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Older Adults, "Malignant" Left Ventricular Hypertrophy, and Associated Cardiac-Specific Biomarker Phenotypes to Identify the Differential Risk of New-Onset Reduced Versus Preserved Ejection Fraction Heart Failure

CHS (Cardiovascular Health Study)

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ABSTRACT

OBJECTIVES This study hypothesized that biomarkers of subclinical myocardial injury (high-sensitivity cardiac troponin T [hs-cTnT]) and hemodynamic stress (N-terminal pro-B-type natriuretic peptide [NT-proBNP]) would differentiate heart failure (HF) risk among older adults with left ventricular hypertrophy (LVH).

BACKGROUND The natural history of LVH, an important risk factor for HF, is heterogeneous.

METHODS NT-proBNP and hs-cTnT were measured at baseline and after 2 to 3 years in older adults without prior HF or myocardial infarction in the CHS (Cardiovascular Health Study). LVH and left ventricular ejection fraction were determined by echocardiography. HF events were adjudicated over a median of 13.1 years and classified as preserved or reduced left ventricular ejection fraction (heart failure with preserved ejection fraction or heart failure with reduced ejection fraction [HFrEF]). Adjusted risk of HF by LVH and biomarker tertiles, and by LVH and longitudinal increase in each biomarker was estimated using Cox regression.

RESULTS Prevalence of LVH was 12.5% among 2,347 participants with complete measures. Adjusted risk of HF (N = 643 events) was approximately 3.8-fold higher among participants with LVH and in the highest biomarker tertile, compared with those with low biomarker levels without LVH (NT-proBNP, hazard ratio [HR]: 3.78; 95% confidence interval [CI]: 2.78 to 5.15 and hs-cTnT, HR: 3.86; 95% CI: 2.84 to 5.26). The adjusted risk of HFrEF was 7.8 times higher among those with the highest tertile of hs-cTnT and LVH (HR: 7.83; 95% CI: 4.43 to 13.83). Those with LVH and longitudinal increases in hs-cTnT or NT-proBNP were approximately 3-fold more likely to develop HF, primarily HFrEF, compared with those without LVH and with stable biomarkers.

CONCLUSIONS The combination of LVH with greater hs-cTnT or NT-proBNP levels, and their longitudinal increase, identifies older adults at highest risk for symptomatic HF, especially HFrEF. These biomarkers may characterize subphenotypes in the transition from LVH to HF and suggest modifiable targets for prevention. (J Am Coll Cardiol HF 2015;3:445-55) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

ARB = angiotensin receptor blocker

BNP = brain natriuretic peptide

CI = confidence interval

EF = ejection fraction

eGFR = estimated glomerular filtration rate

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

HR = hazard ratio

hs-cTnT = high-sensitivity cardiac troponin T

LV = left ventricular

LVEF = left ventricular ejection fraction

LVH = left ventricular hypertrophy

LVM = left ventricular mass

LVMI = left ventricular mass index

NRI = net reclassification improvement

NT-proBNP = N-terminal pro-B-type natriuretic peptide

RWT = relative wall thickness

Hypertension is present in more than 70% of older adults (1) and is commonly associated with left ventricular hypertrophy (LVH) (2). Although LVH is associated with an increased risk of progression to depressed left ventricular (LV) systolic function, heart failure (HF), and death, the progression to a clinical endpoint is heterogeneous, occurring in only a minority (3,4). In a prior study of middle-aged adults, we showed that biochemical evidence of myocardial injury (as measured by the high-sensitivity cardiac troponin T [hs-cTnT] assay) or myocardial hemodynamic stress (as measured by N-terminal pro-B-type natriuretic peptide [NT-proBNP]) identified a "malignant" phenotype of LVH more likely to progress to HF or death (5).

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Currently, routine cardiac imaging to screen for LVH in hypertensive patients is not recommended, and several important questions remain before considering hs-cTnT or NT-proBNP as part of a strategy to identify individuals with LVH at high risk for progression to HF (6). First, HF is heterogeneous with a near equivalent incidence of heart failure with preserved ejection fraction (HFpEF) and heart failure with reduced ejection fraction (HFrEF) (7). Identification of those at highest risk of HFrEF may be particularly advantageous, because specific therapies exist to reduce progression to symptomatic disease (8). However, clinical and echocardiographic characteristics still have a limited ability to differentiate who will progress to HFrEF versus HFpEF (9,10). Our prior study in middle-aged adults was not able to examine this heterogeneity in HF outcomes or determine whether longitudinal changes in cardiac biomarkers may further modify the risk associated with LVH.

