Heart Failure

Multimarker Approach for the Prediction of Heart Failure Incidence in the Community

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Background—Several biological pathways are activated in ventricular remodeling and in overt heart failure (HF). There are no data, however, on the incremental utility of a parsimonious set of biomarkers (reflecting pathways implicated in HF) for predicting HF risk in the community.

Methods and Results—We related a multibiomarker panel to the incidence of a first HF event in 2754 Framingham Heart Study participants (mean age, 58 years; 54% women) who were free of HF and underwent routine assays for 6 biomarkers (C-reactive protein, plasminogen activator inhibitor-1, homocysteine, aldosterone-to-renin ratio, B-type natriuretic peptide, and urinary albumin-to-creatinine ratio). We estimated model c statistic, calibration, and net reclassification improvement to assess the incremental predictive usefulness of biomarkers. We also related biomarkers to the incidence of nonischemic HF in participants without prevalent coronary heart disease. On follow-up (mean, 9.4 years), 95 first HF events occurred (54 in men). In multivariable-adjusted models, the biomarker panel was significantly related to HF risk ($P=0.00005$). On backward elimination, B-type natriuretic peptide and urinary albumin-to-creatinine ratio emerged as key biomarkers predicting HF risk; hazards ratios per 1-SD increment in log marker were 1.52 (95% confidence interval, 1.24 to 1.87) and 1.35 (95% confidence interval, 1.11 to 1.66), respectively. B-type natriuretic peptide and urinary albumin-to-creatinine ratio significantly improved the model c statistic from 0.84 (95% confidence interval, 0.80 to 0.88) in standard models to 0.86 (95% confidence interval, 0.83 to 0.90), enhanced risk reclassification (net reclassification improvement$=0.13$; $P=0.002$), and were independently associated with nonischemic HF risk.

Conclusion—Using a multimarker strategy, we identified B-type natriuretic peptide and urinary albumin-to-creatinine ratio as key risk factors for new-onset HF with incremental predictive utility over standard risk factors. (***Circulation***. 2010; 122:1700-1706.)

Heart failure (HF) is associated with high morbidity and mortality, making its prevention a public health priority.[1] Identification of people who are at higher risk of developing HF is critical for targeting prevention strategies. Investigators from the Framingham Heart Study previously described an HF "risk profile"[2] based on clinical, ECG, and x-ray features, but these clinical factors do not fully explain HF risk.[3] Recently, numerous investigations have highlighted that several biological pathways are activated during left ventricular (LV) remodeling and HF evolution. Several reports focused on individual circulating and urinary biomarkers representing some of these key pathways,[4] but few have assessed the incremental predictive utility of multiple biomarkers considered together.

Clinical Perspective on p 1706

We recently applied a multimarker strategy to identify key biomarkers associated with indexes of LV remodeling[5] and vascular stiffness.[6] In the present investigation, we extend the multimarker strategy to overt HF by relating the panel of

biomarkers to the incidence of a first HF event in a large community-based sample. The biomarker panel included aldosterone-to-renin ratio[5] (ARR; renin-angiotensin-aldosterone axis), C-reactive protein[7] (CRP; inflammation), plasminogen activator inhibitor-1[8] (PAI-I; fibrinolysis), B-type natriuretic peptide[9] (BNP; natriuretic peptide system), homocysteine[10] (oxidative stress), and the urine albumin-to-creatinine ratio[11] (UACR; endothelial function). We hypothesized that 1 or more of these circulating and urinary biomarkers will be associated with HF risk and will incrementally predict HF incidence beyond established risk factors.

Methods

Study Sample

Details of the Framingham Offspring Study have been published previously.[12] In brief, 5124 individuals who were children (or spouses of children) of the original Framingham cohort participants were enrolled in 1971 in the Framingham Offspring Study, and these individuals have been examined approximately every 4 years. For the present investigation, we included attendees at the sixth examination cycle (1995 to 1998; n=3532), referred to as the baseline examination for our analysis. Of these, we excluded 737 participants because of unavailable biomarker information, 10 participants for missing covariate information, and another 31 participants who had prevalent HF. Thus, 2754 participants (54% women) remained eligible for this investigation. All participants provided written informed consent, and the Institutional Review Board of the Boston University Medical Center approved the study protocol.

