ORIGINAL RESEARCH

# Proteomics Profiling and Risk of New-Onset Atrial Fibrillation: Framingham Heart Study

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***Background*—**Prior studies relating proteomics markers to incident AF screened for limited numbers of proteins.

***Methods and Results*—**We performed proteomics assays among participants from the Framingham Heart Study Offspring attending their fifth examination. Plasma protein levels (n=1373) were measured by the SOMAscan proteomic profiling platform. We used robust inference for the Cox proportional hazards model to relate each protein level with incident AF. In addition, we examined the association between AF-related genetic loci and levels of proteins associated with AF. Our study included 1885 participants (mean age 55±10 years, 54% women) who had proteomic profiles measured. A total of 349 participants developed AF during follow-up (mean follow-up 18.3 years). We observed that 8 proteins were significantly associated with incident AF after adjusting for age, sex, technical covariates, and correction for multiple testing ($P<0.05/1373=3.6\times10^{-5}$). After additional adjustments for clinical factors associated with AF, ADAMTS13 and N-terminal pro-B-type natriuretic peptide remained significantly associated with the risk of incident AF (hazard ratio, 0.78; 95% CI, 0.70–0.88; and 1.44; 95% CI, 1.22–1.70, respectively; $P<3.6\times10^{-5}$ for both). None of the 8 proteins were encoded by genes at AF-related genetic loci previously identified by genome-wide association studies.

***Conclusions*—**We identified 8 proteins associated with risk of incident AF after adjustment for age and sex; 2 proteins were associated with AF after adjustment for AF risk factors. Future studies are needed to replicate our findings, identify whether the markers are mechanistically related to AF development, and whether they are clinically useful for identification of future AF risk.
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**Key Words:** atrial fibrillation • biomarker • proteomics • risk

Approximately 1 in 3 whites and 1 in 5 blacks will develop atrial fibrillation (AF) in their lifetime.[1–3] The risk of AF increases with advancing age, European ancestry, smoking, higher height, weight, and blood pressure, antihypertensive medication use, diabetes mellitus, and history of myocardial infarction and heart failure.[4] Independent of traditional clinical factors, various biomarkers have been identified in relation to the risk of incident AF including markers of myocardial necrosis,[5–7] myocardial stress,[7–13] inflammation,[7,14–16] oxidative stress,[17] and mineral metabolism.[18,19] Identification of novel biomarkers may advance our understanding of disease mechanisms, enhance opportunities for risk prediction, and potentially provide new therapeutic targets for AF.

Proteomic profiling enables systematic high-throughput analysis of proteins and holds the promise to substantially accelerate novel biomarker discovery. Relatively unbiased

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## Clinical Perspective

### What Is New?

- In a community-based prospective cohort study, we identified novel biomarkers associated with incident atrial fibrillation after screening for 1373 proteins using proteomics profiling.
- Both ADAMTS13 and N-terminal pro-B-type natriuretic peptide remained significantly associated with incident atrial fibrillation after multivariable adjustment and Bonferroni correction.

### What Are the Clinical Implications?

- Identification of ADAMTS13 may suggest a novel pathophysiological mechanism or a risk marker for atrial fibrillation.

proteomics approaches have the advantage of allowing simultaneous screening for large numbers of proteins involved in different biological pathways. Recently, 2 longitudinal cohort studies have reported proteomic profiling and the risk of new-onset AF.[13,14] The first study used a proximity extension assay to screen 92 proteins in community-based cohorts of older adults in Sweden and identified 7 proteins that were associated with incident AF after adjustment for age and sex.[13] The second study focused on 75 inflammatory marker proteins identified from proximity extension assays, none of which were associated with new-onset AF after age and sex adjustment.[14] In our current study, we report the use of single-stranded DNA-based aptamers as affinity reagents to screen for 1373 proteins and identify novel biomarkers that are associated with risk of incident AF in a prospective cohort study.

## Methods

### Data Sharing

The results of proteomic assay for all 1373 proteins measured in the Framingham Heart Study are available in the database of Genotypes and Phenotypes.[20] Additional results and analyses not shown in the article are available from the authors upon request. The details of the commercially available aptamer-based proteomics assay are included in the article. Noncommercial study materials are available to other researchers for purposes of reproducing the results or replicating the procedure, as respective Institutional Review Board and Material Transfer Agreements permit.

### Study Samples

The Framingham Heart Study is a community-based cohort initiated in 1948. The Framingham Offspring cohort (Second Generation) was recruited in 1971. They are the offspring and the spouses of the offspring of the Original cohort.[21] The present study focused on 1885 Offspring cohort participants who attended the fifth examination (1991–1995) and completed an assessment of proteomics profiling. Twenty-eight individuals with AF at baseline were excluded after proteomics profiling. All participants gave written informed consent. The study was approved by the Institutional Review Boards of Boston University Medical Center, Massachusetts General Hospital, and Beth Israel Deaconess Medical Center. All aspects of the study were performed in compliance with relevant guidelines and regulations.

