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IMPORTANCE Nearly half of all patients with heart failure have preserved ejection fraction (HFpEF) as opposed to reduced ejection fraction (HFrEF), yet associations of biomarkers with future heart failure subtype are incompletely understood.

OBJECTIVE To evaluate the associations of 12 cardiovascular biomarkers with incident HFpEF vs HFrEF among adults from the general population.

DESIGN, SETTING, AND PARTICIPANTS This study included 4 longitudinal community-based cohorts: the Cardiovascular Health Study (1989-1990; 1992-1993 for supplemental African-American cohort), the Framingham Heart Study (1995-1998), the Multi-Ethnic Study of Atherosclerosis (2000-2002), and the Prevention of Renal and Vascular End-stage Disease study (1997-1998). Each cohort had prospective ascertainment of incident HFpEF and HFrEF. Data analysis was performed from June 25, 2015, to November 9, 2017.

EXPOSURES The following biomarkers were examined: N-terminal pro B-type natriuretic peptide or brain natriuretic peptide, high-sensitivity troponin T or I, C-reactive protein (CRP), urinary albumin to creatinine ratio (UACR), renin to aldosterone ratio, D-dimer, fibrinogen, soluble suppressor of tumorigenicity, galectin-3, cystatin C, plasminogen activator inhibitor 1, and interleukin 6.

MAIN OUTCOMES AND MEASURES Development of incident HFpEF and incident HFrEF.

RESULTS Among the 22 756 participants in these 4 cohorts (12 087 women and 10 669 men; mean [SD] age, 60 [13] years) in the study, during a median follow-up of 12 years, 633 participants developed incident HFpEF, and 841 developed HFrEF. In models adjusted for clinical risk factors of heart failure, 2 biomarkers were significantly associated with incident HFpEF: UACR (hazard ratio [HR], 1.33; 95% CI, 1.20-1.48; $P < .001$) and natriuretic peptides (HR, 1.27; 95% CI, 1.16-1.40; $P < .001$), with suggestive associations for high-sensitivity troponin (HR, 1.11; 95% CI, 1.03-1.19; $P = .008$), plasminogen activator inhibitor 1 (HR, 1.22; 95% CI, 1.03-1.45; $P = .02$), and fibrinogen (HR, 1.12; 95% CI, 1.03-1.22; $P = .01$). By contrast, 6 biomarkers were associated with incident HFrEF: natriuretic peptides (HR, 1.54; 95% CI, 1.41-1.68; $P < .001$), UACR (HR, 1.21; 95% CI, 1.11-1.32; $P < .001$), high-sensitivity troponin (HR, 1.37; 95% CI, 1.29-1.46; $P < .001$), cystatin C (HR, 1.19; 95% CI, 1.11-1.27; $P < .001$), D-dimer (HR, 1.22; 95% CI, 1.11-1.35; $P < .001$), and CRP (HR, 1.19; 95% CI, 1.11-1.28; $P < .001$). When directly compared, natriuretic peptides, high-sensitivity troponin, and CRP were more strongly associated with HFrEF compared with HFpEF.

CONCLUSIONS AND RELEVANCE Biomarkers of renal dysfunction, endothelial dysfunction, and inflammation were associated with incident HFrEF. By contrast, only natriuretic peptides and UACR were associated with HFpEF. These findings highlight the need for future studies focused on identifying novel biomarkers of the risk of HFpEF.

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Supplemental content

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Heart failure (HF) is a major worldwide public health burden. The lifetime risk of HF is substantial, occurring in 20% of both men and women.[1,2] With aging populations in the United States and European Union, the overall prevalence of HF is predicted to triple by 2060.[2] There is a strong need to improve methods to identify people who are at high risk for developing HF and to implement effective preventive measures. Several previous studies have demonstrated the utility of targeting HF prevention efforts to higher-risk individuals who were identified by single biomarker assessments.[3,4] Individual assessment of HF risk, however, is still in its infancy, and the clinical applicability of existing models of assessment of HF risk is limited. Furthermore, half of patients presenting with HF are classified as preserved ejection fraction (HFpEF) vs reduced ejection fraction (HFrEF). This distinction has important therapeutic implications, yet differences in antecedent factors preceding each HF subtype are poorly understood.

Challenges in assessment of HF risk include the relatively low incidence rate in asymptomatic community-dwelling individuals, the heterogeneity of the phenotype, and a lengthy subclinical phase requiring long-term follow-up. To fill this gap in the literature, we established an international collaboration to create and validate risk assessment models for incident HF subtypes.[5] We have pooled data from 4 large community-based longitudinal cohorts: the Framingham Heart Study (FHS),[6,7] the Cardiovascular Health Study (CHS),[8] the Prevention of Renal and Vascular End-stage Disease (PREVEND) cohort,[9] and the Multi-Ethnic Study of Atherosclerosis (MESA).[10] A previous study has examined differences in clinical factors traditionally associated with HFpEF vs HFrEF, including age, blood pressure, and body weight.[5] Whether biomarkers can offer additional insights into risk of future HFpEF vs HFrEF remains unknown. We therefore sought to investigate the association of cardiovascular biomarkers representing several biological pathways, including myocyte stretch, stress, inflammation, and renal function, with the development of future HFpEF vs HFrEF. We leveraged pathway biomarkers that were previously measured across at least 2 cohorts. We hypothesized that biomarker profiles preceding HFpEF would be distinct from those preceding HFrEF given that different predominant pathophysiologic drivers are thought to underlie myocardial remodeling in these 2 entities.[11]

Key Points

Question What cardiovascular biomarkers are associated with the development of heart failure with preserved vs reduced ejection fraction?