Measurement of Biomarkers

Biosamples were obtained on the morning of the baseline examination (when covariate information was also collected and follow-up started) after an overnight fast, usually between 8 and 9 AM, and frozen at −80°C without any freeze-thaw cycles until assays were performed. Plasma PAI-1 was determined with an ELISA test for PAI-1 antigen (TintElize PAI-1, Biopool, Ventura, Calif).[13] CRP was measured with the Dade-Behring BN100 nephelometer.[14] Serum aldosterone was measured with a radioimmunoassay[15] (Quest Diagnostics, Cambridge, Mass), and plasma renin concentrations were measured by an immunochemiluminometric assay (Nichols Assay, Quest Diagnostics).[16] Plasma BNP was measured with a high-sensitivity immunoradiometric assay (Shionogi, Osaka, Japan).[17] We used high-performance liquid chromatography with fluorometric detection to measure total plasma homocysteine.[18] We assessed UACR on a morning urine specimen using immunoturbidimetry (Tina-Quant Albumin Assay, Roche Diagnostics, Indianapolis, Ind) to measure urine albumin[19] and the modified Jaffe method to measure urinary creatinine.[20]

The following were the average interassay coefficients of variation for the biomarker measurements: PAI-1, 7.7%; CRP, 2.2%; renin, 2.0% (high concentrations) to 10% (low concentrations); aldosterone, 4.0% (high concentrations) to 9.8% (low concentrations); BNP, 12.2%; homocysteine, 9%; urine albumin, 7.2%; and urine creatinine, 2.3%.

HF Assessment

Follow-up for the present investigation extended from the baseline examination through December 2007. An end-points adjudication committee consisting of 3 physicians evaluated all suspected cardiovascular disease events (including HF) by reviewing Heart Study clinic charts and hospitalization and physician office records and ascertained the incidence of events according to criteria described previously.[21] We used Framingham HF criteria[22] (Table I in the online-only Data Supplement) to adjudicate HF incidence. In secondary analyses, we referred to participants who developed HF without an interim myocardial infarction (MI) or unstable angina (also known as coronary insufficiency) as the "nonischemic" HF group for simplicity.

Statistical Analyses

Biomarker values were natural logarithmically transformed (to account for skewed distributions) and standardized within sex to account for sex-related differences in biomarker distributions. We modeled aldosterone and renin together as a ratio, the ARR, because in our cohort such combined modeling has been most informative.[23] We calculated age- and sex-adjusted Spearman coefficients to evaluate correlations between biomarkers.

To evaluate the predictive utility of biomarkers (with regard to HF risk), we performed the following analyses. First, after confirming that the assumption of proportionality of hazards was met, we fitted Cox models[24] that incorporated age, sex, body mass index, systolic blood pressure, hypertension treatment, diabetes mellitus, ratio of total cholesterol to high-density lipoprotein cholesterol, smoking, prevalent MI, and valvular heart disease. Next, we tested whether the set of 6 biomarkers (denoted m1 through m6 in the equation) was associated with HF risk using a 6-*df* likelihood ratio test of the null hypothesis H0: $\beta_{m1}=\beta_{m2}\ldots=\beta_{m6}=0$. The likelihood ratio test χ^2 statistic was obtained by comparing likelihoods from 2 models: with covariates only and with covariates plus 6 biomarkers. Third, after determining that the set of biomarkers improved the model, we conducted backward elimination (*P* for retention in model=0.05) to identify the biomarker(s) with the strongest association with HF incidence, forcing in the 10 clinical covariates in the model. We also used stepwise selection to confirm the final model.

HF risk portended by a biomarker in any given individual is a function of the concentration of the biomarker and the relative risk associated with that concentration. In addition, biomarkers carry different relative risks and may vary in concentrations independently of each other. Therefore, to assess the composite HF risk associated with several biomarkers in any individual, we constructed a weighted biomarker score (including only biomarkers that emerged in backward elimination): Biomarker score=(β coefficient estimate of biomarker$_1$×sex-standardized log-biomarker$_1$ concentration)+(β coefficient estimate of biomarker$_2$×sex-standardized log-biomarker$_2$ concentration), etc.