### Covariate Assessments

Current smoking was defined as smoking ≥1 cigarettes per day within 1 year preceding the Framingham Heart Study visit, similar to our previously studies.[1] Systolic and diastolic blood pressures were measured twice with subjects in the seated position. Participants were classified as having diabetes mellitus if their blood glucose was ≥200 mg/dL or fasting glucose was ≥126 mg/dL or if they were using insulin or oral hypoglycemic medications.[22] A panel of 3 physicians determined myocardial infarction and heart failure based on the criteria used previously.[23]

### AF Ascertainment

The AF status was ascertained through multiple sources in the Framingham Heart Study. A 12-lead ECG was conducted on each participant during clinic visits scheduled every 4 to 8 years. The cardiovascular history was also solicited during surveillance interviews biennially,[24,25] and from hospitalizations related to cardiovascular disease and clinician visits. All ECGs, including the Framingham Heart Study ECG, and other electrocardiographic data (ie, Holter monitoring) performed for clinical reasons, were reviewed by at least 2 cardiologists to adjudicate incident AF. Participants with prevalent AF at baseline were excluded from the analysis.

### Proteomics Profiling

Details of proteomics profiling have been described previously.[26,27] In brief, citrate-plasma was obtained from blood samples that were collected during clinical visits and stored at −80°C.[28] Protein levels in the plasma samples were measured by the SOMAscan platform, which uses single-stranded DNA-based aptamers to capture conformational protein epitopes.[29] The technology has been validated in a study of cardiovascular disease.[26,30] Samples were assayed in 2 batches (n=821 and 1092, respectively). The measurements were $\log_e$ transformed and standardized to mean=0 and SD=1 in each batch separately after adjusting for age and sex. The distribution of the significant $\log_e$-transformed protein

concentrations is shown in Table S1. We previously published median intra-assay coefficient of correlation of 8.2% and interassay coefficient of correlation of 7.8% using the same assay in the Framingham Heart Study.[26] A total of 1373 proteins were assayed.

## Statistical Analyses

Baseline characteristics were described as mean±SD for continuous covariates and counts (%) for dichotomous covariates. Our primary analysis tested the association between protein level and incident AF. Cox proportional hazards regression models with clustering on pedigrees and robust sandwich estimators were used to relate each protein level to incident AF (censored at the last follow-up time or death). The analysis was adjusted for age and sex. In addition, we conducted a multivariable analysis adjusted for previously reported AF risk factors,[4] including smoking, height, weight, systolic blood pressure, diastolic blood pressure, antihypertensive treatment, diabetes mellitus, prevalent myocardial infarction, and prevalent heart failure. In an exploratory analysis, we performed a forward selection analysis by first adjusting for height and weight, followed by systolic and diastolic blood pressures, and finally by adjusting for the rest of covariates. Given the difference in the protein profiling batches, the 2 batches were analyzed separately, and the summary results from both batches were meta-analyzed using the inverse-variance weighting approach. Bonferroni correction was used to correct for multiple testing; we considered $P<0.05/1373=3.64\times10^{-5}$ statistically significant.

## Association With AF-Related Genetic Loci

We also examined the association between AF-related genetic loci and the circulating proteins that were significantly associated with incident AF after age- and sex-adjustment, and Bonferroni correction. The analysis was restricted to the 97 genetic loci that were previously reported to associate with AF susceptibility by genome-wide association studies.[31–34] Linear mixed effects regression models were used to test the association between each genetic variant and protein levels, in which protein levels were treated as the dependent measures and genetic variants were treated as the predictors. The analysis was adjusted for age, sex, and the family structure in the Framingham Heart Study. We used Bonferroni correction to account for multiple testing, and the significance was claimed if the $P$ value of the association was $>0.05/$(number of proteins$\times$97 single nucleotide polymorphisms).

# Results

The descriptive characteristics of the 1885 participants are provided in Table 1. The mean age of the sample was 55±10 years and 54% were women. A total of 349 participants developed new-onset AF during follow-up (mean follow-up 18.3 years).

## Association of Protein Levels With Incident AF

Table 2 reports 8 proteins that were significantly associated with incident AF after age and sex adjustment and correction for multiple testing ($P<3.64\times10^{-5}$). The concentration distribution of these proteins is shown in Table S1. Six were associated with decreased risk and 2 were associated with increased risk of incident AF. Neural cell adhesion molecule 1 to 120-kDa isoform had the most significant association. After further adjusting for clinical factors associated with incident AF, a disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13) protein and N-terminal pro-B-type natriuretic peptide remained significantly associated with risk of incident AF. In exploratory analyses with forward covariate selection, the remaining 6 proteins were no longer significant after adjusting for weight and height (Table S2).

Among the 349 incident AF/atrial flutter cases in our study, 39 participants had atrial flutter. We performed a performed a sensitivity analysis by excluding the atrial flutter sample, and the association remained largely the same (Table S3).

