol/L)	22.8 (12.0, 37.0)	22.7 (12.1, 35.5)	24.1 (11.9, 43.5)	0.134

Continued

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Table 1. (continued)

	Total n = 1099 (100%)	Non-AF n = 838 (76.2%)	AF n = 261 (23.8%)	*P*-value
MR-proADM (nmol/L)	0.97 (0.74, 1.34)	0.93 (0.71, 1.24)	1.10 (0.82, 1.55)	<0.001*
MR-proANP (pmol/L)	280 (171, 414)	259 (149, 392)	331 (231, 455)	<0.001*
CNP (ng/L)	234 (142, 338)	223 (125, 323)	277 (195, 372)	<0.001*
NT-proCNP (pmol/L)	6.2 (4.3, 9.6)	6.2 (4.3, 9.8)	6.4 (4.5, 9.3)	0.892

Values are expressed as mean ± SD, n (%) or median (interquartile range).
AF, atrial fibrillation; ACE-I, angiotensin-converting-enzyme inhibitor; ARB, angiotensin-II receptor blocker; BMI, body mass index; CKD, chronic kidney disease; CNP, C-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; GDF-15, growth differentiation factor-15; hs-cTnI, high-sensitivity troponin-I; hs-cTnT, high-sensitivity troponin-T; LAVI, left atrial volume index; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MR-proADM, mid-regional propeptide adrenomedullin; MR-proANP, mid-regional-pro-atrial natriuretic peptide; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NT-proCNP, N-terminal pro C-type natriuretic peptide; PAVP, co-peptin; PCT, procalcitonin; SHOP. the Singapore Heart Failure Outcomes and Phenotypes (SHOP) study; sST2, soluble Suppressor of Tumorigenicitiy.

Table 2. Association of biomarker plasma concentrations with primary composite outcome of HF-hospitalization or all-cause mortality and individual components.

	Composite event[a] AHR (95% C.I.)	First HF-hospitalization[a] AHR (95% C.I.)	All-cause mortality[a] AHR (95% C.I.)	Composite event[b] AHR (95% C.I.)	First HF-hospitalization[b] AHR (95% C.I.)	All-cause mortality[b] AHR (95% C.I.)
NT-proBNP	1.96 (1.59 – 2.42)	1.75 (1.39 – 2.01)	3.20 (2.17 – 4.73)	1.39 (1.28-1.51)	1.34 (1.22-1.47)	1.75 (1.51-2.04)
hs-cTnT	2.09 (1.68 – 2.59)	1.82 (1.43 – 2.32)	3.63 (2.44 – 5.42)	1.65 (1.48-1.84)	1.49 (1.30-1.70)	2.19 (1.85-2.58)
GDF-15	2.26 (1.79 – 2.87)	1.13 (1.64 – 2.77)	2.89 (1.90 – 4.38)	2.27 (1.88-2.74)	1.98 (1.61-2.45)	3.39 (2.46-4.68)
sST2	1.61 (1.31 – 1.98)	1.39 (1.11 – 1.75)	2.60 (1.80 – 3.76)	1.78 (1.52-2.08)	1.56 (1.30-1.87)	2.30 (1.82-2.89)
hs-cTnI	1.90 (1.54 – 2.33)	1.58 (1.26 – 1.99)	3.49 (2.39 – 5.10)	1.26 (1.18-1.35)	1.19 (1.10-1.29)	1.47 (1.33-1.62)
Galectin-3	1.27 (1.04 – 1.55)	1.25 (1.00 – 1.56)	1.15 (0.83 – 1.58)	1.41 (1.06-1.87)	1.26 (0.92-1.73)	1.54 (0.97-2.46)
PAVP	1.51 (1.22 – 1.87)	1.44 (1.13 – 1.83)	2.02 (1.41 – 2.90)	1.40 (1.22-1.59)	1.35 (1.17-1.57)	1.70 (1.37-2.11)
MR-proADM	2.23 (1.77 – 2.80)	2.25 (1.73 – 2.92)	2.59 (1.72 – 3.91)	2.40 (2.00-2.88)	2.27 (1.83-2.80)	3.03 (2.31-3.97)
MR-proANP	2.03 (1.64 – 2.52)	1.84 (1.45 – 2.35)	3.09 (2.07 – 4.60)	2.02 (1.69-2.40)	1.85 (1.52-2.25)	3.19 (2.38-4.30)
CNP	1.71 (1.38 – 2.11)	1.51 (1.19 – 1.92)	2.43 (1.66 – 3.58)	1.66 (1.40-1.97)	1.48 (1.23-1.78)	2.90 (2.06-4.09)
NT-proCNP	1.26 (1.01 – 1.57)	1.11 (0.86 – 1.42)	1.79 (1.22 – 2.61)	1.34 (1.12-1.62)	1.29 (1.05-1.59)	1.44 (1.08-1.93)
PCT	1.62 (1.31-1.99)	1.39 (1.10-1.75)	2.48 (1.72-3.57)	1.20 (1.08-1.34)	1.11 (0.97-1.27)	1.36 (1.18-1.56)

