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Relation between soluble ST2, GDF-15 and hsTnI and Incident Atrial Fibrillation

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Abstract

Background—We investigated whether circulating concentrations of soluble ST2, growth differentiation factor-15 (GDF-15), and high-sensitivity troponin I (hsTnI) are associated with incident atrial fibrillation (AF), and whether these biomarkers, improve current risk prediction models including AF risk factors, B-type natriuretic peptide (BNP) and C-reactive protein (CRP).

Methods—We studied the relation between soluble ST2, GDF-15, and hsTnI and development of AF in Framingham Heart Study participants without prevalent AF. We used Cox proportional hazard regression analysis to examine the relation of incident AF during a 10-year follow-up period with each biomarker. We adjusted for standard AF clinical risk factors, BNP, and CRP.

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Disclosures

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Results—The mean age of the 3,217 participants was 59±10 years and 54% were women. During 10 years of follow-up, 242 participants developed AF. In age- and sex-adjusted models, GDF-15 and hsTnI were associated with risk of incident AF; however, after including the AF risk factors and BNP and CRP, only hsTnI was significantly associated with AF (hazard ratio per 1 standard deviation of log_e hsTnI, 1.12; 95% CI, 1.00–1.26; *P*=0.045). The C-statistic of the base model including AF risk factors, BNP and CRP was 0.803 (95% CI 0.777–0.830), and did not improve by adding individual or all 3 biomarkers. None of the discrimination and reclassification statistics was significant compared to the base model.

Conclusion—In a community-based cohort, circulating hsTnI concentrations were associated with incident AF. None of the novel biomarkers evaluated improved AF risk discrimination or reclassification beyond standard clinical AF risk factors and biomarkers.

Keywords

atrial fibrillation; biomarker; risk factor

Many risk factors predispose individuals to atrial fibrillation (AF) including advancing age, diabetes, hypertension, obesity, and cardiovascular conditions such as heart failure, valve disease, and myocardial infarction.^{1–3} In 2009, the Framingham Heart Study investigators described a multivariable model based on these risk factors to predict incident AF, which was recently updated and expanded to other populations from other regions in the United States and Western Europe, and includes both individuals of African and European origin.^{4,5}

There is an ongoing search for new markers that will improve risk prediction of AF.⁶ Recent research has focused on biomarkers to enhance prediction of incident AF and to understand the pathophysiological mechanisms underlying AF risk. An examination of a panel of 10 biomarkers, each representing distinct pathophysiological pathways, found only B-type natriuretic peptide (BNP) to improve AF risk stratification beyond well-established clinical risk factors. The inflammatory biomarker C-reactive protein (CRP) also was associated with AF, but did not further improve risk prediction beyond BNP.⁷

We sought to examine the relations between incident AF and 3 novel biomarkers, all of which are expressed or released by cardiovascular tissue. Specific pathophysiological data linking these circulating biomarkers to incident AF is currently lacking. However, these biomarkers are known to be related to heart failure and myocardial infarction. Thus, given the inter-relations between heart failure, myocardial infarction, and cardiac remodeling, we hypothesized that a role for these biomarkers in the prediction of incident AF.⁸ ST2 belongs to the Toll-interleukin-1 receptor family. A soluble form of ST2 is released from the myocardium in response to pressure or volume overload, and relates to indices of hemodynamic load.^{9,10} GDF-15 is a member of the transforming growth factor- β cytokine superfamily. GDF-15 expression is upregulated in cardiac myocytes in response to mechanical stretch. GDF-15 promotes anti-apoptotic, anti-hypertrophic, and anti-remodeling effects on the injured heart.¹¹ Cardiac troponin I (TnI) is a sarcomeric protein that serves as marker of myocardial damage in acute myocardial infarction.¹² New, high-sensitivity assays may reflect ongoing myocardial damage, proteolysis or myocardial contractile proteins turnover in heart failure.^{8,13} Recently, each of these biomarkers were reported to improve risk prediction for mortality, overall cardiovascular events and heart failure in the community.⁸

We hypothesized that the novel biomarkers soluble ST2, hsTnI, and GDF-15, are associated with incident AF. Further, we postulated that a combined analysis of these biomarkers would improve risk stratification beyond established AF risk factors, BNP and C-reactive protein (CRP).