We plotted the cumulative incidence of HF (accounting for competing risk of mortality) according to tertiles of the biomarker score, ascertained HF event proportions in each tertile, and evaluated whether participants in the second and third tertiles had higher HF risk compared with those in the first tertile in the multivariable-adjusted models described above. We also repeated these analyses in a subsample with Framingham Risk Score–predicted baseline 10-year coronary heart disease (CHD) risk ≥10%. In addition, we used the top tertile of the biomarker score as a threshold to calculate the sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of positive test, and likelihood ratio of negative test to evaluate the performance characteristics of the score for possible HF risk screening.

To assess the utility of biomarkers associated with HF, we evaluated several metrics. First, we assessed model calibration (ie, concordance of observed risk and that predicted by the model with biomarkers) by calculating the Hosmer-Lemeshow χ^2 statistic for Cox models. Second, we calculated the c statistic for the model with clinical covariates alone and compared it with that for the model with clinical covariates and biomarkers to estimate the increase in the c statistic in the latter.[25,26] Third, we classified participants into 3 categories of absolute 12-year HF risk (the maximum follow-up duration): low risk (<2%), intermediate risk (2% to 8%), and high risk (>8%). We evaluated whether inclusion of biomarkers improved risk classification of participants by calculating the net reclassification improvement (NRI).[27] The NRI is used to assess how well a new marker "reclassifies" people from 1 risk category to another (higher or lower). It is calculated as a sum of 2 separate components (1 for individuals with events and 1 for individuals without events) as follows: NRI=[(events reclassified higher−events reclassified lower)/events]+[(nonevents reclassified lower−nonevents reclassified higher)/nonevents].

Table 1. Baseline Clinical and Biochemical Characteristics of Study Participants

Variable	Men (n=1278)	Women (n=1476)
Clinical characteristics		
Age, y	59 (10)	58 (10)
Body mass index, kg/m^2	28.7 (4.4)	27.4 (5.8)
Systolic blood pressure, mm Hg	130 (17)	127 (20)
Ratio of total to high-density lipoprotein cholesterol	4.9 (2.0)	3.9 (1.4)
Hypertension treatment, %	30	25
Current smoking, %	14	16
Diabetes mellitus, %	12	9
Valvular heart disease, %	3	2
Prevalent MI, %	7	1
Biochemical characteristics		
CRP, mg/L	1.81 (0.90, 3.91)	2.40 (0.99, 5.63)
PAI-1, ng/mL	25.6 (17.1, 36.0)	20.2 (12.1, 31.8)
Homocysteine, mmol/L	9.81 (8.26, 11.92)	8.30 (6.97, 10.13)
ARR	0.65 (0.38, 1.14)	1.00 (0.55, 1.67)
BNP, pg/mL	6.10 (4.00, 15.9)	9.70 (4.00, 19.65)
Urine albumin/creatinine ratio, mg/g	4.88 (2.15, 10.93)	8.55 (3.57, 17.24)

Values are mean (SD) for clinical characteristics and median (first quartile, third quartile) for biochemical parameters.

Table 2. Relations of Biomarkers to HF Risk

	Adjusted HR* (95% CI)	P
Primary analyses		
Relations of biomarkers to all HF (n=2754)		
Log BNP	1.52 (1.24–1.87)	<0.0001
Log UACR	1.35 (1.11–1.66)	0.004
Secondary analysis		
Relations of niomarkers to all HF (n=2754), adjusting for interim MI†		
Log BNP	1.52 (1.24–1.86)	<0.0001
Log UACR	1.38 (1.13–1.69)	0.002
Relations of biomarkers to nonischemic HF (n=2636)‡		
Log BNP	1.78 (1.37–2.31)	<0.0001
Log UACR	1.39 (1.06–1.82)	0.02

HR indicates hazard ratio.

*Hazard ratios are per 1-SD increment in log biomarker and are adjusted for age, sex, body mass index, systolic blood pressure, hypertension treatment, diabetes mellitus, current smoking, ratio of total to high-density lipoprotein cholesterol, valvular heart disease, and prevalent MI.

†Model adjusted for interim MI in addition to age, sex, body mass index, systolic blood pressure, hypertension treatment, diabetes mellitus, current smoking, ratio of total to high-density lipoprotein cholesterol, valvular heart disease, and prevalent MI.