Findings Among 22 756 participants enrolled in 4 longitudinal community-based cohorts, several biomarkers of renal dysfunction, endothelial dysfunction, and inflammation, in addition to natriuretic peptides and high-sensitivity troponin, were associated with incident heart failure with reduced ejection fraction. By contrast, only natriuretic peptides and urinary albumin to creatinine ratio were associated with heart failure with preserved ejection fraction.

Meaning These findings highlight the need for future studies focused on identifying novel biomarkers of heart failure with preserved ejection fraction.

Methods

Study Sample

We harmonized and pooled individual-level data from 4 prospective, observational community-based cohorts with adjudicated incident HF outcomes as previously described.[5] We included 24 803 participants with at least 1 biomarker assessment available from the following baseline examinations: FHS offspring cohort exam 6 (1995-1998), CHS exam 1 (1989-1990; 1992-1993 for supplemental African-American cohort), PREVEND exam 1 (1997-1998), and MESA exam 1 (2000-2002). Individuals with prevalent HF (n = 326), age younger than 30 years (n = 124), missing covariates (n = 1570), or without follow-up available (n = 27) were excluded, leaving 22 756 individuals for analysis. Written informed consent was obtained for all study participants, and institutional review board approval was obtained separately for all 4 cohorts (from Boston University [FHS]; Columbia University [MESA]; Johns Hopkins University [CHS and MESA]; Northwestern University [MESA]; University of California, Davis [CHS]; University of California, Los Angeles [MESA]; University of Groningen [PREVEND]; University of Minnesota [MESA]; University of Pittsburgh [CHS]; and Wake Forest University [CHS and MESA]).

Clinical Assessment

A detailed medical history, physical examination, fasting blood draw, and electrocardiography were performed on all participants at the baseline examinations. Risk factors were evaluated and harmonized across cohorts whenever possible, as described.[5] Blood pressure was taken as the mean of 2 seated measurements. Body mass index was calculated as weight in kilograms divided by height in meters squared. Diabetes was defined as a fasting glucose level of 126 mg/dL or more (to convert to millimoles per liter, multiply by 0.0555), random glucose level of 200 mg/dL or more, or the use of hypoglycemic medications. Electrocardiographic left ventricular (LV) hypertrophy was defined based on accepted voltage and ST-segment criteria, as described previously.[5]

Definition of Incident HF Subtypes

Individuals were followed prospectively for the occurrence of incident HF or death. Outcomes were adjudicated using established protocols by study investigators within each cohort after review of all available outpatient and hospital records. Heart failure was defined using a combination of signs and symptoms, as described previously.[5] Each first incident HF event was categorized as HFpEF (LV ejection fraction [LVEF], ≥50%), HFrEF (LVEF, <50%), or unclassified (no LV function assessment available).[5] After an incident HF event, participants were censored and were not at risk for the other HF subtype or unclassified HF.

Biomarker Assays

eTable 1 in the Supplement summarizes cohort-specific assay details of the following 12 biomarkers, which were available in

at least 2 of 4 cohorts: C-reactive protein, interleukin 6, plasminogen activator inhibitor 1, D-dimer, fibrinogen, galectin-3, N-terminal pro B-type natriuretic peptide (NT-proBNP), renin, aldosterone, high-sensitivity cardiac troponin (hs-Tn) T or I, soluble suppressor of tumorigenicity 2, urinary albumin to creatinine ratio (UACR), and cystatin C. For natriuretic peptides, brain natriuretic peptide was measured in the FHS cohort and NT-proBNP in the other cohorts. Similarly, hs-TnI was measured in the FHS cohort and hs-TnT in the remaining cohorts.

Statistical Analysis

Statistical analysis was performed from June 25, 2015, to November 9, 2017. Baseline clinical characteristics for participants with at least 1 biomarker available were summarized by cohort. Biomarker concentrations were natural log transformed. To account for interassay and cohort-specific factors, we performed direct standardization within each cohort to center mean values to 0 and set each unit change to 1 SD. Individual-level data from each of the 4 cohorts were then pooled for the subsequent analyses. Follow-up time was truncated at 15 years.

We used Fine-Gray proportional subdistribution hazards models to evaluate the association of each individual biomarker with overall HF and HF subtypes of HFpEF and HFrEF in the pooled sample.[12] These models accounted for the competing risks of death, other HF subtype, and unclassified HF. This technique was chosen to account for informative censoring when evaluating the association of biomarkers and incident HF subtypes. Models were adjusted for age and sex, and then additionally for race/ethnicity, previous myocardial infarction, hypertension treatment, systolic blood pressure, smoking status, presence of LV hypertrophy or left bundle branch block, and diabetes.[5] The "strata" statement was included to account for study cohort as well as for stratified recruitment in PREVEND (24-hour urine albumin excretion >10 mg/L vs <10 mg/L at recruitment [to convert to grams per liter, multiply by 10.0]). Secondary analyses accounted for both cohort and recruitment center among CHS and MESA participants, without substantial differences in findings. Results for primary analyses were considered significant using a Bonferroni-corrected, 2-sided *P* value threshold corrected for the 12 biomarkers tested, $P = .05/12 = .004$. Results with $.004 < P < .05$ were considered suggestive. The β coefficients associating each biomarker with HFpEF vs HFrEF were formally tested for equality using the method of Lunn and McNeil.[13]

In secondary analyses, we additionally adjusted for estimated glomerular filtration rate, interim myocardial infarction, and natriuretic peptides. We examined a multimarker model containing biomarkers available in all 4 cohorts (hs-Tn, natriuretic peptides, C-reactive protein, and cystatin C) along with clinical factors. We also conducted cohort-specific analyses (age- and sex-adjusted and multivariable-adjusted) and tested for age × biomarker associations.