The primary objectives of this study were to: 1) determine whether our prior findings in middle-age adults with LVH would be applicable to older adults and whether there were differential associations with HFrEF versus HFpEF (older adults have a markedly higher incidence of HF, especially HFpEF, compared with younger adults, but also greater comorbidities that can confound the interpretation of cardiac-specific biomarkers); and 2) determine whether longitudinal changes in NT-proBNP and/or hs-cTnT in those with LVH are associated with the preferential development of HFrEF rather than HFpEF.

METHODS

STUDY PARTICIPANTS. The CHS (Cardiovascular Health Study) is a prospective observational study of cardiovascular risk factors in older adults. Detailed descriptions of the methods have been described (11). Study participants included community-dwelling adults aged 65 years or more enrolled at 4 participating centers. Participants (n = 5,201) initially enrolled in 1989 and 1990, and an African-American supplemental cohort (n = 687) enrolled in 1992 and 1993. For the present analysis, we excluded participants with a history of HF, myocardial infarction, or estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 at the time of the initial echocardiogram (described in the next section).

The CHS was approved by the Institutional Review Boards of the University of Washington and participating centers. All participants gave written informed consent. The present analysis was approved by the Institutional Review Board of the University of Maryland.

ECHOCARDIOGRAPHY. The methods for echocardiographic assessment have been described (12). Briefly, 2-dimensional echocardiography was performed in 1989 and 1990 (main cohort only) and again among both cohorts in 1994 and 1995. M-mode measurement of left ventricular mass (LVM) was performed using the method of Devereux et al. (13). LVM could not be

Study investigators and institutions can be found at CHS-NHLBI.org. Funding for measurement of NT-proBNP and hs-cTnT was provided by investigator-initiated grants from Roche Diagnostics Corporation. Dr. Seliger has received grant support from Singulex, Inc. Drs. Seliger, Christenson, and deFilippi have received grant support from Roche Diagnostics. Drs. Seliger, de Lemos, Christenson, and deFilippi have a patent pending relating to combined left ventricular hypertrophy and cardiac biomarkers for heart failure risk stratification. Dr. de Lemos has received grant support and consulting income from Roche Diagnostics and Abbott Diagnostics. Dr. Sorkin is funded by National Institute of Diabetes and Digestive and Kidney Diseases P30 DK072488, National Institute on Aging P30 AG028747, and the Baltimore Veterans Affairs Geriatric Research Education Clinical Center. Dr. deFilippi is a consultant to Siemens Healthcare Diagnostics; receives honorarium from Radiometer; and receives investigator-initiated research funding from Critical Diagnostics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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TABLE 1 Characteristics of Study Participants at Baseline, by LVH and Initial hs-cTnT (N = 2,347)