Multivariate adjustment for age, sex, diabetes, CKD, ischemic etiology of HF, LBBB, NYHA class, AF.
[a]Biomarkers analyzed as above compared to below median concentrations.
[b]Biomarkers analyzed as continuous variables (log convert).
AHR, adjusted hazard ratio; C.I., confidence interval; rest of abbreviations as per Table 1.

proADM ($P_{interaction}$ for HF-hospitalization = 0.03). sST2 concentrations had a stronger prognostic relationship to the primary composite outcome in AF (AF: AHR 2.28, 95% C.I. 1.27-4.09 vs non-AF: AHR 1.51, 95% C.I. 1.21-1.89), and HF-hospitalization (AF: AHR 1.88, 95% C.I. 0.98-3.61 vs non-AF: AHR 1.31, 95% C.I. 1.02-1.67) than without AF in multivariable models. Similarly, MR-proADM concentrations had stronger independent prognostic relationship to HF-hospitalization (AF: AHR 3.92, 95% C.I. 1.67-9.17 vs non-AF: AHR 2.14, 95% C.I. 1.62-2.83) in those with, compared to without, AF (online Supplemental Figs. 5 and 6). Interactions between ECG-AF and the other biomarkers with respect to prognostic outcomes were not detected, including galectin-3 ($P_{interaction}$ for primary outcome = 0.18). When only patients with paroxysmal AF were considered, interactions between AF and the prognostic performance of biomarkers were not observed.

ASSOCIATION OF CLINICAL CORRELATES WITH GALECTIN-3 AND SST2

In multivariable linear regression models, the association of clinical variables with galectin-3 and sST2 differed by

