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CLINICAL RESEARCH
Atrial fibrillation

B-type natriuretic peptide and C-reactive protein in the prediction of atrial fibrillation risk: the CHARGE-AF Consortium of community-based cohort studies

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Aims B-type natriuretic peptide (BNP) and C-reactive protein (CRP) predict atrial fibrillation (AF) risk. However, their risk stratification abilities in the broad community remain uncertain. We sought to improve risk stratification for AF using biomarker information.

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Methods and results We ascertained AF incidence in 18 556 Whites and African Americans from the Atherosclerosis Risk in Communities Study (ARIC, n=10 675), Cardiovascular Health Study (CHS, n = 5043), and Framingham Heart Study (FHS, n = 2838), followed for 5 years (prediction horizon). We added BNP (ARIC/CHS: N-terminal pro-B-type natriuretic peptide; FHS: BNP), CRP, or both to a previously reported AF risk score, and assessed model calibration and predictive ability [C-statistic, integrated discrimination improvement (IDI), and net reclassification improvement (NRI)]. We replicated models in two independent European cohorts: Age, Gene/Environment Susceptibility Reykjavik Study (AGES), n = 4467; Rotterdam Study (RS), n = 3203. B-type natriuretic peptide and CRP were significantly associated with AF incidence (n = 1186): hazard ratio per 1-SD ln-transformed biomarker 1.66 [95% confidence interval (CI), 1.56–1.76], $P < 0.0001$ and 1.18 (95% CI, 1.11–1.25), $P < 0.0001$, respectively. Model calibration was sufficient (BNP, $\chi^2 = 17.0$; CRP, $\chi^2 = 10.5$; BNP and CRP, $\chi^2 = 13.1$). B-type natriuretic peptide improved the C-statistic from 0.765 to 0.790, yielded an IDI of 0.027 (95% CI, 0.022–0.032), a relative IDI of 41.5%, and a continuous NRI of 0.389 (95% CI, 0.322–0.455). The predictive ability of CRP was limited (C-statistic increment 0.003). B-type natriuretic peptide consistently improved prediction in AGES and RS.

Conclusion B-type natriuretic peptide, not CRP, substantially improved AF risk prediction beyond clinical factors in an independently replicated, heterogeneous population. B-type natriuretic peptide may serve as a benchmark to evaluate novel putative AF risk biomarkers.

Keywords Atrial fibrillation • Risk prediction • Epidemiology • Biomarker • B-type natriuretic peptide • C-reactive protein

Introduction

Prediction of atrial fibrillation (AF), a common cardiac arrhythmia, has been the focus of various recent publications. Based on factors easily obtained during a standard office visit, a first AF risk score was developed by investigators from the Framingham Heart Study (FHS).[1] The score was subsequently validated in the Age Gene/Environment Susceptibility-Reykjavik (AGES) Study and the Cardiovascular Health Study (CHS),[2] and different, yet comparable scores were established in the Atherosclerosis Risk in Communities (ARIC) Study[3] and the Malmö Cancer and Diet Study.[4] Most recently, the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) AF consortium proposed a new risk model, combining individuals of heterogeneous racial and geographical backgrounds. This model predicted AF reasonably well in both derivation and validation cohorts.[5]

The CHARGE-AF risk score comprises only clinical risk factors for AF.[5] Factors included are age, race, height, weight, systolic and diastolic blood pressure, smoking status, use of antihypertensive medication, presence of diabetes mellitus, a history of heart failure, and a history of myocardial infarction.

Abundant literature describes the relation between laboratory biomarkers and AF. B-type and N-terminal pro B-type natriuretic peptides (BNP)[4,6–12] and C-reactive protein (CRP),[10,13–16] two biomarkers routinely determined in clinical practice, have repeatedly been shown to be associated with AF. However, their role in AF risk reclassification has not been studied in large racially and geographically diverse populations.

We investigated whether the addition of BNP and CRP measurements to the CHARGE-AF risk score improved the prediction of AF in racially and geographically diverse cohorts. We hypothesized that information on these biomarkers improves AF risk reclassification.