We assessed the incremental effect of each biomarker on its association with HFpEF and HFrEF. C statistics were compared between models with clinical covariates alone (based on a previously validated prediction model)[5] and models including both clinical covariates and the given biomarker. We calculated the category-free net reclassification index using previously described methods.[14] We created a biomarker risk score from significant biomarkers that were available in 3 or more cohorts.[15] The biomarker risk score for HFpEF was composed of UACR, natriuretic peptides, and hs-Tn, and the risk score for HFrEF included UACR, natriuretic peptides, hs-Tn, cystatin C, and C-reactive protein. We then examined the risk of HF subtype by quartiles of biomarker risk score. All statistical analyses were conducted with SAS, version 9.4 software (SAS Institute).

Results

There were 22 756 participants for analysis: 3431 (15.1%) from FHS, 5277 (23.2%) from CHS, 7369 (32.4%) from PREVEND, and 6679 (29.4%) from MESA. Mean (SD) baseline ages of participants ranged from 49 (12) years in PREVEND to 73 (6) years in CHS, with a mean (SD) age of 60 (13) years for the total cohort; 12 087 of the participants (53.1%) were women. Baseline clinical characteristics by cohort are detailed in **Table 1**. Over a mean (SD) follow-up of 12 (3) years, there were a total of 2095 incident HF events. Within this group, 1474 (70.4%) had cardiac imaging available at or around the time of HF presentation, allowing for classification of HF subtypes. Among the participants whose HF subtype was classified, there were 633 HFpEF events (42.9%) and 841 HFrEF events (57%.1). Over the same follow-up period, there were 5187 deaths (22.8%).

Biomarker Distribution in the Cohort

Mean biomarker concentrations at baseline are displayed in eTable 2 in the Supplement and generally were within the normal range, as expected in community-based samples. There were modest intrabiomarker correlations, with the 5 largest age- and sex-adjusted partial correlation coefficients for hs-Tn and natriuretic peptides ($r = 0.29$; $P < .001$), galectin-3 and cystatin-C ($r = 0.30$; $P < .001$), C-reactive protein and fibrinogen ($r = 0.49$; $P < .001$), interleukin 6 and fibrinogen ($r = 0.40$; $P < .001$), and interleukin 6 and C-reactive protein ($r = 0.53$; $P < .001$) (eTable 3 in the Supplement).

Biomarker Associations With HF Subtypes

Cohort-specific associations of biomarkers with HFpEF and HFrEF are presented in **Table 2** and show some differences in effect sizes between cohorts. In pooled analyses, after adjusting for age, sex, race/ethnicity, systolic blood pressure, hypertension treatment, body mass index, diabetes, smoking status, presence of LV hypertrophy, and left bundle branch block, only UACR (hazard ratio [HR], 1.33; 95% CI, 1.20-1.48; $P < .001$) and natriuretic peptides (HR, 1.27; 95% CI, 1.16-1.40; $P < .001$) were associated with risk for HFpEF (**Table 3** and **Figure**). Suggestive associations were observed with hs-Tn (HR, 1.11; 95% CI, 1.03-1.19; $P = .008$), plasminogen activator inhibitor 1 (HR, 1.22; 95% CI, 1.03-1.45; $P = .02$), and fibrinogen (HR, 1.12; 95% CI, 1.04-1.22; $P = .01$) (Table 3 and Figure). By contrast, 6 individual biomarkers were positively associated with HFrEF: natriuretic peptides (HR, 1.54; 95% CI, 1.41-1.68; $P < .001$), UACR (HR, 1.21; 95% CI, 1.11-1.32; $P < .001$), hs-Tn (HR, 1.37; 95% CI, 1.29-1.46; $P < .001$), cystatin C (HR, 1.19; 95% CI, 1.11-1.27; $P < .001$), D-dimer (HR, 1.22; 95% CI, 1.11-1.35; $P < .001$), and