‡Analysis restricted to participants without prevalent MI or unstable angina. Model adjusted for age, sex, body mass index, systolic blood pressure, hypertension treatment, diabetes mellitus, current smoking, ratio of total to high-density lipoprotein cholesterol, and valvular heart disease.

We calculated NRI using an extension to survival analysis that uses Kaplan-Meier estimates of event probabilities at 12 years.[27] A large NRI indicates that the marker causes a large improvement in reclassification. Because there are no previously established categories for the absolute risk of HF, we defined these strata empirically on the basis of the distribution of the risk estimates from the model with clinical covariates. We also implemented a 10-fold jackknife cross-validation approach to correct for overoptimism associated with validating the model on the same sample on which it was developed. The sample was split into 10 subsamples, and predictions for each one-tenth were obtained from models developed on the remaining nine-tenths. These cross-validated probabilities were used to calculate jackknife c statistics.

In secondary analyses, we performed additional adjustments for prevalent and intervening ischemic events and evaluated the relations of biomarkers to nonischemic HF. We also addressed confounding related to changing values of covariates over time, assessed underlying renal function (as estimated glomerular filtration rate), and evaluated the utility of biomarkers in a subgroup with normal estimated glomerular filtration rate. We also tested for interactions with age, sex, and body mass index. Statistical methods for these analyses are described in Section III of the online-only Data Supplement.

All statistical analyses were performed with SAS software version 9.1 (SAS institute, Cary, NC). A 2-sided value of P=0.05 denoted statistical significance.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Baseline clinical and biochemical characteristics of our sample are displayed in Table 1. Of the 2754 participants in our sample, 118 had a history of MI or unstable angina at baseline. Approximately half the participants in our sample had a baseline Framingham Risk Score–predicted 10-year CHD risk ≥10%, and a fifth had predicted 10-year CHD risk ≥20%. Of note, women made up ≈70% of the group with 10-year CHD risk <10%. Approximately 80% of the HF events were concentrated in the subgroup of participants with Framingham Risk Score–predicted 10-year CHD risk ≥10%. Age- and sex-adjusted correlations among the biomarkers are presented in Table II in the online-only Data Supplement. The strongest positive and inverse correlations were between CRP and PAI-1 and between PAI-1 and BNP, respectively (Table II in the online-only Data Supplement).

Over a mean follow-up of 9.4 years (maximum, 12.8 years), 95 participants (41 women) developed HF. The panel of biomarkers was significantly related to HF risk (P=0.00005). On backward elimination, BNP and UACR emerged as significant correlates; each 1-SD increase in log BNP and log UACR was associated with a 52% and 35% higher risk of developing HF, respectively (Table 2). When BNP and UACR were modeled together as a biomarker score, unadjusted HF proportions increased 10-fold across tertiles. Cumulative HF incidence curves by tertile of biomarker score are presented in the Figure. Participants in the second and third tertiles of biomarker score carried multivariable-adjusted HF hazards that were 3-fold and 4-fold higher, respectively, than those with a biomarker score in the first tertile (Table 3). Results were similar when we repeated these analyses in a subsample with Framingham Risk Score–predicted baseline 10-year CHD risk ≥10% (Table III in the
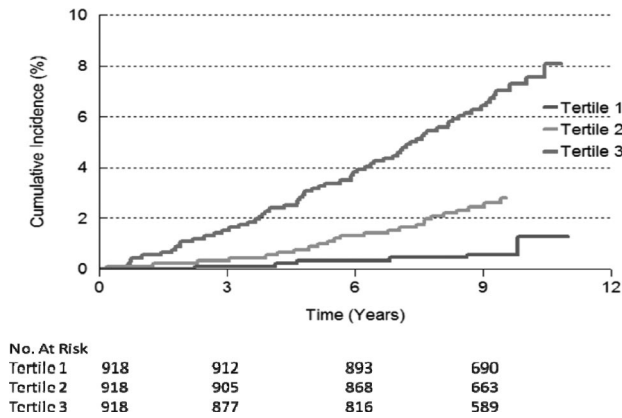
Figure. Cumulative incidence of HF according to tertiles of the biomarker score incorporating BNP and UACR.

online-only Data Supplement). The sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratio of positive test, and likelihood ratio of negative test of the top tertile of biomarker score were 68%, 68%, 7%, 98%, 2.13, and 0.46, respectively. When these metrics were recalculated using a sample of individuals with at least 6 years of follow-up, the estimates were very similar.