Methods

Sample

The community-based Framingham Heart Study was founded in 1948 by enrolling 5,209 participants in the Original cohort. Starting in 1971, the offspring of the Original cohort and their spouses were enrolled in the Framingham Offspring Study (n=5124) and were followed every 4 to 8 years. We evaluated participants of the Framingham Heart Study Offspring Cohort who attended the sixth examination cycle (1995-1998; n=3532). Enrollment and follow up details have been described elsewhere.¹⁴ Participants with prevalent AF (n=115), missing biomarker data (n=183), or missing covariates (n=17) were excluded, leaving 3217 participants eligible for study. Follow up ended at the first AF event, death, or last contact out to 10 years from baseline (examination 6 date), whichever came first. The Institutional Review Board at Boston University Medical Center approved the study protocols for all examination cycles, and participants signed informed consents at each visit.

Clinical ascertainment—At the study visit, a physician-administered medical history and physical examination, and laboratory assessment was performed.¹⁵ AF was diagnosed if either atrial flutter or AF was present on an electrocardiogram obtained at a Framingham Heart Study clinic visit, an outside clinician visit, Holter monitor, or hospital records. A Heart Study cardiologist reviewed all AF electrocardiograms. Ascertainment of medications was by self-report. A Heart Study clinic physician measured blood pressure as the average of two measurements obtained in a sitting position. Current smoking was defined as self-reported regular use of cigarettes in the preceding year. Diabetes was defined by blood glucose of 126 mg/dL or greater, or the use of insulin or oral hypoglycemic agents. A clinically significant cardiac murmur was diagnosed in the presence of a systolic murmur that exceeded grade 2 of 6, or if any diastolic murmur was auscultated by a Heart Study clinic physician. A committee of three Framingham Heart Study physicians adjudicated heart failure¹⁶ and myocardial infarction¹⁷ events using published criteria.

Laboratory analyses

Blood samples were obtained at the Framingham Heart Study visit after an overnight fast, immediately centrifuged and frozen at -80°C . Biomarkers were measured as described,^{8,18} on samples that were not thawed previously. Plasma CRP concentration was measured with Dade Behring BN100 nephelometer (Deerfield, Illinois). Plasma BNP was measured with a high-sensitivity immunoradiometric assay (Shionogi, Osaka, Japan). The intra-assay coefficients of variation (CV) were 2.2% for CRP and 12.2% for BNP. Soluble ST2 concentration was measured using a high-sensitivity, second-generation enzyme-linked immunosorbent assay with a detection limit of 2 ng/mL (Presage® ST2, Critical Diagnostics), and interassay CV of 7.5% at low (25.6 ng/mL) and 6.0% at high ST2 concentrations (70.9 ng/mL). Plasma GDF-15 concentrations were measured with a pre-commercial, automated electrochemiluminescent immunoassay on a Cobas e 411 analyzer (Roche Diagnostics). The limit of detection was 10 ng/L, a linear measuring range up to 20,000 ng/L, an intra-assay CV of 0.8% and inter-assay CV of 2.3% at low concentrations (1,120 ng/L), and intra-assay CV of 1.1% and inter-assay CV of 1.0% at high concentrations (9,031 ng/L). Measurement of hsTnI was performed with an ultra-sensitive immunoassay for cardiac troponin I (Erenna hsTnI, Singulex). The limit of detection was 0.2 pg/mL, with an assay range of 0.5 to 70 pg/mL, and an interassay CV of 10.0% at low (4.7 ng/L) and 7.7% at high hsTnI concentrations (19.0 ng/L).

Statistical analysis

Since all biomarker measurements were right skewed, values were natural logarithmically-transformed ($\log_e$) and standardized (mean 0 and standard deviation 1) for analysis. We

present hazard ratios per one standard deviation of $\log_e$ -transformed marker concentration. For the multivariable-adjusted models, we used covariates including sex plus those published in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)-AF risk prediction model:⁵ age, smoking status, height, weight, systolic and diastolic blood pressure, hypertension treatment, diabetes status, heart failure and myocardial infarction. Multivariable-adjusted proportional hazards regression models were estimated to relate incident AF to each biomarker. The proportional hazard assumption was tested for every marker. In our primary analyses, we analyzed each biomarker separately in three models: (1) adjusting for sex and age; (2) model 1 plus AF risk factors; and (3), model 2 plus CRP and BNP. Adjusted cumulative AF incidence curves by tertiles of each marker were calculated using corrected group prognosis method.¹⁹