Table 1. Baseline Clinical and Laboratory Covariates by Cohort

Characteristic	Patients, No. (%)				
	CHS (n = 5277)	FHS (n = 3431)	MESA (n = 6679)	PREVEND (n = 7369)	Total (n = 22 756)
Demographics					
Age, mean (SD), y	73 (6)	59 (10)	62 (10)	49 (12)	60 (13)
Women	3038 (57.6)	1826 (53.2)	3521 (52.7)	3702 (50.2)	12 087 (53.1)
Race/ethnicity					
White	4470 (84.7)	3431 (100)	2561 (38.3)	7001 (95.0)	17 463 (76.7)
Black	778 (14.7)	0	1838 (27.5)	65 (0.9)	2681 (11.8)
Asian	3 (0.06)	0	798 (11.9)	159 (2.2)	960 (4.2)
American Indian	11 (0.2)	0	0	0	11 (0.05)
Hispanic	0	0	1482 (22.2)	0	1482 (6.5)
Other	15 (0.3)	0	0	89 (1.2)	104 (0.5)
Clinical covariates					
Systolic blood pressure, mean (SD), mm Hg	136 (21)	128 (19)	127 (22)	129 (20)	130 (21)
Diastolic blood pressure, mean (SD), mm Hg	71 (11)	75 (9)	72 (10)	74 (10)	73 (10)
Heart rate, mean (SD), beats/min	68 (11)	64 (10)	63 (10)	69 (10)	66 (11)
BMI, mean (SD)	26.7 (4.7)	27.9 (5.2)	28.3 (5.5)	26.1 (4.2)	27.1 (4.9)
Hypertension treatment	2396 (45.4)	962 (28.0)	2479 (37.1)	1001 (13.6)	6838 (30.0)
Diabetes	819 (15.5)	334 (9.7)	841 (12.6)	272 (3.7)	2266 (10.0)
Current smoker	626 (11.9)	525 (15.3)	872 (13.1)	2518 (34.2)	4541 (20.0)
Prior myocardial infarction	418 (7.9)	113 (3.1)	0	405 (5.5)	936 (4.1)
Laboratory covariates					
Total cholesterol, mean (SD), mg/dL	212 (39)	206 (40)	194 (36)	218 (44)	208 (41)
High-density lipoprotein cholesterol, mean (SD), mg/dL	54 (16)	51 (16)	51 (15)	51 (15)	52 (15)
Electrocardiographic covariates					
Left ventricular hypertrophy	227 (4.3)	74 (2.2)	242 (3.6)	174 (2.4)	717 (3.2)
Left bundle branch block	83 (1.6)	35 (1.0)	23 (0.3)	30 (0.4)	171 (0.8)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHS, Cardiovascular Health Study; FHS, Framingham Heart Study; MESA, Multi-Ethnic Study of Atherosclerosis; PREVEND, Prevention of Renal and Vascular End-stage Disease.

SI conversion factors: To convert total cholesterol and high-density lipoprotein cholesterol to millimoles per liter, multiply by 0.0259.

C-reactive protein (HR, 1.19; 95% CI, 1.11-1.28; $P < .001$). All significant biomarkers appeared to have linear associations with incident HF outcomes when examined using restricted cubic splines.

When formally tested, natriuretic peptides, C-reactive protein, and hs-Tn had differential associations with HFrEF vs HFpEF; these biomarkers were more strongly associated with HFrEF compared with HFpEF. Specifically, a 1-SD increase in log-transformed natriuretic peptides was associated with a 1.5-fold increased risk of future HFrEF (95% CI, 1.41-1.68) compared with a 1.3-fold increased risk of HFpEF (95% CI, 1.16-1.40; $P = .005$ for difference). Similarly, a 1-SD increase in hs-Tn was associated with a 1.4-fold increased risk of HFrEF (95%, CI, 1.29-1.46), whereas hs-Tn was more weakly associated with HFpEF (HR, 1.11; 95% CI, 1.03-1.19; $P = .008$; $P < .001$ for difference).

Incremental Performance Metrics of Biomarkers in Clinical Models

To further investigate if the addition of biomarkers to our base clinical model would improve estimation of risk, we calculated the increment in C statistics from the addition of individual biomarkers to clinical models estimating HFpEF and HFrEF (**Table 4**). Several biomarkers increased the C statistics, especially for HFrEF, such as natriuretic peptides (+0.022) and hs-Tn (+0.021). For HFpEF, the increment was smaller, with the largest increment for UACR (+0.010). Similarly, the category-free net reclassification index was modest for single biomarker models—the largest net reclassification index for HFpEF was with the addition of natriuretic peptides (0.16; 95% CI, 0.06-0.26). High-sensitivity troponin also had the largest net reclassification index for association with HFrEF (0.25; 95% CI, 0.17-0.33).

Multimarker Models

In a multimarker model including biomarkers available in all 4 cohorts (hs-Tn, natriuretic peptides, C-reactive protein, and cystatin C), only natriuretic peptides remained associated with HFpEF after accounting for clinical HF risk factors (HR, 1.27; 95% CI, 1.14-1.41; $P < .001$), whereas other biomarkers were not significant. By contrast, hs-Tn (HR, 1.24; 95% CI, 1.15-1.34; $P < .001$) and natriuretic peptides were associated with HFrEF (HR, 1.44; 95% CI, 1.30-1.58; $P < .001$), with a suggestive association for C-reactive protein (HR, 1.10; 95% CI, 1.01-1.20; $P = .03$). For HFpEF, the C statistic increment with addition of multimarkers was limited (0.787- 0.795); for HFrEF, addition

Table 2. Cohort-Specific Associations of Individual Biomarker With HFpEF and HFrEF