## Association of AF-Related Genetic Variants With Protein Levels

We also examined whether any of the 8 circulating proteins that were significantly associated with incident AF were also associated with any of the reported 97 AF-related genetic

**Table 1.** Baseline Characteristics of Study Sample by Whether or Not Participants Developed Incident AF

| Variable | AF Cases (n=349) | Referents (N=1536) |
|---|---|---|
| Age, y | 61±9 | 54±10 |
| Women | 144 (41.3%) | 872 (56.8%) |
| Height, cm | 169±10 | 167±9 |
| Weight, kg | 82±17 | 76±16 |
| Current smoker | 52 (14.9%) | 315 (20.5%) |
| Systolic blood pressure, mm Hg | 134±20 | 125±18 |
| Diastolic blood pressure, mm Hg | 75±10 | 74±10 |
| Antihypertensive medication use | 117 (33.7%) | 241 (15.8%) |
| Diabetes mellitus | 49 (14.0%) | 94 (6.1%) |
| Prevalent heart failure | 1 (0.3%) | 4 (0.3%) |
| Prevalent myocardial infarction | 19 (5.4%) | 31 (2.0%) |

AF indicates, atrial fibrillation.
Values are n (%), or mean±SD.

**Table 2.** Protein Biomarkers Associated With Incident AF

| | Age and Sex Adjusted | | Multivariable Adjusted* | |
|---|---|---|---|---|
| Protein | HR (95% CI)† | *P* Value‡ | HR (95% CI)† | *P* Value‡ |
| NCAM-120 | 0.74 (0.67–0.82) | $4.29\times10^{-8}$ | 0.84 (0.74–0.95) | $5.20\times10^{-3}$ |
| WFIKKN2 (WFKN2) | 0.75 (0.67–0.83) | $1.58\times10^{-7}$ | 0.86 (0.76–0.96) | $1.09\times10^{-2}$ |
| Ntrk3 (TrkC) | 0.75 (0.68–0.84) | $6.06\times10^{-7}$ | 0.82 (0.73–0.92) | $9.90\times10^{-4}$ |
| EGFR (ERBB, ERBB1) | 0.75 (0.67–0.84) | $1.18\times10^{-6}$ | 0.82 (0.72–0.93) | $1.48\times10^{-3}$ |
| ADAMTS13 (ATS13) | 0.77 (0.69–0.86) | $2.23\times10^{-6}$ | 0.78 (0.70–0.88) | $1.75\times10^{-5}$ |
| Angiopoietin-2 | 1.27 (1.15–1.41) | $3.09\times10^{-6}$ | 1.16 (1.04–1.31) | $1.09\times10^{-2}$ |
| NT-proBNP§ | 1.44 (1.24–1.69) | $4.17\times10^{-6}$ | 1.44 (1.22–1.70) | $1.46\times10^{-5}$ |
| BMPR1A | 0.75 (0.66–0.85) | $5.93\times10^{-6}$ | 0.82 (0.72–0.93) | $2.32\times10^{-3}$ |

ADAMTS13 indicates a disintegrin and metalloproteinase with thrombospondin motifs 13; AF, atrial fibrillation; BMPR1A, bone morphogenetic protein receptor type-1A; EGFR, epidermal growth factor receptor; HR, hazard ratio; NCAM-120, neural cell adhesion molecule 1, 120 kDa isoform; NT-proBNP, N-terminal pro-brain natriuretic peptide; TrkC, tropomyosin receptor kinase C; WFKN2, WAP, Kazal, immunoglobulin, Kunitz and NTR domain-containing protein 2.

*Covariates include smoking, height, weight, systolic blood pressure, diastolic blood pressure, antihypertensive treatment, diabetes mellitus, prevalent myocardial infarction, and prevalent heart failure.

†Hazard ratio expressed per standard deviation of the protein concentration.

‡Significance level of $P<0.05/1373=3.64\times10^{-5}$.

§This protein was only measured in 1075 samples because of differences in SOMAscan platform between Batch 1 and Batch 2.

loci.[31–33] None of the 776 associations (8 proteins×97 single nucleotide polymorphisms) reached the significance cutoff ($P<6.44\times10^{-5}$). The top 20 associations out of 776 are listed in Table S4. In addition, none of the 8 proteins were encoded by the AF-related genetic loci.

## Discussion

In our community-based prospective cohort study, we tested 1373 plasma proteins and observed that 8 proteins were associated with risk of incident AF after adjustment for age and sex. The currently known biological functions of the 8 proteins are described in Table S5. Both ADAMTS13 and N-terminal pro-B-type natriuretic peptide remained significantly associated with incident AF after multivariable adjustment and Bonferroni correction.

N-terminal pro-B-type natriuretic peptide, a marker of ventricular remodeling, previously has been reported to be associated with incident AF by multiple prospective population-based studies.[8–13] ADAMTS13 is a von Willebrand factor protease, and its deficiency is found in thrombotic thrombocytopenic purpura. Previous case–control studies have shown that lower ADAMTS13 protein level was associated with chronic and paroxysmal AF.[35] In addition, higher von Willebrand factor/ADAMTS13 ratio was significantly associated with chronic AF and left atrial remodeling[35] and higher von Willebrand factor/ADAMTS13 ratio drawn 24 hours after cardioversion was associated with higher risk of AF recurrence.[36] It is possible that atrial remodeling, which promotes AF, also promotes prothrombotic milieu; ADAMTS13 may be a marker of the prothrombotic environment. Alternatively, the prothrombotic dysregulation as represented by decreased levels of ADAMTS13 may directly promote AF formation. Interestingly, prior prospective cohort studies have shown that ADAMTS13 is associated with incident myocardial infarction and ischemic stroke.[37,38] Whether ADAMTS13 dysregulation leads to the thrombotic events or AF was unrecognized in these studies merits further investigation.