Methods

Study sample

We combined individual-level data from three US community-based studies (ARIC, CHS, and FHS) to estimate the predictive performance of the previously derived CHARGE-AF risk score[5] after addition of the biomarker information. Subsequently, we replicated our results in two community-based studies of individuals of European descent [AGES, Rotterdam Study (RS)]. We excluded participants with prevalent AF at baseline, age ≤45 or ≥95 years, with impaired renal function affecting biomarker clearance (defined as serum creatinine levels ≥2.0 mg/dl), not of European or African ancestry, and missing covariates, BNP, or CRP (described in Supplementary material online, *Table S1*). Detailed descriptions of cohorts, AF ascertainment methods, and assessment of clinical variables are found in the Supplementary material online. Written informed consent was obtained from all participants, Institutional Review Boards at each participating institution approved each cohort study, and all procedures complied with the principles outlined in the Declaration of Helsinki.

Assessment of biomarkers

Details on BNP and CRP assays used in each study are provided in the Supplementary material online, *Table S2*. All biomarkers were determined from blood samples drawn at the index visit (see Supplementary material online, Supplemental methods). Framingham Heart Study measured BNP, whereas all other cohorts measured N-terminal proBNP. N-terminal proBNP is more reproducible at the lower end of the distribution range, and more stable at room temperature.[17] However, both BNP and N-terminal proBNP are clinically available and have been shown to be strongly correlated: $r = 0.89$,[18] and $r > 0.87$.[19]

Statistical methods

We expressed continuous variables as mean ± standard deviation (SD) and categorical variables as frequency and percentage. Individual-level

data from ARIC, CHS, and FHS were pooled into a single derivation cohort. Values for N-terminal proBNP were divided by 10 to achieve values of similar numerical magnitude as the BNP values. Prior research had shown that values of N-terminal proBNP are ~10 times larger compared with values of BNP obtained from the same patient.[20] Biomarkers were then natural logarithm-transformed (ln-transformed) to avoid undue influence of large values. Finally, biomarker measurements in our study were standardized by cohort, sex, and race (if applicable), allowing us to combine BNP and N-terminal proBNP in our models. Values below the assays' detection limits were set to the respective detection limits.

The initial CHARGE-AF risk score calculated a proportional hazard prediction model adjusted for age, race, height, weight, systolic and diastolic blood pressure, antihypertensive treatment, smoking status, diabetes, heart failure, and myocardial infarction. Variables were selected from a larger pool using backward selection.[5] For all models, we tested the proportionality of hazards assumption using time-dependent covariates. For inclusion of BNP, CRP, or BNP and CRP, performance was assessed for a 5-year prediction horizon; the maximum follow-up until censoring was 7 years. We tested for interactions of each biomarker with age, sex, race, and body mass index. Effect estimates for biomarkers are reported as hazard ratios (HRs) per 1-SD increase of ln-transformed values. Hazard ratios for other covariates are presented per clinically meaningful unit. We plotted curves for the cumulative incidence of AF by biomarker quartile, not adjusting for the competing risk of death. We also investigated the relation between AF risk and continuous biomarker levels using spline regression.[21]

We assessed the model's performance to predict the 5-year risk of AF by calculating the C-statistic. Model calibration was determined by the Hosmer–Lemeshow χ^2 statistic, modified for survival analysis.[22] The added predictive ability of the biomarkers was assessed by the difference in C-statistics of models before and after biomarker inclusion. We additionally investigated the integrated discrimination improvement (IDI) and relative IDI.[23] Reclassification of participants was assessed by categorical net reclassification improvement (NRI) into risk categories of the cumulative proportion developing AF over 5 years. The categories were defined as <2.5, 2.5–5.0, and >5.0% based on experience from prior studies.[5,24] We also calculated the continuous NRI.[23,25]

The models including biomarker information were subsequently replicated in AGES and RS. All analyses, including the assessment of model calibration and predictive performance, were performed as described for the derivation cohort, applying the CHARGE-US models to the European replication cohorts. Calibration, discrimination, and reclassification were compared between the discovery cohort and the replication cohorts.