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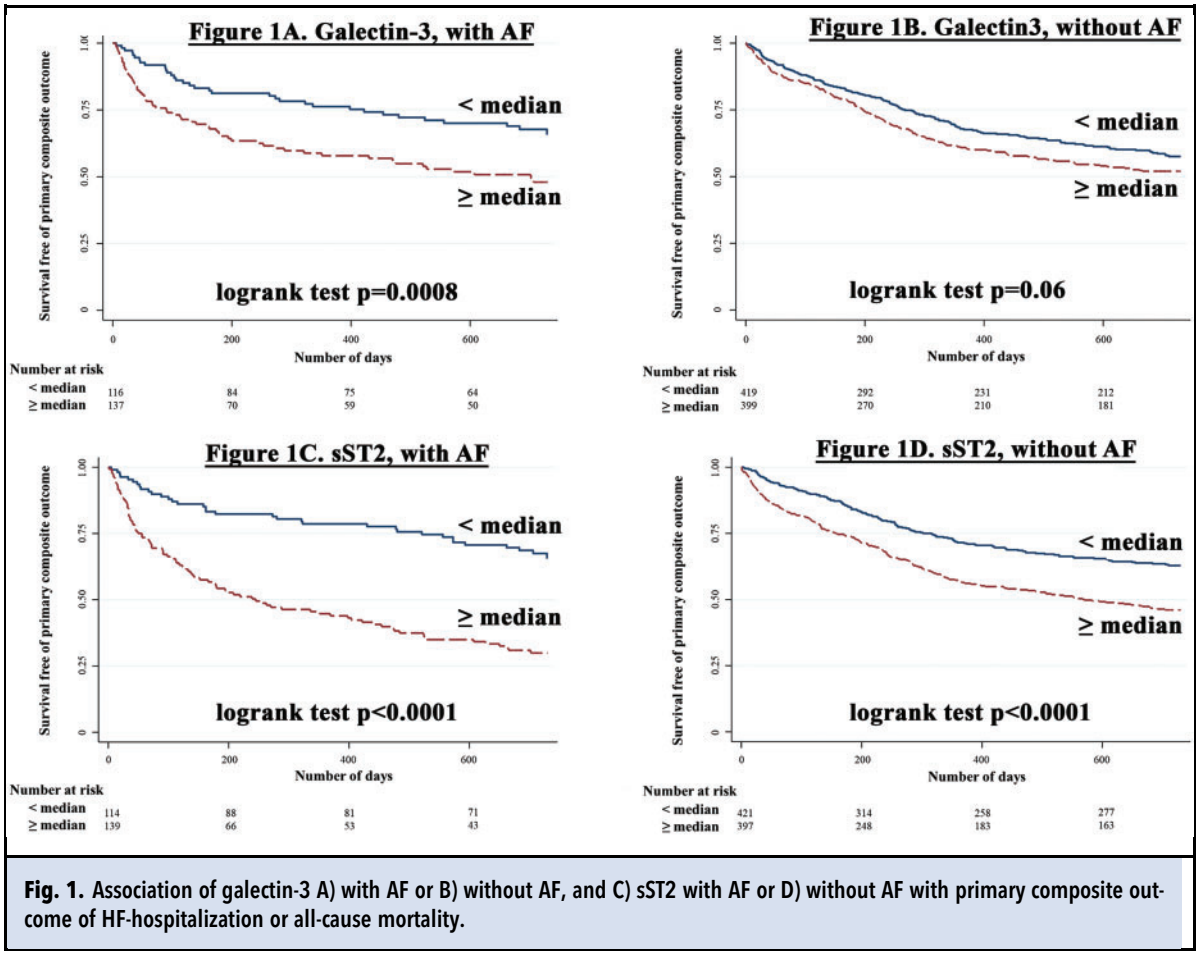

Fig. 1. Association of galectin-3 A) with AF or B) without AF, and C) sST2 with AF or D) without AF with primary composite outcome of HF-hospitalization or all-cause mortality.

AF status (Supplemental Table 3). With respect to galectin-3, only CKD demonstrated independent associations among patients with AF, while age, male sex and CKD were independently associated with galectin-3 among non-AF patients. However, when ranked by magnitude of *t*-statistic scores, CKD was the most significant independent variable associated with galectin-3 in both patients with and without AF. After CKD, diabetes and age were the next ranked variables in patients with AF but did not attain statistical significance. In patients without AF, age followed by male sex, were the next most important variables associated with galectin-3 after CKD. With respect to sST2, male sex, CKD, and NYHA class showed independent associations among patients with AF, while only NYHA class and left atrial volume index (LAVI) showed independent associations with sST2 without AF. When ranked by *t*-statistic scores, CKD was the most important variable, followed by NYHA status and male sex in patients with AF. Among patients without AF, NYHA class followed by LAVI and male sex/diabetes were ranked in order of importance with sST2.

Discussion

Increasing plasma concentrations of NT-proBNP, MR-proANP, CNP, NT-proCNP, hs-cTnT, hs-cTnI, MR-proADM, PAVP, GDF-15, galectin-3, sST2, and PCT were all independently associated with lower event-free survival in HF. We provide for the first time, evidence of an interaction between AF and the prognostic performance of selected HF biomarkers. The predictive value of increased HF-hospitalization and mortality conferred by galectin-3 appeared limited to those with AF, while increased sST2 was more strongly related to prognosis among patients with AF compared to those without. In additive risk stratification to NT-proBNP, the prognostic effects of galectin-3 and sT2 in primary outcome were confined only to those with AF.