	No LVH			p Value Test for Trend	LVH			p Value Test for Trend
	Tertile 1	Tertile 2	Tertile 3		Tertile 1	Tertile 2	Tertile 3	
N	932	584	535		87	79	128	
Range, pg/ml*								
Men	<3.00–4.82	4.84–9.23	9.32–43.89		<3.00–4.73	5.29–7.78	9.80–49.60	
Women	<3.00	3.00–6.00	6.02–36.12		<3.00	3.12–5.98	6.55–71.82	
Age, yrs	71.2 ± 4.6	72.7 ± 5.1	73.1 ± 5.6	<0.001	71.5 ± 4.4	73.7 ± 5.8	73.8 ± 5.9	0.006
Male	247 (26.5%)	250 (42.8%)	216 (40.4%)	<0.001	24 (27.6%)	29 (36.7%)	61 (47.7%)	0.003
African American	143 (15.4%)	74 (12.7%)	88 (16.5%)	0.80	12 (13.8%)	8 (10.1%)	16 (12.5%)	0.80
Diabetes	92 (9.8%)	90 (15.4%)	119 (22.2%)	<0.001	12 (13.8%)	9 (11.4%)	28 (21.9%)	0.01
Coronary heart disease	78 (8.4%)	65 (11.1%)	58 (10.8%)	0.09	7 (8.0%)	15 (20.3%)	21 (16.4%)	0.13
Body mass index, kg/m^2	26.1 ± 4.1	26.3 ± 4.4	27.0 ± 4.8	<0.001	26.4 ± 4.4	27.4 ± 4.7	27.1 ± 4.7	0.50
SBP	132.4 ± 19.8	133.6 ± 20.3	140.1 ± 22.5	<0.001	139.2 ± 22.8	143.8 ± 19.6	144.9 ± 24.0	0.07
DBP	70.2 ± 10.3	70.4 ± 10.8	71.4 ± 11.4	0.06	71.4 ± 11.6	72.2 ± 11.2	70.9 ± 13.2	0.70
Hypertensive medications	330 (35.4%)	245 (42.0%)	277 (52.0%)	<0.001	39 (44.8%)	46 (58.3%)	76 (59.4%)	0.04
Smoking				0.90				0.12
Current	112 (12.0%)	51 (8.7%)	51 (9.6%)		13 (13.9%)	6 (7.6%)	16 (12.5%)	
Former	363 (39.0%)	260 (44.6%)	208 (39.0%)		24 (27.6%)	25 (31.7%)	55 (43.0%)	
Never	455 (48.9%)	272 (46.7%)	275 (51.5%)		50 (57.5%)	48 (60.8%)	57 (44.5%)	
$eGFR_{MDRD}$ <60	132 (14.2%)	100 (17.1%)	148 (27.7%)	<0.001	8 (9.2%)	17 (21.5%)	41 (32.0%)	<0.001
Abnormal LVEF†	4 (0.4%)	5 (0.9%)	7 (1.3%)	0.06	1 (1.2%)	2 (2.5%)	14 (10.9%)	0.002
RWT	0.34 (0.30–0.39)	0.35 (0.30–0.40)	0.35 (0.30–0.40)	0.003	0.35 (0.28–0.43)	0.38 (0.31–0.42)	0.37 (0.30–0.43)	0.06
LVMI, g/m^2								
Male	82.6 (71.5–92.9)	82.7 (68.5–96.2)	81.6 (69.8–95.3)	0.90	129.2 (119.8–147.5)	131.7 (126.2–138.8)	128.5 (121.4–152.4)	0.90
Female	71.3 (62.4–80.5)	72.4 (61.7–81.7)	73.8 (64.2–85.1)	0.04	106.4 (103.0–122.4)	112.8 (103.4–121.0)	113.1 (104.7–123.1)	0.10

Values are mean ± SD, n (%), or median (interquartile range). *Biomarker categories are stratified by age and sex; range for age 70 to 75 years shown. †LVEF <45% on initial echocardiogram.

DBP = diastolic blood pressure; $eGFR_{MDRD}$ = estimated glomerular filtration rate Modification of Diet in Renal Disease; hs-cTnT = high-sensitivity cardiac troponin T; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; RWT = relative wall thickness; SBP = systolic blood pressure.