In secondary analyses, we reanalyzed the association between biomarkers and incident AF, excluding 121 individuals with baseline heart failure or myocardial infarction. We also evaluated for effect modification by sex. We performed exploratory analyses to examine if there was a non-linear association of soluble ST2, GDF-15, hsTnI using 5 knots at the 1st, 25th, 50th, 75th and 99th percentiles of each marker. For discrimination and reclassification analyses, we examined the incremental utility of each biomarker, separately and together, using the C statistic for time-to-event data,²⁰ reclassification and discrimination of predicted AF risk with integrated discrimination and net reclassification improvement indexes.²¹ We used risk thresholds of less than 5%, 5% to 10%, and greater than 10% over 10 years follow-up⁴ for the net reclassification improvement index.

To evaluate the performance of the models, we calculated a population attributable risk like statistic (pseudo PAR). We used predicted probabilities of AF at 10 years, grouped people into quintiles, treated these as “risk factor” levels and calculated PAR using Rockhill’s method 1998.²² Specifically, with the lowest risk group as the reference, we obtained the

relative risk (RR) for other groups. PAR was calculated as $100 * \sum_i p d_i \frac{(RR_i - 1)}{RR_i}$, where $p d_i$ is the proportion of total cases in risk group i . All analyses were performed using SAS software, version 9.2 (SAS Institute, Cary, NC), and a two-tailed p-value <0.05 was considered statistically significant.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. The Framingham Heart Study is supported by the National Heart, Lung and Blood Institute (contract NO1-HC-25195).

Results

Our study sample consisted of 3217 participants with a mean age of 59±10 years, and 54% were women. During 10 years of follow-up, 242 participants developed AF. Characteristics of participants are reported in Table 1. Pearson correlation coefficients varied from 0.03 (BNP and soluble ST2) to 0.31 (BNP and GDF-15) as shown in Supplementary Table 1.

Biomarkers and incident AF

The proportional hazards assumption was satisfied for every marker we tested. The covariates-adjusted cumulative incidence of AF according to tertiles of each biomarker is depicted in Figure 1. In multivariable models including each single biomarker in relation to incident AF, adjusted for age and sex, GDF-15 and hsTnI, but not soluble ST2, were associated with incident AF (Table 2). In multivariable models adjusting for AF risk factors, BNP, and CRP, only hsTnI remained significantly associated to AF (HR, 1.12; 95% CI, 1.00-1.26; $P=0.045$) (Table 2).

Incident AF risk prediction

The C-statistic of the base model including AF risk factors, BNP and CRP was 0.803 (95% CI 0.777–0.830); it was not improved by adding individual biomarkers or by adding all three (Table 3). None of the discrimination and reclassification statistics was significant, compared to the base model including AF risk factors, BNP and CRP. All models fit the data well. The pseudo PAR of a basic model (age and sex only) is 80.8%; for our full model (age, sex, AF risk factors, BNP, CRP and hsTnI) the pseudo PAR is 86.0% (Supplementary Table 3).

Secondary analyses

Eliminating individuals with heart failure or myocardial infarction at baseline did not substantively change our results (Supplementary Table 2). We did not observe effect modification by sex. As exploratory analyses, we performed spline modeling of multivariable-adjusted soluble ST2, GDF-15, and hsTnI to test whether there was a nonlinear relation between the $\log_e$ of GDF-15 and hsTnI and the risk of incident AF. Spline modeling revealed no evidence for nonlinear relations ($p=0.41$ for $\log_e$ GDF-15, $p=0.35$ for $\log_e$ ST2 and $p=0.11$ for $\log_e$ hsTnI). Thus, we did not observe a threshold effect for any marker tested (Supplementary Figure 1).

Discussion

In the present study, hsTnI was significantly related with incident AF, even after adjustment for well known clinical risk factors, BNP and CRP. The base model including AF risk factors, BNP and CRP, performed reasonably well (C-statistic of 0.803) and was not further improved by adding soluble ST2, GDF-15, hsTnI, individually or together.