Biomarker	Subdistribution Hazard Ratio (95% CI)[a]			
	CHS	FHS	MESA	PREVEND
HFpEF				
UACR	NA	1.27 (1.02-1.57)	1.32 (1.10-1.58)	1.32 (1.14-1.53)
Natriuretic peptide	1.12 (0.99-1.28)	1.51 (1.23-1.86)	1.80 (1.39-2.33)	1.17 (0.94-1.45)
PAI-1	NA	1.23 (0.93-1.61)	2.28 (1.38-3.77)	1.11 (0.87-1.42)
Fibrinogen	1.08 (0.96-1.20)	1.25 (1.01-1.54)	1.16 (0.95-1.41)	NA
IL-6	1.10 (0.97-1.24)	NA	1.18 (0.94-1.47)	NA
hs-Tn	1.15 (1.02-1.29)	1.12 (0.98-1.29)	1.28 (1.06-1.56)	1.00 (0.86-1.17)
Cystatin C	1.13 (1.01-1.27)	1.07 (0.90-1.28)	1.08 (0.87-1.34)	1.01 (0.85-1.19)
D-dimer	1.03 (0.86-1.22)	0.98 (0.75-1.28)	1.11 (0.90-1.38)	NA
sST2	1.01 (0.90-1.14)	1.19 (0.96-1.48)	NA	NA
CRP	1.08 (0.95-1.22)	0.95 (0.73-1.22)	1.25 (1.01-1.56)	0.82 (0.64-1.04)
Aldosterone to renin ratio	NA	1.01 (0.87-1.18)	NA	1.05 (0.90-1.24)
Galectin-3	1.10 (0.98-1.23)	1.05 (0.85-1.30)	NA	0.79 (0.66-0.96)
HFrEF				
UACR	NA	1.42 (1.11-1.82)	1.26 (1.10-1.45)	1.08 (0.96-1.22)
Natriuretic peptide	1.30 (1.14-1.48)	1.31 (1.06-1.61)	2.33 (1.92-2.84)	1.80 (1.51-2.13)
PAI-1	NA	1.21 (0.92-1.59)	1.02 (0.60-1.73)	0.99 (0.83-1.18)
Fibrinogen	1.09 (0.99-1.20)	1.17 (0.96-1.43)	1.09 (0.92-1.30)	NA
IL-6	1.11 (1.00-1.23)	NA	1.15 (0.95-1.39)	NA
hs-Tn	1.21 (1.08-1.36)	1.46 (1.28-1.66)	1.62 (1.42-1.84)	1.44 (1.30-1.60)
Cystatin C	1.16 (1.07-1.27)	1.43 (1.20-1.71)	1.26 (1.13-1.41)	1.09 (0.93-1.28)
D-dimer	1.16 (1.00-1.36)	1.33 (1.04-1.71)	1.24 (1.06-1.46)	NA
sST2	0.94 (0.84-1.06)	1.28 (1.01-1.64)	NA	NA
CRP	1.15 (1.04-1.28)	1.59 (1.33-1.90)	1.15 (0.95-1.40)	1.19 (1.02-1.38)
Aldosterone to renin ratio	NA	1.03 (0.85-1.25)	NA	1.08 (0.96-1.22)
Galectin-3	0.99 (0.89-1.10)	1.26 (1.03-1.53)	NA	1.09 (0.94-1.26)

Abbreviations: CHS, Cardiovascular Health Study; CRP, C-reactive protein; FHS, Framingham Heart Study; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hs-Tn, high-sensitivity troponin; IL-6, interleukin 6; MESA, Multi-Ethnic Study of Atherosclerosis; NA, not available; PAI-1, plasminogen activator inhibitor 1; PREVEND, Prevention of Renal and Vascular End-stage Disease; sST2, soluble suppressor of tumorigenicity; UACR, urinary albumin to creatinine ratio.

[a] Subdistribution hazard ratio (Fine-Gray model) per 1-SD increase in natural log-transformed biomarker. Multivariable model is adjusted for age, sex, race/ethnicity, previous myocardial infarction, body mass index, hypertension treatment, systolic blood pressure, smoking status, presence of left ventricular hypertrophy or left bundle branch block, and diabetes.

of the 4 biomarkers to the model was associated with a modest increment (0.804-0.839).

We created a biomarker risk score of significant biomarkers available across at least 3 cohorts and found an increase in HR across risk score quartiles (eTable 4 in the Supplement). For HFpEF, HR among the fourth quartile was 4.96 (95% CI, 2.54-9.70), with the first quartile serving as the reference. For HFrEF, the HR among the fourth quartile was 10.95 (95% CI, 5.67-21.17) compared with the first quartile.

Secondary Analyses and Effect Modification

We calculated cohort-specific associations of the biomarkers with HF subtypes to query if outcomes could be driven by the results in 1 cohort, with age- and sex-adjusted analyses presented in eTable 5 in the Supplement and multivariable models in Table 2. The direction of associations between the biomarkers and incident HF subtypes was generally consistent across cohorts despite modest differences in individual β coefficients. In further analyses, we additionally adjusted multivariable models for estimated glomerular filtration rate, interim myocardial infarction, and natriuretic peptides (eTable 6A and 6B in the Supplement). Overall, these adjustments resulted in minor changes in effect estimates.

We tested for effect modification by age on the associations of biomarkers and HF subtypes using cohort-specific models (eTable 7 in the Supplement). In models adjusted for clinical covariates, statistically significant interactions between biomarkers and age were observed for the association of HFpEF with UACR, natriuretic peptides, hs-Tn, and aldosterone to renin ratio in at least 1 cohort. For the HFrEF analyses, statistically significant age × biomarker associations were observed for UACR, natriuretic peptides, and C-reactive protein.