Of the remaining 6 proteins that were significantly associated with incident AF after adjusting for age and sex, BMPR1A and angiopoietin-2 may be of particular interest in cardiovascular research. BMP ligands and receptors including BMPR1A are essential for embryonic and cardiac development, and mutations in the proteins are associated with pulmonary arterial hypertension and hereditary hemorrhagic telangiectasia.[39] In addition, recent work has shown that the BMP signaling pathway plays an important role in the development of atherosclerosis and myocardial remodeling.[39–41] Angiopoietins are endothelial growth factors that regulate angiogenesis and vascular function. Increased levels of angiopoietin-2 have been observed in patients with myocardial infarction,[42] heart failure,[43] peripheral artery disease,[44] and end-stage renal disease.[45] The results of our study may suggest a novel downstream effect of BMPR1A and angiopoietin-2.

To date, there have been 2 longitudinal cohort studies that have used the *proteomic approach to study protein biomarkers* associated with incident AF.[13,14] The Swedish cohort study[13] used the Olink Proseek Multiplex Cardiovascular 96×96 kit to screen for 92 proteins. The study sample included 2 community-based samples from Uppsala, Sweden: the Prospective Investigation of the Vasculature in Uppsala

Seniors (PIVUS) and the Uppsala Longitudinal Study of Adult Men (ULSAM) cohorts. In PIVUS (mean age 70 years, 51% women), there were 148 incident AF cases among 978 participants during the median follow-up of 10 years. In ULSAM (mean age 77.5 years, 0% women), there were 123 incident AF cases among 725 participants during the median follow-up of 7.9 years. In the combined analysis of both cohorts, the study found 7 proteins to be associated with the risk of incident AF after age and sex adjustment. Two of the 7 proteins, N-terminal pro-B-type natriuretic peptide and IL-6, remained significantly associated after multivariable adjustment in the Swedish cohort study (Table S6). The second cohort study used a community-based sample from Bruneck, Italy[14] (mean age 58.8 years, 49% women) to screen specifically for inflammatory biomarkers using the Olink Proseek Multiplex Cardiovascular 96×96 and the Proseek Multiple Inflammation I 96×96 kits. There were 117 new AF cases among 880 participants during 20-year follow-up. The Italian study reported the results of 75 inflammatory biomarkers including fibroblast growth factor-23, IL-6, fatty acid binding protein 4, none of which were associated with AF after age and sex adjustment in their sample (Table S6). In our study, we did not find evidence of nominally or Bonferroni corrected statistically significant association for fibroblast growth factor-23 or IL-6.

In our study, we did not find evidence of a nominally or Bonferroni corrected statistically significant association for previously reported AF-related proteins from *nonproteomic immunoassays* including troponin,[5–7] C-reactive protein,[11,12,14] vascular cell adhesion molecule 1,[14] fibroblast growth factor-23,[18,19] and IL-6[46] (Table S6). Various factors could have contributed to the discrepancy. In the current study, we tested 1373 proteins in a modest-size cohort; modest power and accounting for multiple testing may have led to false-negative findings. Differences in the characteristics of the cohorts could be another important factor. We measured the proteins levels at a relatively young age (55±10 years versus 70 and 77 years for the 2 cohorts in the Swedish study[13]) and had a relatively long follow-up period (mean 18.3 years versus median 7.9 and 10 years for the 2 cohorts in the Swedish study[13]). Previous studies measured protein levels using targeted single protein immunoassays or proximity extension assay; it may be challenging to compare them directly with the current study because of differences in sensitivity and specificity of the different assays. Further investigation is necessary to understand the variations between different assays in capturing different protein isoforms.

Our study has several limitations. We combined atrial flutter and AF despite their distinct electrophysiological differences in disease mechanisms. We also acknowledge that we were limited in our ability to correctly classify paroxysmal versus persistent AF, and hence we did not distinguish AF subtypes in our AF outcome. New-onset AF may have been underreported in our study because we did not have continuous ECG monitoring, and AF is often paroxysmal and asymptomatic. Protein levels were measured at a single time point, and therefore we were unable to test whether changes in protein concentrations over time are associated with development of new-onset AF. The lack of association between the protein levels and the AF-related genetic variants may be in part because of lack of power and false-negative findings because of correction for multiple testing but also because of the fact that the proteins are likely regulated by multiple genetic loci. Another possible reason may include the heterogeneous nature of AF mechanisms such as genetic predisposition to AF, atrial fibrosis, prothombotic dysregulation, and other mechanisms.[47] In addition, the fact that the 8 proteins were not encoded by the AF-related genetic variants suggests that these proteins might not be causal to AF pathogenesis. For instance, they might be biomarkers for underlying AF mechanisms or subclinical AF. Future investigation such as a gene-annotation approach would be helpful to test our proteins on a genomic level and better understand the connection between genetic loci and protein concentration.[48]

Our study cohort was predominantly of European ancestry, and our results may not be generalizable to other races or ethnicities. In addition, as with any high-throughput "-omics" studies, batch effects may limit reproducibility of our results. Finally, although our proteomics platform is the one of the largest to date in cardiovascular research, we were only able to detect proteins that were included in the platform.