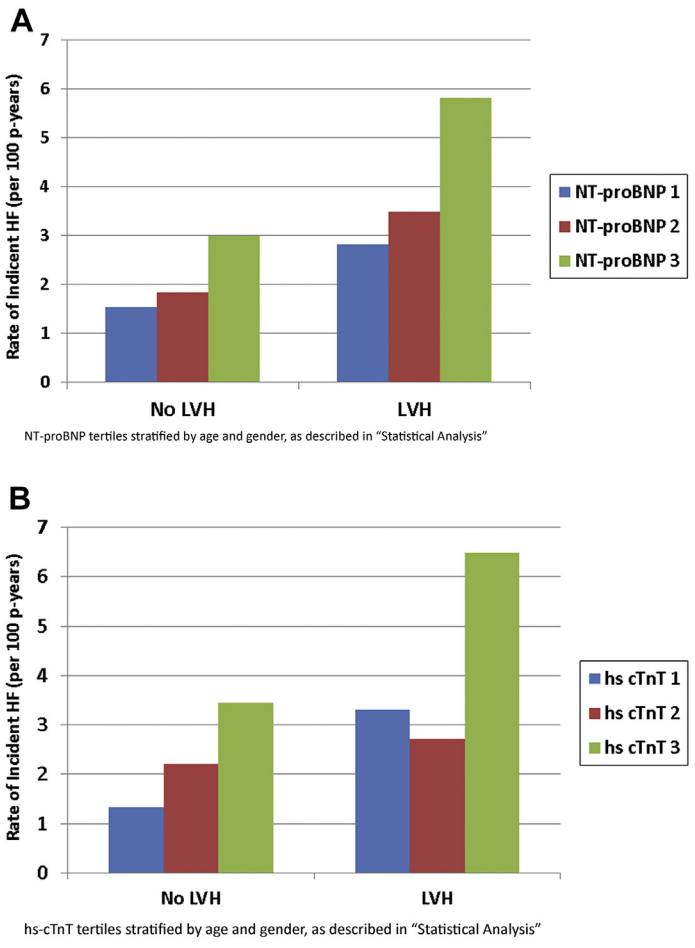
estimated in approximately 34% of the main cohort, who were more likely to be older, Caucasian, male, and of greater height and weight, and to have hypertension, diabetes, and coronary disease (12). Expected LVM was calculated on the basis of normative equations from CHS participants with neither clinical heart disease nor hypertension; LVH was defined as an observed/expected LVM >1.45 (12,14). Left ventricular mass index (LVMI) was calculated as LVM divided by body surface area. For analyses of baseline biomarkers, LVM measured at baseline (main cohort) or in 1994 and 1995 (supplemental cohort) was used as the primary predictor variable; for analyses of change in biomarkers, LV mass measured in 1994 and 1995 in both cohorts was used. Left ventricular ejection fraction (LVEF) was defined as abnormal if visually interpreted as <45%. Relative wall thickness (RWT) was computed as previously described as (2*posterior wall thickness)/(end-diastolic LV diameter) (15). Eccentric LVH was defined as LVH with RWT ≤0.42, and concentric LVH was defined as LVH with RWT >0.42 (15).

Biomarker measurement. NT-proBNP and hs-cTnT were measured in serum samples collected at baseline and again after 3 years (main cohort) or 2 years (supplemental cohort) and stored at −70°C to −80°C. NT-proBNP and cardiac troponin T were measured on the Elecsys 2010 analyzer (Roche Diagnostics, Indianapolis, Indiana), as previously reported (16,17). The performance characteristics of both assays have been described (18).

PRIMARY OUTCOME. The primary outcome was incident HF, ascertained by participant interview at semiannual study visits, medical record review, and examination of Medicare claims data and confirmed by an expert adjudication panel as described previously (19). An HF event was confirmed if a physician diagnosis was present along with documentation in the medical record of a constellation of symptoms and physical signs, supporting clinical findings, or a medical therapy for HF. Events were characterized as HFpEF (LVEF ≥45%) or HFrEF (LVEF <45%) on the basis of clinical echocardiograms or other cardiac imaging performed within 30 days of the HF event (14).

STATISTICAL ANALYSES. Participants were divided into age- and sex-specific tertiles of each biomarker, and differences across these tertiles were compared

FIGURE 1 Rate of Incident HF, by LVH and Tertile of NT-proBNP or hs-cTnT



Incident HF ascertained as described in the Methods section and expressed as number of incident events per 100 person-years. The study sample was divided into age- and sex-specific tertiles of each biomarker, as described in the Methods section. Rate of incident HF varied between those with and without LVH ($p < 0.001$) and by tertile of NT-proBNP **(A)** or hs-cTnT **(B)** ($p < 0.001$ for both). HF = heart failure; hs-cTnT = high-sensitivity cardiac troponin T; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

separately for those with and without LVH, using analysis of variance for continuous variables and Cuzick's score test for binary variables. A total of 895 participants (38%) had undetectable hs-cTnT below the level of blank (<3 ng/l) and were all placed in the first tertile with an imputed value of 2.99 ng/l. Cumulative rates of HF among subjects stratified by LVH and biomarker categories were compared with the log-rank test. Cox proportional hazards models were used to estimate the joint association of LVH and biomarker levels with incident HF, adjusting for potential confounding factors selected a priori. The method of Breslow (20) was used to handle tied events. Joint associations were estimated using LVH*biomarker interaction terms in adjusted models. Similar analyses were performed using LVMI categories in place of LVH. We estimated improvements in reclassification and discrimination of 10-year HF risk among those with LVH from the addition of each biomarker measurement to traditional risk factors with the net reclassification improvement (NRI) and integrated discrimination improvement statistics (21). Consistent with recent recommendations (22), we used the category-less form of the NRI, because there are no consensus thresholds for classifying HF risk among those with LVH. Bootstrapping was used to estimate 95% confidence intervals (CIs) of each NRI.