To minimize confounding sources of BNP and CRP elevation, we also performed a sensitivity analysis excluding all participants with a history of heart failure or myocardial infarction at baseline, repeating all analyses.

All analyses were performed using SAS 9.2. *P*-values <0.05 were considered significant. A risk calculator with instructions is in the Supplementary material online.

Results

Overall, 18 556 participants in the derivation cohorts had full data available, and were included in the analysis. Demographic and biomarker characteristics can be found in *Table 1* and *Tables S3* and *S4* (see Supplementary material online). The mean age in the CHARGE-US cohorts was 65 years; African American participants were included from ARIC and CHS, and made up 17% of the derivation sample. The proportion of women was 56% in Whites and 65% in African Americans. During follow-up, 1186 individuals developed AF (419 in ARIC, 624 in CHS, 143 in FHS). Generally, women had higher mean BNP and CRP than men. Regardless of sex, African American participants had lower mean BNP than Whites, but higher mean CRP.

Association of B-type natriuretic peptide and C-reactive protein with atrial fibrillation risk

In our derivation cohort, the levels of BNP and CRP were significantly associated with the risk of AF, when added to the established predictors derived from the CHARGE-AF risk score (*Table 2*, see Supplementary material online, *Table S5*).[5] A 1-SD difference of lnBNP was associated with a HR for AF of 1.66 [95% confidence interval (CI), 1.56–1.76; $P < 0.0001$]; the HR of lnCRP for AF was 1.18 (95% CI, 1.11–1.25; $P < 0.0001$). Similar HRs were found when both BNP and CRP were added simultaneously to the model. Apart from age (per 5-year increase), BNP (per 1-SD increase) had the highest χ^2 values suggesting the greatest association with AF risk. Cumulative incidence curves for AF by quartiles of BNP and CRP are presented in *Figure 1*. Spline regressions confirmed a lack of non-linear relation between ln-biomarker concentrations and ln HR (see Supplementary material online, *Figures S1* and *S2*). Effect estimates for all other included variables have been reported previously investigating the same individuals. These detailed results can be found in a publicly available open access publication using the following URL: http://jaha.ahajournals.org/content/2/2/e000102.full.[5]

Improvement of atrial fibrillation risk prediction with B-type natriuretic peptide and C-reactive protein

In the CHARGE-US derivation cohorts, the risk prediction model without biomarkers achieved a C-statistic of 0.765 (95% CI, 0.748–0.781).[5] The increase in C-statistic is a measure to assess the magnitude of improvement of an added factor. Adding BNP increased the C-statistic notably by 0.025 (95% CI, 0.015–0.034). By contrast, adding CRP marginally increased the C-statistic: 0.003 (95% CI, <0.000–0.006). The model including both biomarkers reached a C-statistic similar to the one of BNP alone (*Table 3*). Calibration was sufficient in all models. Hosmer–Lemeshow χ^2 values were 17.0 ($P = 0.05$) for the model with BNP added, 10.5 ($P = 0.31$) for the model with CRP added, and 13.1 ($P = 0.16$) for the model with both biomarkers. A calculator for AF risk is available (see Supplementary material online).

Similar to the increase in C-statistic, the IDI quantifies the increase in the difference between mean predicted risks for participants who do and do not experience AF events, after adding new predictor(s).[23,25] Addition of BNP yielded an IDI of 0.027 (95% CI, 0.022–0.032), which demonstrated the biggest improvement in prediction apart from a 5-year increase in age. The relative IDI compares the predictive values of variables added to the model. In a model with 11 variables, the average contribution of each is 9%. Adding biomarker information, the relative IDI of BNP was 41.5%, much greater than the expected average increase beyond variables already included in the model.[26] The IDI of CRP was small (*Table 3*).