Despite the great interest in soluble ST2, GDF-15 and hsTnI in coronary heart disease,^{23,24} heart failure,²⁵⁻²⁸ and ischemic stroke,^{29,30} and in the general population where concentrations of each have been shown to predict future heart failure, coronary heart disease, and mortality,^{8,31-33} only sparse data are available relating these biomarkers to risk of incident AF. To date, contradictory results have been published regarding the value of elevated TnI levels to predict AF in the post-operative setting after coronary artery bypass graft surgery.³⁴ There have been few reports on the predictive utility of hsTnI for AF in community- or hospital-based settings. One small community-based Japanese study including 220 residents without apparent cardiovascular disease reported that hsTnT concentrations were higher in the 12 (6%) patients with AF at health checkup examination than in those without AF.³⁵ Another study including 382 patients from the GISSI-AF trial, a prospective randomized study to determine the effect of valsartan on reduction of recurrent AF, found that hsTnT was related to recurrence of AF after 6 and 12 months.³⁶ To our knowledge, there has been only one prior study evaluating GDF-15 levels in hypertrophic cardiomyopathy patients that were higher in individuals with prevalent AF.³⁷

Since AF and other cardiovascular diseases, such as heart failure and coronary heart disease share many risk factors and underlying pathophysiologic mechanisms, we hypothesized that biomarkers linked to these cardiovascular disorders could be of value in predicting incident AF. Based on the concept that elevated levels of these biomarkers may be detectable long before the onset of overt cardiovascular disease, biomarkers may have prognostic value.⁸ To date, there are no studies of these three biomarkers, single or in combination, in relation to incident AF in a large community-based cohort. We found a low correlation between each biomarker, suggesting that each biomarker may provide non-redundant information. Only, hsTnI was found significantly related with incident AF; however, AF risk prediction was not improved. These biomarkers may be of prognostic value in individuals with diagnosed AF,

as was demonstrated for troponin. TnI predicts death, myocardial infarction, revascularization,³⁸ and thromboembolic events (i.e. stroke or systemic embolus),³⁹ in individuals with known AF. It is possible that soluble ST2, GDF-15 and hsTnI may be useful as markers of elevated risk after AF onset, rather than markers of incident AF.

Strengths and limitations

The Framingham Heart Study is a well-characterized, community-based sample with extensive routine ascertainment of clinical risk factors for AF and other cardiovascular conditions, rigorous clinical ascertainment of incident AF, and long-term follow up. However, our analysis has some limitations that merit consideration. First, we had excellent power for modest but clinically meaning effects, but low power to detect small effects (80% power for HR of 1.16 and 90% power to detect a HR >1.17 at $p=0.05$). Second, we considered the expected number of events across the three levels of risk, when setting the cutoffs for the risk levels in the net reclassification improvement index to evaluate the incremental utility of each biomarker, but acknowledge that the cutpoints may vary by data set. Third, we cannot rule out the possibility that a sample with a greater burden of cardiovascular risk factors may have had an association between one of the biomarkers and incident AF. Fourth, we did not have serial biomarker measurements during follow-up, precluding a detailed study of the time course between change in biomarker concentration and incident AF. Fifth, we did not distinguish between AF types (e.g. paroxysmal vs. persistent vs. permanent atrial fibrillation vs. atrial flutter), and we may have overlooked asymptomatic AF. Therefore we cannot exclude the possibility of reverse causation; asymptomatic undetected AF may be a causative factor for higher concentrations of biomarkers. Lastly, our analyses were limited to a cohort of middle age to older adults of European ancestry, and the results may not be generalizable to other racial/ethnic groups or younger individuals.

Conclusion

Of the three novel biomarkers we investigated in a large community-based cohort, hsTnI was associated with incident AF, though with modest effect size. None of the 3 biomarkers substantively increased risk prediction of AF beyond known AF risk factors and markers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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B.

Time (yr)	0	2	4	6	8	10
Number at risk	3217	3156	3063	2962	2843	2677

C.

Figure 1. Adjusted cumulative risk of atrial fibrillation, according to tertiles of each biomarker (Figure 1A: soluble ST2, Figure 1B: GDF-15, Figure 1C: hsTnI). Presented are 1-average of cause-specific survival functions,¹⁹ for which death was deemed a censoring factor. Covariates included age, sex, height, weight, systolic and diastolic blood pressure, hypertension treatment, smoking status, diabetes, prevalent heart failure, prevalent myocardial infarction, CRP and BNP.

Table 1

Baseline characteristics (n=3217).