Discussion

In the current analysis, we evaluated the associations of 12 cardiovascular biomarkers with incident HFpEF and HFrEF among 4 longitudinal community-based cohorts with more than 2000 incident HF events.[5] Our principal findings were as follows: natriuretic peptides and hs-Tn were more strongly associated with HFrEF compared with HFpEF, UACR was associated with both HFpEF and HFrEF, fewer biomarkers were associated with HFpEF compared with HFrEF, and the incremental value of individual biomarkers when added to a robust clinical model was modest. Whereas HFpEF and HFrEF have a shared clinical presentation and common clinical risk factors, these findings suggest that some antecedent factors preceding HFpEF and HFrEF may be distinct. For example, myocyte necrosis (hs-Tn) appears to play a larger role in the development of HFrEF, whereas low-grade albuminuria, a

Table 3. Multivariable-Adjusted Pooled Associations of Individual Biomarkers With HF Subtypes

	Overall HF		HFpEF		HFrEF		*P* Value for Equality[a]
Biomarker	sHR (95% CI)[b]	*P* Value	sHR (95% CI)[b]	*P* Value	sHR (95% CI)[b]	*P* Value	HFpEF vs HFrEF
UACR	1.26 (1.18-1.35)	<.001	1.33 (1.20-1.48)	<.001	1.21 (1.11-1.32)	<.001	.16
Natriuretic peptides[c]	1.50 (1.41-1.59)	<.001	1.27 (1.16-1.40)	<.001	1.54 (1.41-1.68)	<.001	.005
PAI-1	1.10 (0.99-1.23)	.07	1.22 (1.03-1.45)	.02	1.06 (0.92-1.22)	.42	.23
Fibrinogen	1.11 (1.06-1.16)	<.001	1.12 (1.03-1.22)	.01	1.10 (1.01-1.18)	.02	.73
IL-6	1.10 (1.03-1.16)	.001	1.10 (0.99-1.22)	.09	1.11 (1.01-1.21)	.03	.92
hs-Tn[c]	1.31 (1.26-1.38)	<.001	1.11 (1.03-1.19)	.008	1.37 (1.29-1.46)	<.001	<.001
Cystatin C	1.16 (1.10-1.21)	<.001	1.07 (0.98-1.16)	.11	1.19 (1.11-1.27)	<.001	.08
D-dimer	1.16 (1.09-1.24)	<.001	1.06 (0.94-1.19)	.35	1.22 (1.11-1.35)	<.001	.08
sST2	1.10 (1.03-1.17)	.004	1.05 (0.95-1.16)	.37	1.00 (0.90-1.11)	.98	.53
CRP	1.15 (1.09-1.20)	<.001	1.04 (0.95-1.14)	.77	1.19 (1.11-1.28)	<.001	.02
Aldosterone to renin ratio	1.04 (0.97-1.12)	.29	1.03 (0.92-1.16)	.60	1.05 (0.95-1.17)	.33	.90
Galectin-3	1.07 (1.02-1.12)	.01	1.02 (0.93-1.12)	.13	1.05 (0.97-1.13)	.28	.65

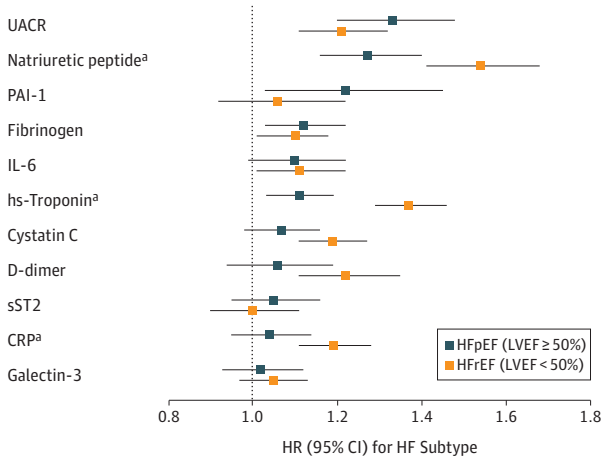
Abbreviations: CRP, C-reactive protein; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hs-Tn, high-sensitivity troponin; IL-6, interleukin 6; PAI-1, plasminogen activator inhibitor 1; sHR, subdistribution hazard ratio; sST2, soluble suppressor of tumorigenicity; UACR, urinary albumin to creatinine ratio.

[a] Comparing sHR for individual biomarker association with HFpEF vs HFrEF (Lunn McNeil test).

[b] Subdistribution hazard ratio (Fine-Gray model) per 1-SD increase in natural log-transformed biomarker. Adjusted for age, sex, race/ethnicity, systolic blood pressure, hypertension treatment, body mass index, diabetes, smoking, presence of left ventricular hypertrophy or left bundle branch block, and previous myocardial infarction. Strata statement included.

[c] Brain natriuretic peptide assay performed in the Framingham Heart Study. N-terminal pro B-type natriuretic peptide performed in the Cardiovascular Health Study, Prevention of Renal and Vascular End-stage Disease and Multi-Ethnic Study of Atherosclerosis; hs-TnI performed in the Framingham Heart Study, hs-TnT performed in the Cardiovascular Health Study, Multi-Ethnic Study of Atherosclerosis, and Prevention of Renal and Vascular End-stage Disease.