Table 1 Baseline characteristics of the cohorts

Variable	CHARGE-US[a]	AGES	RS
N	18 556	4467	3203
Incident AF events	1186 (6%)	408 (9%)	177 (6%)
Clinical variables			
Age, years	65 (8)	76 (6)	72 (7)
Sex, % women	57% (10 614)	60% (2697)	59% (1887)
Race, % African American	17% (3099)	–	–
Current smoker, %	13% (2487)	12% (546)	16% (499)
Height, cm			
Women	161 (6)	161 (6)	161 (6)
Men	175 (7)	175 (6)	174 (7)
Weight, kg			
Women	73 (17)	70 (13)	70 (11)
Men	85 (15)	83 (13)	80 (11)
Body mass index, kg/m^2	28.1 (5.3)	27.1 (4.4)	26.9 (3.9)
Systolic blood pressure, mmHg	130 (20)	143 (21)	143 (21)
Diastolic blood pressure, mmHg	72 (11)	74 (10)	75 (11)
Hypertension treatment, %	42% (7719)	61% (2735)	37% (1189)
Diabetes, %	15% (2839)	12% (512)	10% (327)
Heart failure history, %	4% (705)	2% (77)	4% (112)
Myocardial infarction history, %	6% (1113)	7% (313)	11% (346)
Biomarkers			
BNP			
Median (IQR), pmol/ml	7.9 (11.90)	16.71 (21.65)	11.04 (13.41)
Ln, mean (SD)	2.08 (1.11)	2.86 (0.94)	2.48 (0.94)
CRP			
Median (IQR), mg/dl	2.21 (3.87)	1.80 (2.80)	2.34 (3.24)
Ln, mean (SD)	0.82 (1.10)	0.67 (1.06)	0.83 (1.03)

[a]CHARGE-US data comprised 10 675 participants from ARIC, 5043 from CHS, 2838 from FHS. African Americans from ARIC and CHS only. N-terminal proBNP values were divided by 10 for easier comparison with BNP. Data are percentage of the sample, or mean (SD) for continuous variables unless otherwise stated. IQR, Inter-quartile range; ln, natural ln-transformed.

Table 2 Hazard ratios per 1-SD difference in BNP, CRP, and BNP plus CRP

Variable	CHARGE-US		AGES		RS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
BNP	1.66 (1.56, 1.76)	<0.0001	2.05 (1.85, 2.27)	<0.0001	1.67 (1.43, 1.96)	<0.0001
CRP	1.18 (1.11, 1.25)	<0.0001	1.21 (1.09, 1.34)	0.0002	1.09 (0.93, 1.27)	0.30
Model with both						
BNP	1.64 (1.54, 1.74)	<0.0001	2.02 (1.82, 2.24)	<0.0001	1.67 (1.42, 1.95)	<0.0001
CRP	1.12 (1.06, 1.19)	0.0001	1.12 (1.01, 1.23)	0.03	1.03 (0.88, 1.20)	0.73

Estimates for 1-SD increase of the respective natural ln-transformed biomarker. All estimates for BNP and CRP are adjusted for all predictors of AF established in the CHARGE-AF risk score: age, race, smoking status, body mass index, height, weight, systolic and diastolic blood pressure, antihypertensive treatment, diabetes, histories of heart failure and myocardial infarction.[5] CI, confidence interval; HR, hazard ratio.

A third measure of prediction improvement is the NRI. The categorical NRI reclassifies individuals into higher or lower categories of pre-specified risk.[23,25] The results with user-defined NRI categories (<2.5, 2.5–5.0, and >5.0% per 5 years) are presented in *Table 4*. Overall, the user-defined NRI for BNP was 0.065 (95% CI, 0.029–0.102). Among participants who developed AF, addition of BNP reclassified 11% of participants into correct, higher risk categories, but also reclassified 11% of participants into incorrect, lower risk categories. Conversely, among those who did not develop AF, inclusion of BNP correctly reclassified 15% of individuals into lower risk