In conclusion, in our proteomics screening of 1373 proteins in a longitudinal cohort study, we found 8 proteins to be associated with the risk of incident AF after adjustment for age and sex, and 2 proteins were associated with multivariable adjustment. Further studies are needed to replicate our findings and identify the pathophysiological mechanisms underlying the reported associations and their clinical implications.

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# Supplemental Material

**Table S1. Distribution of the significant $log_e$-transformed protein concentration among samples.**

| Protein | Batch 1† | | Batch 2† | |
|---|---|---|---|---|
| | AF cases | Referents | AF cases | Referents |
| NCAM-120 | 8.30±0.20 | 8.30±0.20 | 9.19±0.21 | 9.25±0.20 |
| WFKN2 | 7.79±0.28 | 7.82±0.26 | 8.33±0.28 | 8.43±0.29 |
| TrkC | 7.35±0.21 | 7.39±0.22 | 7.77±0.20 | 7.83±0.23 |
| ERBB1 | 9.83±0.16 | 9.90±0.14 | 10.14±0.15 | 10.21±0.15 |
| ADAMTS13 | 7.97±0.20 | 8.05±0.23 | 8.25±0.26 | 8.38±0.25 |
| Angiopoietin-2 | 6.24±0.26 | 6.17±0.24 | 4.60±0.29 | 4.56±0.24 |
| NT-proBNP§ | | | 8.37±0.78 | 8.06±0.73 |
| BMPR1A | 5.86±0.29 | 5.92±0.35 | 6.27±0.28 | 6.35±0.26 |

ADAMTS13: a disintegrin and metalloproteinase with thrombospondin motifs 13; BMPR1A: bone morphogenetic protein receptor type-1A; NCAM-120: Neural cell adhesion molecule 1, 120 kDa isoform; NT-proBNP: N-terminal pro-brain natriuretic peptide; SBP: systolic blood pressure; DBP: diastolic blood pressure; TrkC: tropomyosin receptor kinase C; WFKN2: WAP, Kazal, immunoglobulin, Kunitz and NTR domain-containing protein 2

†Data are expressed as mean ± SD
§This protein was only measured in Batch 2 samples due to differences in SOMAscan platform between Batch 1 and Batch 2.

**Table S2.** Stepwise forward selection analysis for the 8 proteins significantly associated incident AF after age and sex adjustment.

| | Adjusted for age and sex | | Adjusted for age and sex, weight, height | | Adjusted for age and sex, weight, height, SBP, DBP | | Multivariable-adjusted model* | |
|---|---|---|---|---|---|---|---|---|
| **Protein** | **HR (95% CI)†** | **p value‡** | **HR (95% CI)†** | **p value‡** | **HR (95% CI)†** | **p value‡** | **HR (95% CI)†** | **p value‡** |
| NCAM-120 | 0.74 (0.67-0.82) | $4.29x10^{-8}$ | 0.8 (0.71-0.89) | $1.30x10^{-4}$ | 0.81 (0.72-0.91) | $4.83x10^{-4}$ | 0.84 (0.74-0.95) | $5.20x10^{-3}$ |
| WFKN2 | 0.75 (0.67-0.83) | $1.58x10^{-7}$ | 0.81 (0.72-0.91) | $3.27x10^{-4}$ | 0.83 (0.74-0.93) | $1.62x10^{-3}$ | 0.86 (0.76-0.96) | $1.09x10^{-2}$ |
| TrkC | 0.75 (0.68-0.84) | $6.06x10^{-7}$ | 0.8 (0.72-0.9) | $2.19x10^{-4}$ | 0.81 (0.72-0.91) | $3.81x10^{-4}$ | 0.82 (0.73-0.92) | $9.90x10^{-4}$ |
| ERBB1 | 0.75 (0.67-0.84) | $1.18x10^{-6}$ | 0.78 (0.7-0.88) | $6.88x10^{-5}$ | 0.79 (0.7-0.89) | $1.34x10^{-4}$ | 0.82 (0.72-0.93) | $1.48x10^{-3}$ |
| ADAMTS13 | 0.77 (0.69-0.86) | $2.23x10^{-6}$ | 0.77 (0.69-0.85) | $1.70x10^{-6}$ | 0.78 (0.7-0.87) | $9.18x10^{-6}$ | 0.78 (0.7-0.88) | $1.75x10^{-5}$ |
| Angiopoietin-2 | 1.27 (1.15-1.41) | $3.09x10^{-6}$ | 1.23 (1.11-1.37) | $1.29x10^{-4}$ | 1.2 (1.07-1.34) | $1.12x10^{-3}$ | 1.16 (1.04-1.31) | $1.09x10^{-2}$ |
| NT-proBNP§ | 1.44 (1.24-1.69) | $4.17x10^{-6}$ | 1.53 (1.3-1.79) | $1.51x10^{-7}$ | 1.51 (1.29-1.78) | $5.40x10^{-7}$ | 1.44 (1.22-1.7) | $1.46x10^{-5}$ |
| BMPR1A | 0.75 (0.66-0.85) | $5.93x10^{-6}$ | 0.79 (0.7-0.9) | $2.44x10^{-4}$ | 0.8 (0.71-0.91) | $7.01x10^{-4}$ | 0.82 (0.72-0.93) | $2.32x10^{-3}$ |