Figure. Association of Individual Biomarkers With Incident Heart Failure With Preserved Ejection Fraction (HFpEF) and Heart Failure With Reduced Ejection Fraction (HFrEF) in Multivariable-Adjusted Analyses



Hazard ratios (HRs) and 95% CIs for HFpEF are shown in blue and for HFrEF in grey. Three biomarkers had significantly greater HRs for HFrEF compared with HFpEF, including natriuretic peptides, high-sensitivity troponins (hs-troponins), and C-reactive protein (CRP). IL-6 indicates interleukin 6; LVEF, left ventricular ejection fraction; PAI-1, plasminogen activator inhibitor 1; sST2, soluble suppressor of tumorigenicity; and UACR, urinary albumin to creatinine ratio.

[a] Statistically significant difference between HRs for HFpEF vs HFrEF (using Lunn-McNeil test).

marker of endothelial dysfunction, seems to precede both HFpEF and HFrEF. Overall, our findings also suggest that traditional cardiovascular biomarkers are associated with HFrEF more so than HFpEF, highlighting the need for further studies focused on elucidating drivers of HFpEF.

Heart failure is expected to become even more prevalent in the decades to come,[1,2] a trend that will undoubtedly result in growing morbidity, mortality, and associated costs.[2] This trend underlines the need for HF prevention strategies in light of major challenges of treating clinically overt HF.[1,2] An integral component of disease prevention is a refined understanding of risk estimation. Numerous publications of individual population-based cohorts have examined the association of biomarkers with cardiovascular end points, including new-onset HF.[15-30] By far, the strongest evidence exists for natriuretic peptides: individual studies have consistently shown that natriuretic peptides are among the strongest associations with new-onset HF, which was recently confirmed for the estimation of new-onset HF in an individual patient data meta-analysis with more than 95 000 participants and more than 2000 HF events.[30] Therefore, in recent years, several trials were launched that reported the feasibility of acting on elevated levels of natriuretic peptides, which appeared to lower the risk of new onset-HF.[3,4] A downside of this potential strategy is that a sizeable number of participants will need to be treated; therefore, strategies to further enrich risk estimation to target biomarker-based prevention strategies have been put forward.[31] Furthermore, the usefulness of other biomarkers for the estimation of new-onset HF remains largely unclear,[32] with previous studies being limited by modest power and by a limited set of biomarkers.

Although previous community-based studies have focused largely on biomarker associations with overall HF,[15-18,20,21,27,28,30] our unique multicohort collaboration enabled an initial look at specific biomarkers preceding HFpEF vs HFrEF. Interestingly, the association of biomarkers

Table 4. C Statistics and NRI for Multivariable-Adjusted Models

Characteristic	HFpEF		HFrEF	
	C Statistic (95% CI)	*P* Value	C Statistic (95% CI)	*P* Value
UACR				
C statistic, base model[a]	0.817 (0.791 to 0.842)	NA	0.815 (0.793 to 0.836)	NA
C statistic, +UACR	0.827 (0.802 to 0.852)	NA	0.819 (0.798 to 0.840)	NA
Delta C statistic	0.010 (0.001 to 0.018)	.03	0.004 (0.000 to 0.008)	.08
NRI	0.05 (−0.03 to 0.13)	.33	−0.05 (−0.19 to 0.01)	.24
Natriuretic peptide				
C statistic, base model[a]	0.794 (0.775 to 0.814)	NA	0.807 (0.790 to 0.823)	NA
C statistic, +natriuretic peptide	0.799 (0.780 to 0.818)	NA	0.829 (0.813 to 0.844)	NA
Delta C statistic	0.005 (0.000 to 0.011)	.04	0.022 (0.013 to 0.030)	<.001
NRI	0.16 (0.06 to 0.26)	.002	0.17 (0.09 to 0.25)	<.001
hs-Tn				
C statistic, base model[a]	0.783 (0.766 to 0.802)	NA	0.793 (0.777 to 0.809)	NA
C statistic, +hs-Tn	0.787 (0.768 to 0.806)	NA	0.817 (0.802 to 0.832)	NA
Delta C statistic	0.004 (-0.001 to 0.008)	.02	0.021 (0.014 to 0.028)	<.001
NRI	0.11 (0.01 to 0.21)	.03	0.25 (0.17 to 0.33)	<.001
Cystatin C				
C statistic, base model[a]	NA	NA	0.806 (0.790 to 0.822)	NA
C statistic, +cystatin C	NA	NA	0.811 (0.795 to 0.827)	NA
Delta C statistic	NA	NA	0.005 (0.002 to 0.009)	.004
NRI	NA	NA	0.04 (−0.04 to 0.12)	.29
D-dimer				
C statistic, base model[a]	NA	NA	0.792 (0.771 to 0.814)	NA
C statistic, +D-dimer	NA	NA	0.793 (0.771 to 0.815)	NA
Delta C statistic	NA	NA	0.001 (−0.002 to 0.006)	.37
NRI	NA	NA	0.18 (0.11 to 0.25)	<.001
CRP				
C statistic, base model[a]	NA	NA	0.802 (0.787 to 0.818)	NA
C statistic, +CRP	NA	NA	0.806 (0.791 to 0.821)	NA
Delta C statistic	NA	NA	0.004 (0.000 to 0.007)	.047
NRI	NA	NA	0.16 (0.08 to 0.25)	<.001

Abbreviations: CRP, C-reactive protein; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hs-Tn, high-sensitivity troponin; NA, not applicable; NRI, net reclassification index; UACR, urinary albumin to creatinine ratio.