The addition of biomarkers to the model with clinical characteristics improved the model c statistic from 0.84 (95% confidence interval [CI], 0.80 to 0.88) to 0.86 (95% CI, 0.83 to 0.90; $P=0.007$ for improvement), and the model with biomarkers had excellent calibration (Hosmer-Lemeshow $\chi^2=9.45$; $P=0.40$). The contributions of BNP and UACR to the improvement in c statistic were of equal magnitude (0.01 each); c statistics for models with clinical covariates alone, with covariates and BNP, and with covariates and BNP and UACR were 0.84, 0.85, and 0.86, respectively. When participants who developed HF and those who did not were classified separately into risk categories based on clinical characteristics alone, the addition of biomarkers reclassified 13% of participants in the appropriate direction; ie, those without HF on follow-up in the intermediate-risk group were reclassified "downward," and those with HF on follow-up in the intermediate-risk group were reclassified "upward" (NRI=0.13; $P=0.002$; Table 4).

In secondary analyses, relations of BNP and UACR to HF risk remained robust on adjustment for interim MI (Table 2). Results of the jackknife cross-validation showed that the basic model not including the 2 biomarkers produced a jackknife c statistic of 0.838 (95% CI, 0.797 to 0.879), whereas addition of the 2 markers to the basic model produced a jackknife c statistic of 0.862 (95% CI, 0.825 to

Table 3.   Relations of Biomarker Score to HF Risk

	Tertile 1	Tertile 2	Tertile 3
Events/at risk, n (%)*	6/918 (0.7)	24/918 (2.6)	65/918 (7.1)
HF risk (95% CI)†	Referent	2.9 (1.7–7.0)	4.2 (1.8–10.2)

*Event proportions by tertile of biomarker score based on BNP and UACR.
†Multivariable-adjusted HF hazards compared with the referent group. Model adjusted for age, sex, body mass index, systolic blood pressure, hypertension treatment, diabetes mellitus, current smoking, ratio of total to high-density lipoprotein cholesterol, valvular heart disease, and prevalent MI.

Table 4.   Classification of Participants Into HF Risk Groups Based on Multivariable Models With and Without Biomarkers

	Risk <2 %*	Risk 2–8 %*	Risk >8 %*	Total
Risk reclassification in participants without HF, n (row %)				
<2%†	1529 (93)	115 (7)	0 (0)	1644
2%–8%†	176 (23)	540 (71)	49 (6)	765
>8%†	0 (0)	74 (30)	176 (70)	250
Total	1705	729	225	2659
Risk reclassification in participants with HF, n (row %)				
<2%†	26 (79)	7 (21)	0 (0)	33
2%–8%†	3 (8)	25 (69)	8 (22)	36
>8%†	0 (0)	3 (12)	23 (88)	26
Total	29	35	31	95

NRI=[(7+8)−(3+3)]/95+[(176+74)−(115+49)]/2659=0.13; $P=0.009$.
*HF risk categories based on clinical covariates plus biomarker score.
†HF risk categories based on clinical covariates alone.

0.899), yielding a jackknife overoptimism estimate of 0.024 (95% CI, 0.007 to 0.041; $P=0.007$), therefore suggesting only a modest degree of overoptimism. In the subsample of participants without baseline MI or unstable angina (n=2636), 57 developed nonischemic HF on follow-up. In these analyses, each 1-SD increment in log BNP and log UACR was associated with a 78% ($P<0.001$) and 39% ($P=0.02$) higher HF risk, respectively (Table 2). When analyses evaluating the relations of biomarker score to HF risk were adjusted for all incident and prevalent ischemic events (MI, unstable angina, and angina pectoris), the results were unchanged (Table IV in the online-only Data Supplement). Additional adjustment of the multivariable model with biomarker score for incident and prevalent unrecognized MI did not alter the results (Table V in the online-only Data Supplement). In addition, results did not differ when our analyses were repeated in a subgroup of participants with normal LV systolic function (data not shown).