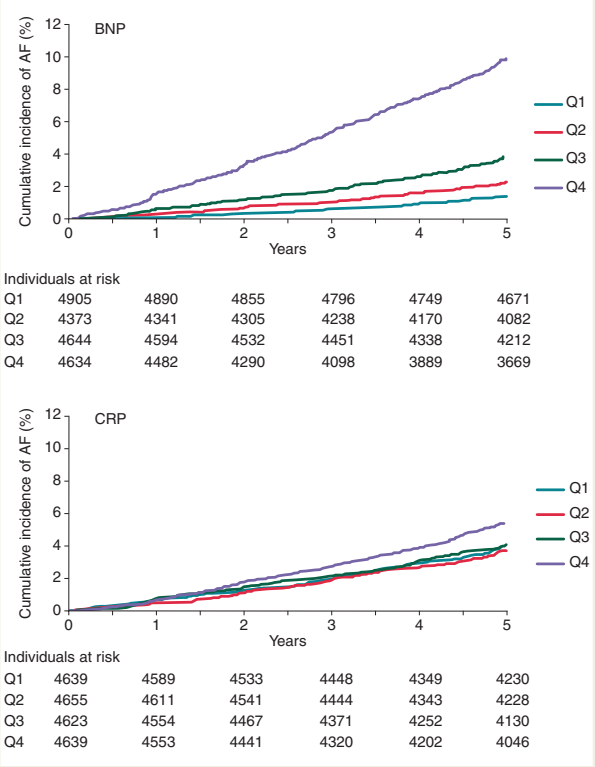

Figure 1 Cumulative incidence of AF, by biomarker quartiles. The cumulative incidence of AF in the pooled CHARGE-US cohorts over 5 years of follow-up, not adjusting for the competing risk of death, is plotted for quartiles of BNP (upper panel) and CRP (lower panel). AF, atrial fibrillation; BNP, B-type natriuretic peptide; CRP, C-reactive protein; Q1–Q4, Quartiles 1–4.

categories, and incorrectly reclassified 9% into higher risk categories. The continuous NRI does not require pre-specified categories and quantifies any change of predicted risk in the correct direction. For BNP, we estimated a moderate continuous NRI of 0.389 (95% CI, 0.322–0.455); the continuous NRI for CRP was weak (*Table 3*).

Replication in two European cohorts

We replicated the new risk score with biomarkers in 4467 individuals from AGES and 3203 from RS (*Table 1*). In AGES, the HR per 1-SD increase of the ln-transformed biomarker was 2.05 (95% CI, 1.85–2.27; $P < 0.0001$) for BNP, and 1.21 (95% CI, 1.09–1.34; $P = 0.0002$) for CRP. Comparably, the HRs in RS were 1.67 (95% CI, 1.43–1.96; $P < 0.0001$) for BNP, and 1.09 (95% CI, 0.93–1.27; $P = 0.30$) for CRP. Simultaneous inclusion of both biomarkers yielded similar results (*Table 2*).

Models with added biomarkers showed good calibration in AGES [Hosmer–Lemeshow χ^2: BNP: 5.8 ($P = 0.76$); CRP: 8.2 ($P = 0.52$); BNP + CRP: 8.5 ($P = 0.48$)], and borderline acceptable calibration in RS [BNP: 16.1 ($P = 0.06$); CRP: 15.4 ($P = 0.08$); BNP + CRP: 25.6 ($P < 0.01$)]. In both replication cohorts, BNP strongly predicted AF. Compared with the CHARGE-AF risk score, its inclusion increased the C-statistic from 0.664 by 0.058 (95% CI, 0.040–0.075) to 0.722 in AGES, and from 0.705 by 0.041 (95% CI, 0.019–0.062) to 0.746 in RS. The IDI, relative IDI, and continuous NRI results for added BNP, CRP, or both, in AGES and RS, respectively, are presented in *Table 3*.

In a sensitivity analysis, we excluded participants in the derivation and replication cohorts with prevalent heart failure or history of myocardial infarction at baseline. CHARGE-US then comprised 16 946 individuals, AGES studied 4108, and RS 3203 participants. Effect estimates and predictive performance for BNP and CRP remained virtually unchanged (see Supplementary material online, *Tables S6* and *S7*).