The panel of biomarkers assessed in our study reflects the underlying pathophysiological processes of neurohormonal activation, myocardial stretch, myocyte injury, inflammation, and matrix remodeling in HF (1). We have previously described the prognostic

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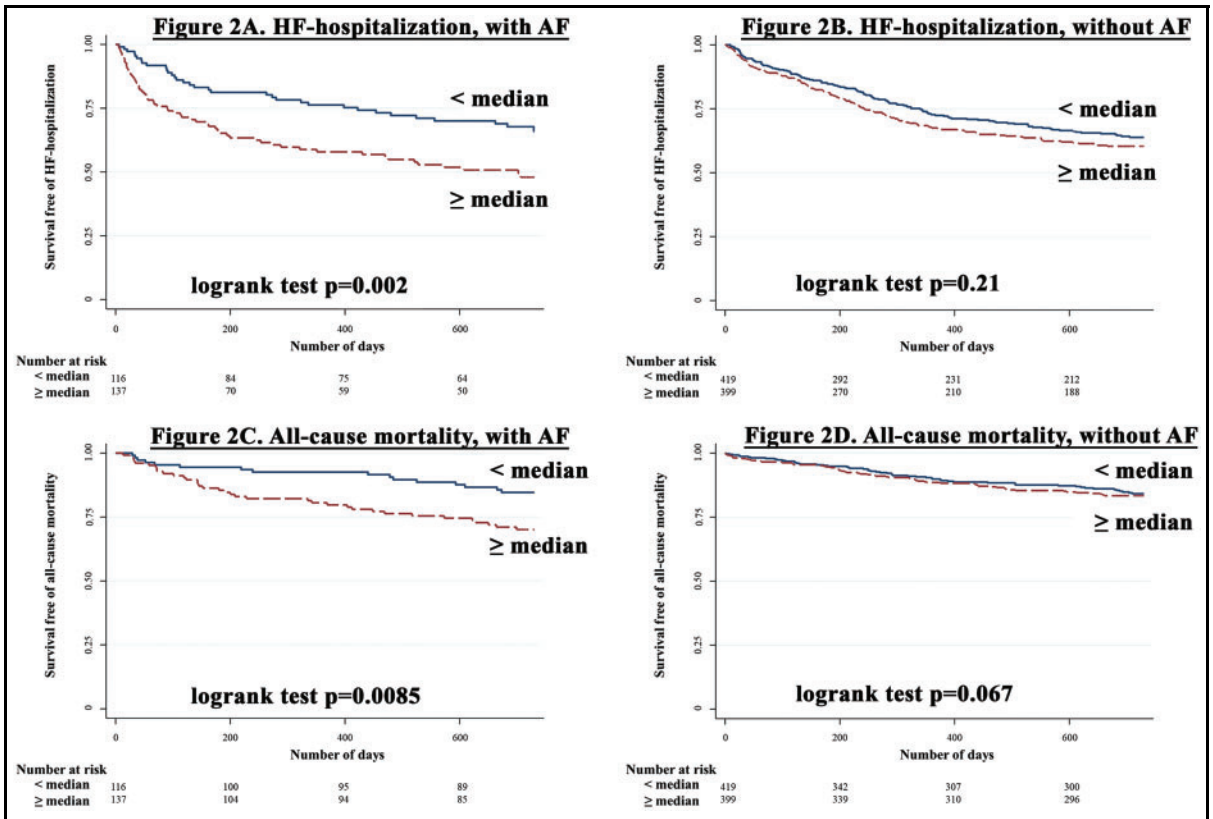

Fig. 2. Association of galectin-3 with HF-hospitalization in A) the presence of AF or B) absence of AF, and C) all-cause mortality in the presence of AF or D) absence of AF.

Table 3. Association of Galectin-3 and sST2 (median) with prognostic outcomes by AF-status.

	Primary composite event[a] Adjusted HR (95% C.I.)	First HF-hospitalization[a] Adjusted HR (95% C.I.)	All-cause mortality[a] Adjusted HR (95% C.I.)	Primary composite event[b] Adjusted HR (95% C.I.)	First HF-hospitalization[b] Adjusted HR (95% C.I.)	All-cause mortality[b] Adjusted HR (95% C.I.)
Galectin-3						
AF	1.74 (1.71-2.59) [c]	1.75 (1.10-2.77) [c]	1.95 (1.04-3.63) [c]	1.64 (1.09-2.45) [c]	1.64 (1.03-2.62) [c]	1.77 (0.94-3.34)
Non-AF	1.13 (0.90-1.43)	1.11 (0.85-1.44)	0.90 (0.61-1.33)	1.08 (0.86-1.37)	1.07 (0.83-1.40)	0.80 (0.54-1.18)
sST2						
AF	2.06 (1.32-3.21) [c]	1.65 (1.01-2.69) [c]	3.34 (1.54-7.24) [c]	1.85 (1.17-2.91) [c]	1.46 (0.88-2.42)	2.82 (1.28-6.21) [c]
Non-AF	1.49 (1.18-1.88) [c]	1.32 (1.02-1.71) [c]	2.47 (1.61-3.79) [c]	1.23 (0.96-1.57)	1.12 (0.86-1.47)	1.78 (1.14-2.76) [c]