[a] Base model includes age, sex, race/ethnicity, systolic blood pressure, hypertension treatment, body mass index, diabetes, smoking, presence of left ventricular hypertrophy or left bundle branch block, and previous myocardial infarction. Strata statement included.

with risk of HFpEF was clearly less convincing than it was for risk of HFrEF. Likely, the pathophysiology of HFrEF is more easily captured by biomarkers of stretch (NT-proBNP), ischemia (hs-Tn), and inflammation (C-reactive protein). Markers of subclinical renal disease and endothelial dysfunction (indicated by cystatin C and UACR) and subclinical vascular disease (indicated by fibrinogen and D-dimer) were associated with new-onset HFrEF. Whether strategies aimed at targeting these specific pathways may prevent HFrEF remains unknown.

By contrast, only natriuretic peptides and UACR were associated with HFpEF, with suggestive associations for plasminogen activator inhibitor 1, hs-Tn, and fibrinogen. The fact that single biomarker associations overall appeared less powerful at estimating HFpEF highlights the complexity of HFpEF, which is thought to consist of many subphenotypes.[33,34] Natriuretic peptides were associated with HFpEF, albeit with a smaller effect size compared with the association with HFrEF. This finding is recapitulated in clinical HF studies, in which natriuretic peptide levels are observed to be lower in HFpEF vs HFrEF.[35] We observed a strong association of UACR with both HF subtypes, consistent with previous studies, which have demonstrated the association of UACR as a marker of endothelial dysfunction with adverse cardiac mechanics, including diastolic function.[36] The association between cystatin C and HF subtypes was less clear, underscoring that estimated glomerular filtration rate and albuminuria assess distinct components of kidney disease. In a treatment trial of PREVEND, the PREVEND IT (Prevention of Renal and Vascular End-stage Disease Intervention Trial) study, treatment of participants with microalbuminuria but without other signs of overt cardiovascular disease resulted in a reduction of cardiovascular endpoints over the course of 4 to 8 years.[9,37,38] The association of UACR and new-onset HF in individuals with impaired glucose tolerance has been reported,[39] and we extend this association to community-based participants. The interplay between UACR, associated vascular disease, and endothelial dysfunction has been studied in HFpEF.[40] However, the exact association between renal disease, albuminuria, estimated glomerular filtration rate, and HF is complex.[41]

The cohort-specific analyses revealed several interesting findings. First, when we considered the direction of associations between the markers and new-onset HF, we observed that the direction of the association was consistent among

cohorts, adding robustness to our analyses. However, there were clear numerical differences in the effect sizes between the cohorts. The largest differences were observed when comparing FHS and MESA on one hand and PREVEND and CHS on the other hand. In CHS, participants were much older, with a higher prevalence of comorbidities, which possibly resulted in more complex multifactorial HF phenotypes. Indeed, the associations with biomarkers and HF tended to be weaker in CHS, although the direction of the associations again was consistent with the other cohorts. This finding might imply that, in elderly participants with comorbidities, biomarkers are less strongly associated with HF subtypes. In PREVEND, on the other hand, the youngest participants were enrolled with the lowest event rates. A previous study reported that biomarkers are more strongly associated with HF subtypes in participants who have higher (clinical) risk, whereas the association with HF subtypes in a very low-risk population appears less strong.[21] We conclude that the value of biomarkers, as with many diagnostic tests, appears best in the population with intermediate risk.

Limitations

Several limitations deserve mention. We were limited by the available biomarkers in each cohort, and all markers were not available in all cohorts. However, the consistency among cohorts in associations leads us to believe that the biomarkers were measured reliably. Although the availability of 12 biomarkers in a large sample of community-dwelling individuals is a notable strength of our study, several biomarkers previously associated with incident HF were not available for the present analyses. Future studies incorporating additional biomarkers are warranted. The duration between enrollment in the study and the incident HF event was variable; it is well known that the association of biomarkers with HF subtypes may be altered over prolonged periods. In our pooled data set, we defined HFpEF and HFrEF only in individuals who underwent LV function assessment at or around the time of HF presentation, leaving 30% of cases as unclassified HF. We have only a one-time biomarker measurement, while it has been acknowledged that serial sampling over time may be superior in estimation of HF.[42] Biomarker measurements should always be considered in light of their natural variability (assays and individual-dependent); for most biomarkers, such data are available.[43] Last, the LVEF cutpoint that we used to distinguish between HFrEF and HFpEF was 50% and may be debated, although previous sensitivity analyses demonstrate only minor differences when using an LVEF cutpoint of more than 45%,[5] and those with mid-range LVEF between 40% and 50% are largely of intermediate phenotype between HFpEF and HFrEF.

Conclusions

We demonstrate that markers of neurohormonal activation and myocyte necrosis appear to be more strongly associated with HFrEF compared with HFpEF in a unique international collaboration of 4 community-based longitudinal cohorts. Furthermore, biomarkers of renal dysfunction, endothelial dysfunction, and inflammation were associated with incident HFrEF. By contrast, only natriuretic peptides and UACR were associated with HFpEF. In general, biomarkers modestly improved risk estimation, and discrimination metrics overall were lower for HFpEF models, highlighting current limitations in our understanding of factors underlying the development of HFpEF. Although some studies demonstrate the potential utility of biomarker-guided prevention strategies,[3,4] nuances in antecedent factors differentiating HFpEF and HFrEF highlight the need for future studies to examine the role of biomarkers in HF subtype-specific risk estimation.

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