Discussion

Investigating over 26 000 individuals from five distinct community-based cohort studies from the USA and Western Europe, we report that higher mean BNP was highly associated with AF, and, together with age, was one of the strongest predictors of AF. Despite the heterogeneity of our cohorts, including individuals of different ethnic backgrounds, countries, and healthcare settings, BNP significantly improved discrimination and reclassification of AF risk in both the derivation and replication cohorts. C-reactive protein also was associated with incident AF, but its contribution to AF risk prediction remained limited.

B-type natriuretic peptide[4,6–10,12] and CRP[10,13–16] previously have been reported to be associated with and predict AF risk. For both biomarkers, population-based studies have reported HRs well in keeping with our findings. Examples for BNP are studies by Smith *et al.*,[4] Patton *et al.*,[9] and Schnabel *et al.*[10] who detected adjusted HRs of 1.45 in a Swedish cohort, 1.66 in CHS, and 1.62 in FHS, respectively (1.66 in the current study). Similarly, for CRP, Smith *et al.*[4] reported a HR of 1.17, Conen *et al.*[27] of 1.11, Aviles *et al.*[28] of 1.24, and Schnabel *et al.*[10] of 1.25, whereas we detected a HR of 1.18. Such consistency across studies support the interpretation that the associations of BNP and CRP with AF are reasonably stable, despite some overlap in participants between our current analysis and the studies by Patton *et al.*,[9] Aviles *et al.*,[28] and Schnabel *et al.*[10]

The potential pathophysiological contexts relating BNP and CRP to AF have been discussed elsewhere.[10] BNP is expressed in both atria and ventricles, and is a marker of cardiac stress and stretch predominantly in the ventricles, but partly in the atria.[29] Atrial stretch and subsequent atrial remodelling promote the occurrence of AF.[30] Importantly, in study participants free of AF at baseline, elevated levels of BNP, even in the absence of overt heart disease, might constitute an indicator of subclinical pathology, which will eventually predispose to AF. This interpretation is also supported by the comparison between the cohorts in our study. Participants of AGES and RS were markedly older than participants of CHARGE-US. Subclinical cardiovascular conditions become more prevalent in the elderly. Presumably reflecting this higher prevalence of subclinical disease in AGES and RS, the predictive performance of BNP was better in these two cohorts compared with CHARGE-US (e.g. confer to a C-statistic of 0.025 in CHARGE-US vs. 0.058 in AGES and 0.041 in RS, respectively). C-reactive protein is a marker of inflammation and oxidative stress and as such, it might be involved in atrial remodelling and fibrosis, a hallmark of AF pathology.[28,31] As opposed to BNP, which is largely a cardiac-specific marker, CRP is up-regulated in a multitude of inflammatory processes throughout the body. Its lack of predictive

Table 3 Predictive ability of biomarkers added to the CHARGE-AF risk score

	ΔC-statistic (95% CI)	IDI (95% CI)	Relative IDI (95% CI)	Continuous NRI (95% CI)
CHARGE-US				
+ BNP	0.025 (0.015, 0.034)	0.027 (0.022, 0.032)	0.415 (0.342, 0.490)	0.389 (0.322, 0.455)
+ CRP	0.003 (0.000, 0.006)	0.003 (0.002, 0.005)	0.050 (0.029, 0.072)	0.154 (0.081, 0.228)
+ BNP and CRP	0.026 (0.017, 0.035)	0.030 (0.024, 0.035)	0.449 (0.369, 0.530)	0.375 (0.303, 0.448)
AGES				
+ BNP	0.058 (0.040, 0.075)	0.023 (0.019, 0.028)	0.793 (0.656, 0.944)	0.612 (0.497, 0.734)
+ CRP	0.005 (−0.002, 0.013)	0.001 (0.001, 0.002)	0.050 (0.021, 0.079)	0.142 (0.018, 0.269)
+ BNP and CRP	0.059 (0.041, 0.077)	0.024 (0.019, 0.029)	0.827 (0.683, 0.988)	0.633 (0.517, 0.751)
RS				
+ BNP	0.041 (0.019, 0.062)	0.028 (0.020, 0.038)	0.700 (0.525, 0.883)	0.449 (0.248, 0.623)
+ CRP	−0.005 (−0.014, 0.004)	0.001 (0.000, 0.003)	0.032 (−0.001, 0.065)	0.011 (−0.178, 0.184)
+ BNP and CRP	0.039 (0.018, 0.060)	0.029 (0.020, 0.039)	0.716 (0.547, 0.900)	0.470 (0.270, 0.655)