[a]Multivariate adjustment for age, sex, diabetes, CKD, ischemic etiology of HF, LBBB, NYHA class.
[b]Multivariate adjustment for age, sex, diabetes, CKD, ischemic etiology of HF, LBBB, NYHA class, LVEF and median NT-proBNP.
[c]$P < 0.05$.
AHR, adjusted hazard ratio; C.I., confidence interval; rest of abbreviations as per Table 1.

performance of GDF-15, NTpro-BNP, hs-cTnT, and hs-cTnI in HF from the SHOP study (2, 10), and now extend our findings to MR-proANP, MR-proADM, sST2, galectin-3, PAVP, PCT, and CNP. In addition to existing evidence (2, 8–11), we have demonstrated that the strong prognostic effects of the biomarkers in our

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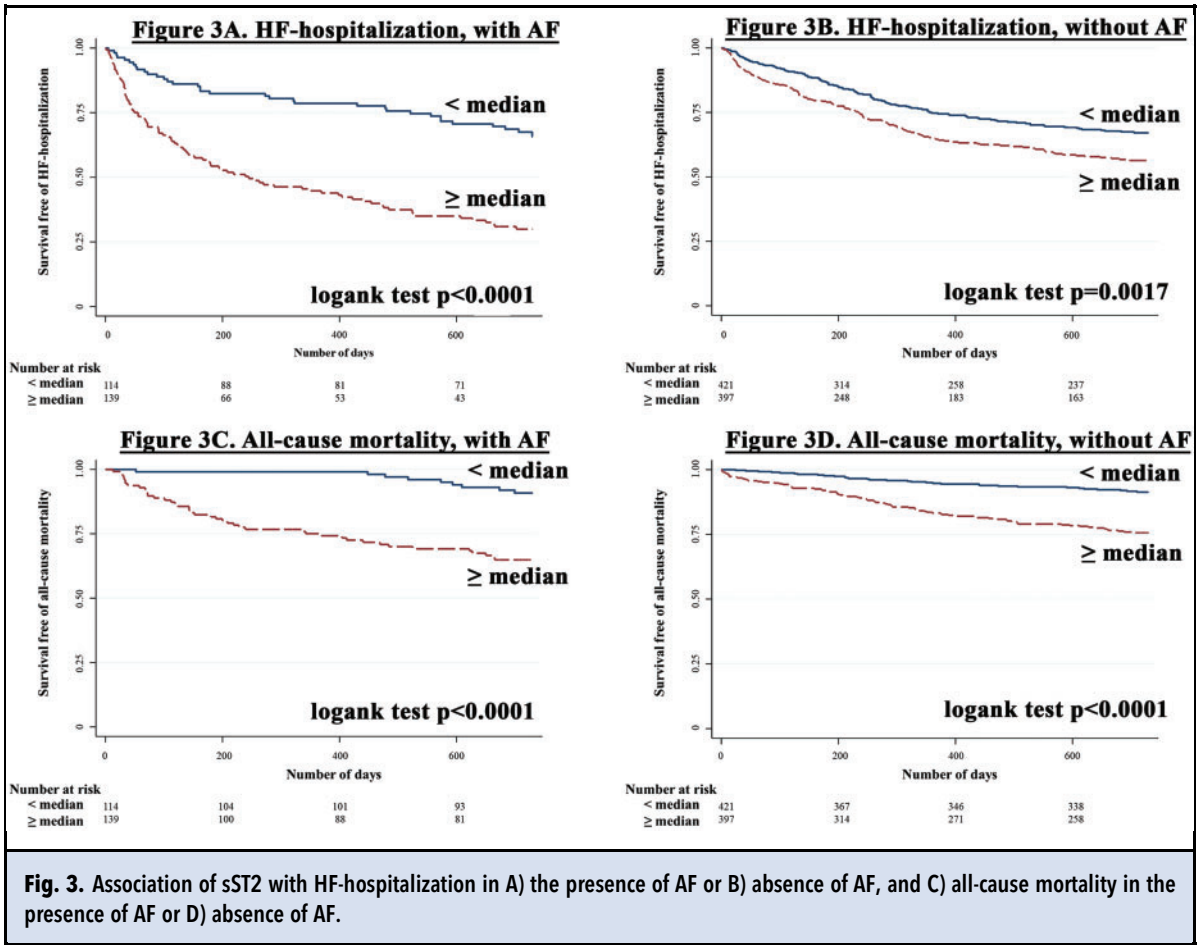