Relations of BNP and UACR to HF risk were not altered by additional adjustment for estimated glomerular filtration rate and were similar in participants with estimated glomerular filtration rate $\geq$60 mL·min^{-1}·1.73 m^{-2} (data not shown). Relations of biomarker score tertiles to HF risk were unchanged when clinical risk factors were modeled as time-dependent covariates (Table VI in the online-only Data Supplement). Finally, relations of BNP and UACR to HF risk were not modified by age, sex, or body mass index (None of the interaction terms was statistically significant).

Discussion

Principal Findings
In our large community-based sample, we identified BNP and UACR (from a multimarker panel) as key predictors of HF risk, emphasizing the importance of natriuretic peptide system activation and endothelial dysfunction as markers of disease progression. BNP and UACR were also indepen-

dently associated with nonischemic HF, suggesting that relations of biomarkers to HF risk are not mediated solely by interim occurrence of ischemic events, and were significantly associated with HF risk in the subgroup with normal LV systolic function, suggesting that our findings were not driven by individuals with LV systolic dysfunction in our sample. In addition, participants who were excluded because of intercurrent ischemic events as having "ischemic HF" may still have nonischemic HF (ie, the intervening event may not be causally related to HF occurrence). These 2 biomarkers improved HF risk prediction very modestly, as evidenced by improvements in model discrimination and risk reclassification. The biomarker score may have potential utility as a screening tool, a premise that would require additional studies; the high negative predictive value may be important to note in this context. We also demonstrate the robustness of the biomarkers in predicting HF risk in participants with high baseline CHD risk; however, we should be cautious in generalizing these findings to people with low baseline CHD risk (10-year risk <10%), and biomarker utility in the latter group needs further study.

Several previous investigations reported the relations of biomarkers from various biological domains to HF risk.[7,11,28–30] However, our investigation is novel in several respects. Whereas earlier studies evaluated biomarkers individually, we used a multimarker strategy, which permitted a comparison of several biomarkers while limiting multiple statistical testing. We also assessed the potential incremental utility of biomarkers (and biomarker scores) for predicting HF risk (above and beyond standard clinical risk factors). An additional strength of our report is the demonstration that both BNP and UACR are associated with the risk of developing nonischemic HF in a large subgroup without history of MI or unstable angina, thereby avoiding potential confounding by preexisting and interim ischemic events, which can activate several of the pathways represented by the biomarkers we investigated.

Although the exact mechanisms underlying the predictive value of BNP and UACR cannot be conclusively determined from epidemiological data alone, the results from our investigation, if confirmed, can potentially be used in clinical settings to evaluate HF risk and to identify specific high-risk individuals. Analogous to the use of multivariable risk profiles in the assessment of CHD risk in people with dyslipidemia, with attendant determination of treatment targets, biomarker risk scores can be used to identify those who are at high risk for HF and may potentially benefit from treatment of currently established HF risk factors (hypertension, diabetes, obesity, etc) to targets that are lower than conventionally recommended to reduce HF incidence. However, this approach (using biomarker scores for risk stratification) has yet to be tested and need validation before use in clinical settings. Indeed, it may be argued that all patients at risk of developing HF warrant aggressive management of their risk factor burden.

Mechanisms Underlying the Relations of Biomarkers to HF Risk

BNP is a hormone with natriuretic, diuretic, and vasodilatory properties that is released in response to increased LV filling pressures[31] and/or greater LV wall stress.[32] BNP has been used in the diagnosis of clinical HF[33] but is also elevated in people with asymptomatic LV dysfunction.[34] Thus, one explanation for the relations of BNP to HF risk is that participants with elevated BNP concentrations are those with subclinical LV remodeling,[35] systolic dysfunction,[36] or diastolic dysfunction[37] and therefore develop HF at higher rates. Another possibility is that relations of BNP to HF risk are mediated by its relations to incident ischemic cardiovascular events.[9] BNP may be released in the setting of ischemic events other than MI or with subclinical ischemia and may therefore predict HF secondary to clinical or subclinical ischemia. In our investigation, a variety of adjustments for ischemic events (including adjustment for unrecognized MI) and exclusion of participants with MI and unstable angina did not alter the results. However, it is possible that BNP released in response to subclinical ischemia may be an explanation for the association between this biomarker and HF risk. Overall, it is likely that BNP is a marker for each of the mechanisms noted above.