Biomarkers are standardized within cohorts in CHARGE-US and presented per 1 SD of the natural ln-transformed biomarker. The CHARGE-AF risk score uses age, race, smoking status, body mass index, height, systolic and diastolic blood pressure, antihypertensive treatment, diabetes, and histories of heart failure and myocardial infarction.[5] Δ, delta; CI, 95% confidence interval; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

performance in our study might thus be a sign of lacking organ specificity. Whereas we cannot rule out subclinical pathology, our sensitivity analyses suggested that pre-existing heart failure or myocardial infarction, two conditions known to elevate both BNP and CRP, were not confounding our results. Information on echocardiographic measurements might further improve our risk prediction models. However, with respect to a broad applicability of our risk model, imaging techniques are more time-consuming and more expensive than laboratory measures.

Like the previously reported version of our risk score involving clinical covariates only,[5] we aimed for our extended biomarker version to potentially be clinically applicable. First, our study is founded on a broad base thanks to the inclusion of over 26 000 individuals and close to 1800 AF events. Being derived from a racially and geographically heterogeneous sample makes our model potentially applicable to large parts of the North American and European population. Unlike prior efforts with 10- or 14-year follow-up,[4,10] our score was designed to predict AF over a 5-year time period. Such a time horizon may be more relevant to clinical trials and more meaningful regarding clinical outcomes for patients. The widest clinical applicability of a risk score is gained by simplicity and the use of readily available covariates. Both BNP and CRP are laboratory markers that have widespread medical use. The increasing availability of point-of-care testing will make both tests also available in more remotely located primary care settings.[32]

Beyond its applicability in principle, we envision several more specific possible applications of our score. Novel AF-related biomarkers are emerging rapidly and an incomplete list includes apelin, urotensin II, soluble CD40 ligand, osteoprotegerin, troponin, endothelin, plasminogen activator inhibitor-1, and YKL-40 (see Supplementary material online, References). Given the strong predictive performance of BNP in particular, our revised score also might be considered a standard for testing the clinical applicability and usefulness of novel markers in the future.

A more speculative field of clinical applicability of our new score lies in the potential future individualized diagnosis and therapy of patients. With healthcare systems under increasing financial pressure, it would be advantageous to identify individuals at high risk for AF before the arrhythmia actually occurs. Individuals with an elevated probability for AF might be followed more closely for the occurrence of AF. An earlier diagnosis could then lead to immediate guideline-recommended treatment for the prevention of thrombo-embolic events, which are both hazardous for the individual and constitute a high socioeconomic burden.[33–35] Similarly, current trials including the EAST trial (confer www.clinicaltrials.gov; NCT01288352) are investigating the importance of early rhythm control treatment strategies for AF. In case of beneficial early treatment, our risk score could support the timely identification of potential patients for such treatment. In lack of specific primary prevention strategies for AF, individuals at high risk might also receive intensified treatment of risk factors to prevent the occurrence of AF and its consequences. Initial results of clinical investigations exemplarily suggest that weight loss and rigorous risk factor management can reduce the burden of AF and its related symptoms.[36] For an easy access to risk estimates for AF, our risk calculator (see Supplementary material online) might also be embedded in electronic health records or electronic case report forms of clinical studies. Whereas the concept of individualized patient care is appealing, its practicability needs to be demonstrated in randomized clinical trials.