Fig. 3. Association of sST2 with HF-hospitalization in A) the presence of AF or B) absence of AF, and C) all-cause mortality in the presence of AF or D) absence of AF.

study were independent of clinical risk factors including ischemic etiology of HF, diabetes, CKD, and AF. Much prior work on the influence of AF on the prognostic significance of biomarkers has focused upon BNP or NT-proBNP. Although AF impaired the diagnostic performance of natriuretic peptides, interactions with prognostic outcomes were not detected in either acute or chronic HF (12, 13). Correspondingly, we did not find significant interactions with frequently measured prognostic HF markers NT-proBNP and the high-sensitivity cardiac troponins, as well as other novel biomarkers. Significant interactions were however detected between AF and the prognostic performance of galectin-3 and sST2, both of which are included in HF guidelines for additive risk stratification (7).

Galectin-3 mediates cardiac remodeling through macrophage migration, fibroblast proliferation and inflammatory response in HF (15). At thresholds above 17.8–30μg/L, galectin-3 is associated with increased HF-hospitalizations, death, and AF recurrence after ablation (5, 6, 16, 17). Although stronger incremental risk of HF-hospitalization or death with galectin-3 was seen in HFpEF (6), formal testing for interaction with AF had not been previously performed. At even lower concentrations (7.7 μg/L), galectin-3 was prognostic in HF, and confined to patients with concomitant AF in our study. Among patients with advanced HF, trans-renal galectin-3 concentration gradient was reduced and correlated with renal function with or without HF (18, 19). Despite CKD being the most important determinant of galectin-3 with and without AF, mean creatinine concentrations were similar regardless of AF status in our patients, and the prognostic performance of galectin-3 was independent of renal function. Additionally, the prognostic performance of galectin-3, increased with beta-adrenergic activation in animal models (18), may in part be due to the adverse hemodynamic effects of increased catecholamine production from enhanced neurohormonal activation and sympathetic activation in the presence of AF (20). Unlike NT-proBNP, which was influenced by underlying AF at time of measurement but not previous episodes (21), AF on ECG alone in sensitivity analyses had no influence on galectin-3. Despite its involvement in atrial

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fibrotic signaling pathways, galectin-3 is not a specific marker of cardiac fibrosis, but may also be increased in other chronic inflammatory cardiometabolic comorbidities including hypertension, diabetes, and obesity (17). This was further shown in the Framingham Heart Study, in which the association of galectin-3 with incident AF was attenuated after multivariable adjustment for clinical factors (22). The presence of these comorbidities predispose to fibrosis, with ventricular fibrosis seen in addition to atrial fibrosis in AF on cardiac imaging (23). The AF-specific nature of the prognostic performance of galectin-3 in HF may thus reflect the summative effects of a multitude of pathophysiological processes and an enhanced pro-fibrotic state associated with AF. Additionally, fibrotic changes in the myocardium may be less responsive to current HF-therapies unlike LV hemodynamics, and may account for the stronger association of galectin-3 with HF-hospitalizations as compared to GDF-15 or MR-proADM in AF. Consequently, the routine application of galectin-3 for HF risk stratification should be performed with consideration for the presence of AF.