ADAMTS13: a disintegrin and metalloproteinase with thrombospondin motifs 13; BMPR1A: bone morphogenetic protein receptor type-1A; NCAM-120: Neural cell adhesion molecule 1, 120 kDa isoform; NT-proBNP: N-terminal pro-brain natriuretic peptide; SBP: systolic blood pressure; DBP: diastolic blood pressure; TrkC: tropomyosin receptor kinase C; WFKN2: WAP, Kazal, immunoglobulin, Kunitz and NTR domain-containing protein 2

*Covariates include smoking, height, weight, systolic blood pressure, diastolic blood pressure, antihypertensive treatment, diabetes mellitus, prevalent myocardial infarction, and prevalent heart failure

†Hazard ratio expressed per standard deviation of the protein concentration

‡Significance level of $p<0.05/1373=3.64x10^{-5}$

§This protein was only measured in 1075 samples due to differences in SOMAscan platform between Batch 1 and Batch 2.

**Table S3. Association of protein biomarkers with incident AF after excluding atrial flutter (n=39).**

| Protein | HR (95% CI)[†] | p value |
|---|---|---|
| NCAM-120 | 0.73 (0.65-0.82) | $6.44 \times 10^{-8}$ |
| WFKN2 | 0.76 (0.68-0.86) | $4.04 \times 10^{-6}$ |
| TrkC | 0.75 (0.67-0.84) | $1.06 \times 10^{-6}$ |
| ERBB1 | 0.74 (0.66-0.84) | $1.46 \times 10^{-6}$ |
| ADAMTS13 | 0.76 (0.68-0.86) | $4.99 \times 10^{-6}$ |
| Angiopoietin-2 | 1.29 (1.17-1.44) | $8.57 \times 10^{-7}$ |
| NT-proBNP[§] | 1.51 (1.28-1.79) | $1.47 \times 10^{-6}$ |
| BMPR1A | 0.75 (0.66-0.86) | $2.38 \times 10^{-5}$ |

ADAMTS13: a disintegrin and metalloproteinase with thrombospondin motifs 13; BMPR1A: bone morphogenetic protein receptor type-1A; NCAM-120: Neural cell adhesion molecule 1, 120 kDa isoform; NT-proBNP: N-terminal pro-brain natriuretic peptide; SBP: systolic blood pressure; DBP: diastolic blood pressure; TrkC: tropomyosin receptor kinase C; WFKN2: WAP, Kazal, immunoglobulin, Kunitz and NTR domain-containing protein 2

[†]Hazard ratio expressed per standard deviation of the protein concentration

**Table S4**. **Top 20 associations out of 776 (8 proteins * 97 SNPs) between the 8 proteins identified in the current study and the 97 previously reported AF-genetic loci.** None of these associations reached the pre-defined statistical significance threshold ($P<6.44x10^{-5}$).

| SNP | Locus | Protein name | HR (95% CI) | P-value |
|---|---|---|---|---|
| rs7508 | 8p22 | ADAMTS13 | 0.89 (0.83-0.96) | $3.37x10^{-3}$ |
| rs60212594 | 10q22.2 | ADAMTS13 | 1.13 (1.03-1.24) | $9.58x10^{-3}$ |
| rs62483627 | 7q22.3 | ADAMTS13 | 1.11 (1.02-1.20) | $1.28x10^{-2}$ |
| rs60212594 | 10q22.2 | Angiopoietin-2 | 0.86 (0.78-0.94) | $1.52x10^{-3}$ |
| rs11001667 | 10q22.3 | BMPR1A | 0.87 (0.79-0.96) | $4.54x10^{-3}$ |
| rs242557 | 17q21.31 | BMPR1A | 1.11 (1.02-1.20) | $1.04x10^{-2}$ |
| rs72700114 | 1q24.2 | BMPR1A | 1.19 (1.04-1.36) | $1.29x10^{-2}$ |
| rs60212594 | 10q22.2 | BMPR1A | 1.12 (1.02-1.24) | $1.64x10^{-2}$ |
| rs12298484 | 12q24.31 | ERBB1 | 1.12 (1.05-1.20) | $4.73x10^{-4}$ |
| rs7508 | 8p22 | ERBB1 | 0.92 (0.86-0.98) | $1.66x10^{-2}$ |
| rs7508 | 8p22 | NCAM-120 | 0.90 (0.84-0.97) | $7.10x10^{-3}$ |
| rs7978685 | 12q13.3 | NT-proBNP | 1.15 (1.05-1.27) | $3.55x10^{-3}$ |
| rs6546620 | 2p23.3 | NT-proBNP | 1.15 (1.02-1.29) | $1.88x10^{-2}$ |
| rs7789146 | 7q36.1 | TrkC | 1.12 (1.03-1.22) | $1.17x10^{-2}$ |
| rs10760361 | 9q33.3 | TrkC | 0.91 (0.85-0.98) | $1.28x10^{-2}$ |
| rs13191450 | 6q22.31 | TrkC | 1.09 (1.02-1.17) | $1.60x10^{-2}$ |
| rs60212594 | 10q22.2 | TrkC | 1.12 (1.02-1.24) | $1.79x10^{-2}$ |
| rs7508 | 8p22 | TrkC | 0.87 (0.80-0.94) | $2.37x10^{-4}$ |
| rs949078 | 11q24.1 | WFKN2 | 0.91 (0.84-0.98) | $1.50x10^{-2}$ |
| rs10760361 | 9q33.3 | WFKN2 | 0.92 (0.85-0.98) | $1.60x10^{-2}$ |