Clinical	
Age (years)	59±10
Sex (women)	1733 (54%)
Height (inches)	66±4
Weight (lbs)	173±38
Systolic blood pressure (mm Hg)	128±19
Diastolic blood pressure (mm Hg)	76±9
Current smoking	502(16%)
Hypertension treatment	882(27%)
Diabetes	352(11%)
Heart failure	19(1%)
Myocardial infarction	113(4%)
Biomarker	
BNP (pg/mL)*	8.3 (4.0, 18.2)
Log _e BNP	2.27±0.88
CRP (mg/L)*	2.03(0.92,4.67)
Log _e CRP	0.75±1.16
ST2 (ng/mL)*	20.8 (16.6, 25.8)
Log _e ST2	3.04±0.35
GDF-15 (ng/mL)*	1031 (809, 1340)
Log _e GDF-15	7.00±0.42
hsTnI (pg/mL)*	1.32 (0.87, 2.11)
Log _e hsTnI	0.45±0.75

Abbreviations: BNP = B-type natriuretic peptide; CRP = C-reactive protein; GDF-15 = growth-differentiation factor-15; hsTnI = high-sensitivity troponin I; ST2 = soluble ST2. Continuous values are mean±SD; untransformed biomarkers are median (25th & 75th percentile); Binary traits are n (%).

Table 2

Multivariable-adjusted proportional hazards regression models for AF, separately for each biomarker.

Adjustment factors	Log _e ST2		Log _e GDF-15		Log _e hsTnI	
	Hazard ratio*	P Value	Hazard ratio*	P Value	Hazard ratio*	P Value
Age and sex	1.06 (0.92-1.22)	0.39	1.31 (1.14-1.49)	<0.0001	1.25 (1.13-1.37)	<0.0001
Sex + CHARGE-AF covariates [†]	1.02 (0.89-1.17)	0.76	1.15 (0.99-1.32)	0.061	1.18 (1.07-1.32)	0.002
Sex + CHARGE-AF covariates [†] + log _e CRP + log _e BNP	1.00 (0.87-1.15)	0.99	1.05 (0.91-1.21)	0.49	1.12 (1.00-1.26)	0.045

Abbreviations: BNP = B-type natriuretic peptide; CRP = C-reactive protein; GDF-15 = growth-differentiation factor-15; hsTnI = high-sensitivity troponin I; ST2 = soluble ST2.

* Hazards ratios for incident AF are shown per 1 SD (0.35 for ST2, 0.42 for GDF-15, and 0.75 for hsTnI) increment in log_e transformed ST2, GDF-15, or hsTnI, respectively, and 95% confidence interval.

[†] CHARGE-AF covariates: age, smoking status, height, weight, systolic and diastolic blood pressure, hypertension treatment, diabetes status, heart failure and myocardial infarction.

Table 3

Models assessed for discrimination and risk reclassification.

Model	C-statistic		Integrated discrimination improvement		Net reclassification improvement index [†]	
	Statistic (95% CI)	P value [‡]	Statistic (95% CI)	Relative value (%)	Statistic (95% CI)	P value [‡]
Base model [§]	0.803 (0.777–0.830)	–	–	–	–	–
Base model + log _e ST2	0.803 (0.777–0.830)	0.66	5 × 10 ^{–6} 8 × 10 ^{–6} –2 × 10 ^{–5}	0.003	0	–
Base model + log _e GDF-15	0.803 (0.777–0.830)	0.32	5 × 10 ^{–4} (–8 × 10 ^{–4} –1.9 × 10 ^{–3})	0.4	–0.010 (–0.026–0.0069)	0.24
Base model + log _e hsTnI	0.804 (0.778–0.831)	0.17	2 × 10 ^{–3} (–6 × 10 ^{–4} –4 × 10 ^{–3})	1.4	–0.011 (–0.036–0.013)	0.37
Base model + all three	0.804 (0.779–0.831)	0.15	2 × 10 ^{–3} (–1 × 10 ^{–3} –5 × 10 ^{–3})	1.5	–0.003 (–0.028–0.022)	0.83
Biomarkers						

Abbreviations: BNP = B-type natriuretic peptide; CRP = C-reactive protein; GDF-15 = growth-differentiation factor-15; hsTnI = high-sensitivity troponin I; ST2 = soluble ST2.

[†]Corresponds to 10-year risk thresholds of <5%, 5–10%, and >10%.

[‡]Versus base model.

[§]Base model includes sex + CHARGE-AF covariates (age, smoking status, height, weight, systolic and diastolic blood pressure, hypertension treatment, diabetes status, heart failure and myocardial infarction) + log_e CRP + log_e BNP