Strengths and limitations

Major strengths of our study include the large sample size, the racially and geographically diverse nature of the cohort, the analysis based on individual-level data, and independent replication. Our study also has limitations. First, individuals of non-European or non-African descent were not included, reducing generalizability to other races and ethnicities. Secondly, our score, derived from community-based studies, may not be relevant to inpatient settings. Thirdly, in our definition of AF, we did not differentiate between different disease patterns like paroxysmal, persistent, or permanent AF, or between AF and

Table 4 Reclassification table for the CHARGE-US derivation cohort

Reclassification based on BNP

Participants who developed AF

	With BNP			
Without BNP	<2.5%	2.5–5.0%	>5.0%	Total
<2.5%	67	28	11	105
2.5–5.0%	35	84	53	172
>5.0%	5	50	479	535
Total	107	162	543	812

Participants who did not develop AF

	With BNP			
Without BNP	<2.5%	2.5–5.0%	>5.0%	Total
<2.5%	7488	726	44	8259
2.5–5.0%	1550	2484	839	4873
>5.0%	125	1066	3422	4612
Total	9163	4276	4305	17 744

NRI: 0.065 (95% CI, 0.029–0.102)

Reclassification based on CRP

Participants who developed AF

	With CRP			
Without CRP	<2.5%	2.5–5.0%	>5.0%	Total
<2.5%	89	15	0	105
2.5–5.0%	13	138	20	171
>5.0%	0	19	514	533
Total	102	172	534	808

Participants who did not develop AF

	With CRP			
Without CRP	<2.5%	2.5–5.0%	>5.0%	Total
<2.5%	7894	366	0	8259
2.5–5.0%	463	4066	345	4874
>5.0%	0	383	4231	4614
Total	8357	4815	4576	17 748

NRI: 0.013 (95% CI, −0.010 to 0.034)

Reclassification based on BNP + CRP

Participants who developed AF

	With BNP and CRP			
Without BNP and CRP	2.5%	2.5–5.0%	>5.0%	Total
<2.5%	69	26	11	106
2.5–5.0%	31	87	54	172
>5.0%	5	48	482	535
Total	104	161	547	813

Participants who did not develop AF

	With BNP and CRP			
Without BNP and CRP	2.5%	2.5–5.0%	>5.0%	Total
<2.5%	7476	733	49	8258
2.5–5.0%	1585	2448	841	4873
>5.0%	128	1071	3413	4612
Total	9189	4252	4303	17 743

NRI: 0.074 (95% CI, 0.040–0.110)

Reclassification was calculated for patients who developed AF and those who did not develop AF. Reclassification categories were pre-specified as <2.5, 2.5–5.0, and >5.0%. Counts represent the number of participants. Cells shaded in green imply favourable reclassification; cells shaded in red imply unfavourable reclassification.

atrial flutter, leaving unresolved whether the utility of our prediction model varies by specific AF pattern. Fourthly, all covariates including biomarkers were assessed only at baseline. We thus cannot comment on whether temporal changes of covariates or biomarkers alter risk for AF. In particular, it remains unclear if therapies reducing BNP and CRP levels are accompanied by reduced risk of AF. Finally, we have only included BNP and CRP as potentially predictive biomarkers, whereas other markers have been suggested and warrant investigation.

Balancing advantages and disadvantages of population-based studies and clinical trials, the former do not allow for specific disease-related measurements, particularly if such measurements are invasive like electrophysiological studies. Also, the ascertainment of medical data and events often has to rely on the review of medical charts rather than direct patient interrogation. At the same time, however, population-based cohorts warrant high numbers of investigated participants, which gives enough statistical power to detect even small effects that might be overlooked in small clinical trials. Also, the generalizability to the general public might be larger compared with patients recruited because of a specific disease or condition.

Conclusion

In conclusion, addition of information on BNP, and to a much smaller extent on CRP, significantly improved the 5-year risk prediction for AF. In particular, BNP was the strongest predictor of AF, apart from a 5-year increase in age. The wide availability of laboratory tests for BNP and CRP, at least in the industrialized world, might facilitate the applicability of our new risk score to a larger clinical population. The usefulness of the score for individualized diagnostic and therapeutic decisions needs to be shown.

Supplementary material

Supplementary material is available at *Europace* online.

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