ADAMTS13: a disintegrin and metalloproteinase with thrombospondin motifs 13; BMPR1A: bone morphogenetic protein receptor type-1A; NCAM-120: Neural cell adhesion molecule 1, 120 kDa isoform; NT-proBNP: N-terminal pro-brain natriuretic peptide; TrkC: tropomyosin receptor kinase C; WFKN2: WAP, Kazal, immunoglobulin, Kunitz and NTR domain-containing protein 2

*Significance level of $p<0.05/(8 \text{ proteins} * 97 \text{ SNPs}) = 6.44x10^{-5}$. None of them reached the significance cutoff.

**Table S5**. **Biological functions of the 8 proteins associated with the risk of incident AF[1,2]**

| Protein | Function |
|---|---|
| NCAM-120 | Immunoglobulin-like glycoprotein. Activates fibroblast growth factor receptor and induces neurite outgrowth. Over-expression in neuroblastoma cells. |
| WFKN2 (WFIKKN2) | Multivalent protease-inhibitor. Inhibits growth differentiation factor and myostatin. |
| TrkC (Ntrk3) | One of tropomyosin receptor kinases that bind to neurotrophin-3, which in turn induces growth and differentiation of neuronal cells. Mutations in the gene associated with medulloblastoma, neuroblastoma, breast cancer, and other cancers. |
| EGFR (ERBB1) | Transmembrane glycoprotein kinase that acts as a receptor for epidermal growth factor. Mutations in the gene associated with different types of cancers. |
| ADAMTS13 (ATS13) | Multivalent protein that cleaves von Willebrand Factor. Mutations in the gene are associated with thrombotic thrombocytopenic purpura. |
| Angiopoietin-2 | Inhibits angiopoietin-1 and endothelial TEK tyrosine kinase, thereby regulating angiogenesis and endothelial function. |
| NT-proBNP | Secreted by ventricular myocardium upon myocardial stretching and causes natriuresis, diuresis, vasodilation, and inhibition of the renin-angiotensin-aldosterone system. |
| BMPR1A | Transmembrane serine/threonine kinase receptor that binds to the members of the TGF-β superfamily. Mutations in the gene are associated with pulmonary arterial hypertension and hereditary hemorrhagic telangiectasia. |

ADAMTS13: a disintegrin and metalloproteinase with thrombospondin motifs 13; BMPR1A: bone morphogenetic protein receptor type-1A; CI: confidence interval; EGFR: epidermal growth factor receptor; HR: hazard ratio; NCAM-120: Neural cell adhesion molecule 1, 120 kDa isoform; NT-proBNP: N-terminal pro-brain natriuretic peptide; TrkC: tropomyosin receptor kinase C; WFKN2: WAP, Kazal, immunoglobulin, Kunitz and NTR domain-containing protein 2