Similarly, UACR is a risk marker for endothelial dysfunction,[38] target organ damage,[39] ischemic events,[40] and an atherogenic risk profile,[41] which may explain why it is related to HF risk. As with BNP, it is likely that UACR is a cumulative measure for all these mechanisms for HF risk.

The other biomarkers in our panel (CRP, PAI-1, ARR, and homocysteine) have previously been implicated in ventricular remodeling, alterations in LV function, and HF incidence.[29,30,42–44] However, in our analysis, we did not observe an independent association between these biomarkers and HF risk. It is conceivable that the relations of these biomarkers to HF risk may be mediated through their relations to clinical risk factors that we adjusted for in our model. Indeed, previous reports have described the associations between CRP and hypertension[45] and diabetes mellitus[46] and between PAI-1 and hypertension[47] and metabolic syndrome.[48] Prior investigations also have noted the relations of ARR to hypertension[23] and both ARR and homocysteine to vascular stiffness.[6,49] Thus, our results do not imply that the pathways represented by these biomarkers do not contribute to HF risk.

Strengths and Limitations

Our study is strengthened by a large sample size, standardized measurements of biomarkers and clinical variables, a rigorous definition of HF events, and a conservative analysis strategy to minimize multiple testing. However, several limitations should be acknowledged. First, we tested only a small set of biomarkers that were available at a routine examination and that have previously been implicated in LV remodeling and/or HF risk; markers of other biological pathways (or other biomarkers of domains we evaluated) that were not tested may be important in influencing HF risk. Second, differences in the analytic precision of the assays for these biomarkers may have influenced the results of analysis. Third, we lack information on quantitative LV ejection fraction, measures of diastolic function, and measures of endothelial or vascular function at the baseline examination; therefore, we could not adjust for these measures in our multivariable models. Fourth, reclassification metrics and

performance characteristics of the biomarker score are susceptible to misclassification of participants (cases versus noncases) in whom follow-up information is not complete. Finally, our sample comprised middle-aged white individuals of European ancestry, and our results may not be generalizable to other age groups or ethnicities.

Conclusions

Refining HF prediction is a fundamental step for preventing the condition. In our prospective investigation of a large community-based sample of middle-aged whites, we identified BNP and UACR as key biomarkers associated with HF risk. However, the incremental usefulness of these biomarkers over standard clinical factors (as assessed by c statistics and NRI) is very modest. Additional investigations are therefore warranted both to replicate our findings and to assess their applicability to routine clinical settings.

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Disclosures
None.

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CLINICAL PERSPECTIVE

Several biological pathways have been individually implicated in left ventricular remodeling and/or heart failure (HF) development, but it is unclear whether biomarkers reflecting these pathways aid in the prediction and stratification of HF risk beyond standard risk factors. In a community-based sample, we prospectively related a panel of circulating biomarkers representing distinct biological pathways, viz, aldosterone-to-renin ratio (renin-angiotensin-aldosterone axis), C-reactive protein (inflammation), plasminogen activator inhibitor-1 (fibrinolysis), B-type natriuretic peptide (natriuretic peptide system), homocysteine (oxidative stress), and the urine albumin-to-creatinine ratio (endothelial function) to the risk of developing new-onset HF. We used a multimarker approach that permitted a comparison of the biomarkers in relation to their contributions to HF risk while limiting multiple testing. We also related a biomarker score (based on biomarkers associated with HF) to HF risk. After adjustment for conventional HF risk factors, B-type natriuretic peptide and urine albumin-to-creatinine ratio emerged as key HF risk predictors. When B-type natriuretic peptide and urine albumin-to-creatinine ratio were modeled as a biomarker score, we observed a striking 10-fold increase in HF incidence across tertiles of biomarker score. Biomarkers provided incremental information over clinical risk factors for predicting HF as assessed by significant improvements in c statistic and net reclassification. The predictive ability of biomarkers was maintained in subgroups with normal left ventricular function, those with renal function, and those without intervening ischemic events. Our findings are consistent with the notion that activation of the natriuretic peptide system and the presence of endothelial dysfunction antedate and predict HF.

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