sST2 is released under states of myocardial and vascular strain, promoting cardiac remodeling through myocardial fibrosis, hypertrophy, and apoptosis by inhibiting the interleukin-33/ST2L pathway (1, 4). sST-2 in chronic HF independently predicted all-cause and cardiovascular mortality (3), and median sST2 concentrations in our study (35.6 μg/L) were consistent with the reference limit of 35 μg/L considered useful for prognostication (4). At this threshold, sST2 provided a stronger prognostic signal in AF than without. To our knowledge, this is the first study to demonstrate an interaction between the predictive value of sST2 and AF. Previous assessments for interactions, including NT-proBNP, age, and rosuvastatin, with sST2 had been negative (24, 25) with the exception of beta-blockade in LV dysfunction (26). sST2's prognostic performance as a marker of mortality in HF has been attributed to a reflection of cumulative myocardial fibrosis (27). Although it is unclear if AF is a trigger or marker of preexisting fibrotic changes, the pro-fibrotic microenvironment in AF is not limited to the atria (23) and the presence and extent of LV late gadolinium enhancement on cardiac magnetic resonance imaging in AF was shown to be a powerful predictor of mortality (28).

Although contemporary HF guidelines recommend the use of galectin-3 and sST2 for additive risk stratification (7), the prognostic performance of both was confined only to AF when considering the effects of NT-proBNP, a widely used conventional biomarker in HF. It should be noted however that galectin-3 and sST2 are not cardiac-specific markers and have extracardiac tissue origins. Compared to NT-proBNP and troponin, both cardiomyocyte specific markers of hemodynamic load and cell damage, sST2 and galectin-3 have multiple origins and reflect background systemic inflammatory and pro-fibrotic diathesis. It has previously been reported that plasma concentrations of biomarkers such as galectin-3 and GDF-15 are influenced by the dynamic contribution of noncardiac tissues (29), while the lungs were the main source of sST2 in heart failure (30). The difference in ranked determinants of sST2 concentrations by AF status observed in our study further suggests that the poorer prognosis conferred by increased sST2 in AF may reflect the extent of organ involvement compared to those without AF. CKD had the strongest association with sST2 in our cohort of AF patients, while the CRIC study of patients with CKD found an association of sST2 with incident HF (31). Given that CKD and HF often coexist, the stronger prognostic performance of sST2 in AF likely represents the shared background pathophysiology with AF, reflecting the systemic inflammatory stimulus for AF, adverse cardiac remodeling and outcomes.

We note several limitations. Patients from SHOP were predominantly Asian and our findings may not be universally representative of other ethnicities with HF. Racial differences in the prognostic value of galectin-3 and sST2 have been suggested (32, 33) although formal testing for ethnic interactions between Asian and western populations in these 2 biomarkers have not been performed. We acknowledge that some patients may have undetected asymptomatic, paroxysmal AF, and their capture in future studies may extend our current results. The cohort of patients with HFpEF was small, precluding valid comparisons of the effects of AF on marker performance stratified by LVEF. Separately, galectin-3 and sST2 can also be increased in other systemic diseases, which may not have been accounted for in our study (18, 19, 33). The exact cause of mortality was not available in this study, and would have provided greater insights into the clinical association of sST2 with death in AF. Data from our study were from a single cohort and will need to be validated in other HF cohorts.

In conclusion, AF modified the prognostic utility of selected guideline-endorsed HF-biomarkers. Galectin-3 and sST2 were associated with increased adverse events only in the presence of AF, with sST2 strongly associated with all-cause mortality and galectin-3 more predictive of HF. Application of markers for prognostic purposes in HF requires consideration of the presence or absence of AF.

Supplemental Material

Supplemental material is available at *Clinical Chemistry* online

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Nonstandard Abbreviations: HF, heart failure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; BNP, B-type natriuretic peptide; sST2, soluble Suppressor of Tumorigenicity 2; MR-proADM, mid-regional propeptide adrenomedullin; AVP, arginine vasopression; GDF-15, growth differentiation factor -15; CNP, C-type natriuretic peptide; AF, atrial fibrillation; SHOP, Singapore Heart Failure Outcomes and Phenotypes; ECG, electrocardiogram; CKD, chronic kidney disease; hs-cTnT, high sensitivity troponin T; hs-cTnI, high sensitivity troponin I; PCT, procalcitonin; PAVP, co-peptin; MR-proANP, mid-regional pro-atrial natriuretic peptide; NT-proCNP, N-terminal pro C-type natriuretic peptide; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; LBBB, left bundle branch block; AHR, adjusted hazard ratio; C.I., confidence interval; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LAVI, left atrial volume index.

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