**Table S6. Protein biomarkers associated with incident AF in prospective cohort studies.**

| Protein[REF] | Type of assay | Study sample | HR (95% CI) | p-value | HR (95% CI) | p-value |
|---|---|---|---|---|---|---|
| | | | Age-, sex-, ± race-adjusted | | Multivariable-adjusted | |
| NT-proBNP[3] | PEA | PIVUS, ULSAM | 1.57 (1.41-1.76) | <0.0001* | 1.57 (1.39-1.76) | <0.0001* |
| NT-proBNP | Aptamer-based | FHS | 1.44 (1.24-1.69) | <0.00001† | 1.44 (1.22-1.70) | 0.000015† |
| NT-proBNP/BNP[4] | Immunoassay§ | CHARGE-US | NR | NR | 1.66 (1.56-1.76) | <0.0001 |
| FGF-23[3] | PEA | PIVUS, ULSAM | 1.26 (1.14-1.4) | <0.0001* | 1.18 (1.06-1.32) | 0.0025 |
| FGF-23[5] | PEA | Bruneck, Italy | 1.04 (0.80-1.36) | 0.75 | NR | NR |
| FGF-23 | Aptamer-based | FHS | 0.95 (0.85-1.06) | 0.052 | 0.93 (0.83-1.04) | 0.18 |
| FGF-23[6] | Immunoassay | ARIC | 1.31 (1.19-1.45) | NR | 1.07 (0.96-1.18) | NR |
| FGF-23[7] | Immunoassay | MESA | 1.79 (1.45-2.21)‖ | <0.001 | 1.41 (1.13-1.76)‖ | 0.003 |
| FGF-23[7] | Immunoassay | CHS | 1.31 (1.07-1.60)‖ | 0.010 | 1.29 (1.05-1.60)‖ | 0.018 |
| IL-6[3] | PEA | PIVUS, ULSAM | 1.26 (1.13-1.4) | <0.0001* | 1.25 (1.11-1.4) | 0.0001* |
| IL-6[5] | PEA | Bruneck, Italy | 1.19 (0.98-1.45) | 0.08 | NR | NR |
| IL-6 | Aptamer-based | FHS | 0.99 (0.89-1.10) | 0.85 | 0.96 (0.86-1.07) | 0.44 |
| IL-6[8] | Immunoassay | FHS | NR | NR | 1.08 (0.91-1.29) | 0.36 |
| FABP4[3] | PEA | PIVUS, ULSAM | 1.32 (1.16-1.5) | <0.0001* | 1.22 (1.05-1.43) | 0.012 |
| FABP4[5] | PEA | Bruneck, Italy | 1.41 (1.07-1.87) | 0.02 | NR | NR |
| GDF-15[3] | PEA | PIVUS, ULSAM | 1.27 (1.13-1.44) | 0.0001* | 1.25 (1.09-1.44) | 0.0018 |
| GDF-15[9] | Immunoassay | FHS | 1.31 (1.14-1.49) | <0.0001 | 1.15 (0.99-1.32) | 0.061 |
| TIM-1[3] | PEA | PIVUS, ULSAM | 1.26 (1.12-1.43) | 0.0002* | 1.23 (1.07-1.4) | 0.0028 |
| AM[3] | PEA | PIVUS, ULSAM | 1.27 (1.11-1.44) | 0.0004* | 1.22 (1.06-1.4) | 0.0044 |
| ST2[3] | PEA | PIVUS, ULSAM | 1.05 (0.92-1.2) | 0.44 | 1.08 (0.94-1.24) | 0.27 |
| ST2[5] | PEA | Bruneck, Italy | 1.19 (0.94-1.50) | 0.14 | NR | NR |
| ST2[9] | Immunoassay | FHS | 1.06 (0.92-1.22) | 0.39 | 1.02 (0.89-1.17) | 0.76 |
| TnI | Aptamer-based | FHS | 1.04 (0.93-1.16) | 0.51 | 1.02 (0.91-1.14) | 0.078 |
| hsTnI[9] | Immunoassay | FHS | 1.25 (1.13-1.37) | <0.0001 | 1.18 (1.07-1.32) | 0.002 |
| hsTnT[10] | Immunoassay | ARIC | 1.43 (1.37-1.51) | <0.0001 | 1.32 (1.25-1.39) | <0.0001 |
| hsTnT[11] | Immunoassay | CHS | 1.67 (1.52-1.83) | NR | 1.45 (1.32-1.59) | NR |
| CRP | Aptamer-based | FHS | 1.10 (0.98-1.25) | 0.11 | 0.94 (0.82-1.08) | 0.38 |
| CRP[4] | Immunoassay | CHARGE-US | NR | NR | 1.18 (1.11-1.25) | <0.0001 |
| hsCRP[5] | Immunoassay | Bruneck, Italy | 0.94 (0.77-1.15) | 0.56 | NR | NR |
| CRP[12] | Immunoassay | FHS | NR | NR | 1.25 (1.07-1.46) | 0.004 |
| VCAM-1 | Aptamer-based | FHS | 1.06 (0.94-1.19) | 0.34 | 0.99 (0.87-1.11) | 0.82 |
| VCAM-1[5] | Immunoassay | Bruneck, Italy | 1.35 (1.12-1.63) | 0.001 | NR | NR |

*Significance level of p-value <0.000588 (Bonferroni correction)

†Significance level of p-value <0.000036 (Bonferroni correction)

§"Immunoassay" refers to standard immunoassay of a single protein with significance level of p-value < 0.05

‖HR per doubling of the protein level

ARIC: The Atherosclerosis Risk in Communities Study; AM: adrenomedullin; CHARGE-US: Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium, which includes multiple international cohorts. CHARGE-US includes the US cohorts – FHS, ARIC, CHS; CHS: Cardiovascular Health Study; CI: confidence interval; CRP: C-reactive protein; IL-6: interleukin-6; FABP4: fatty acid binding protein 4; FGF-23: fibroblast growth factor 23; FHS: Framingham Heart Study; GDF-15: growth differentiation factor 15; HR: hazard ratio; hsTnI/T: high-sensitive troponin I/T; MESA: Multi-Ethnic Study of Atherosclerosis; NR: not reported; NT-proBNP: N-terminal pro-brain natriuretic peptide; PEA: proximity extension assay; PIVUS: The Prospective Investigation of the Vasculature in Uppsala Seniors study; TIM-1: T-cell immunoglobulin and mucin domain 1; ULSAM: Uppsala Longitudinal Study of Adult Men; VCAM-1:  vascular cell adhesion molecule 1;

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