To examine the joint association of LVH and change in biomarkers with incident HF, Cox proportional hazards models were used, with follow-up time defined as the time from the second echocardiogram (1994 to 1995). A significant change in biomarkers was defined as: 1) an increase in NT-proBNP of >25% to a final level of ≥190 pg/ml; or 2) an increase in hs-cTnT of >50% from baseline. For those participants with an initial hs-cTnT below the level of blank, a level of 2.99 ng/l was imputed. Changes of this magnitude for cardiac troponin T and NT-proBNP have been associated with marked increases in risk of incident HF and cardiovascular death in the CHS (16,17). Adjustments were made for baseline biomarker levels and the same confounding factors as described earlier, measured at the time of the second echocardiogram (except for eGFR, which was measured at the 1992 to 1993 visit). LVH*biomarker change interaction was tested in multivariate models using the likelihood ratio test. Similar analyses were performed using LVMI categories in place of LVH.

Survival analyses were performed for all incident HF and separately for incident HFrEF and HFpEF. At-risk time was defined as time from the echocardiogram to incident HF, with censoring on death or last observed follow-up; for analyses of HF subtype, participants also were censored at the time of HF of any other subtype. In sensitivity analyses, we used the Fine and Gray method (23) to model the competing risk of LVH and each biomarker with all-cause mortality. All statistical analyses were performed with Stata/SE 12.1 (StataCorp LP, College Station, Texas).

RESULTS

STUDY PARTICIPANTS. Among 2,347 participants included in the baseline biomarker analyses (Online Figure 1), 294 (12.5%) had LVH, among whom 210

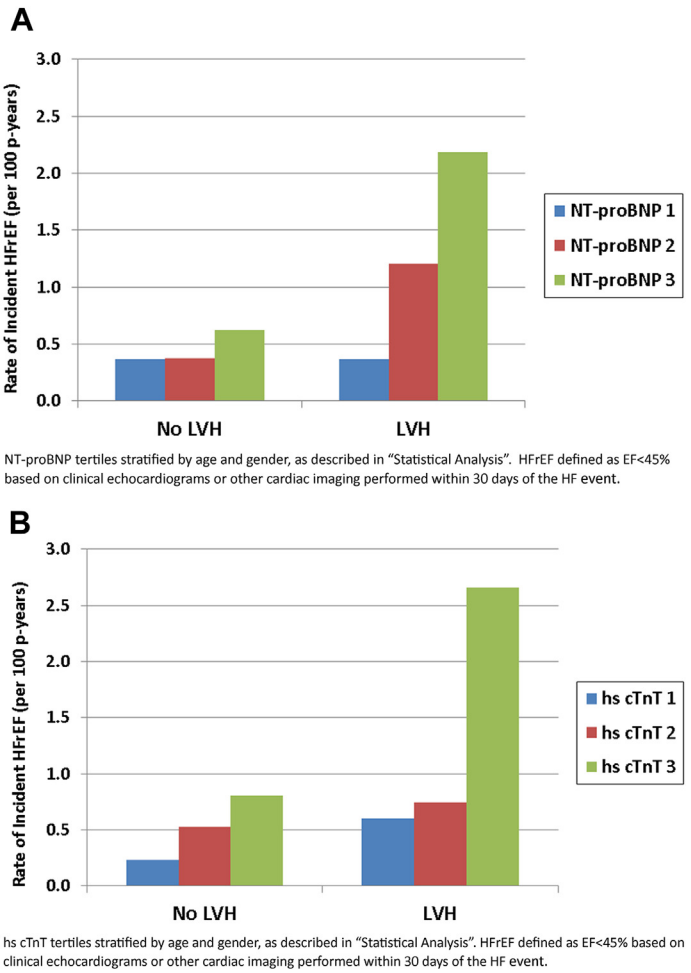
TABLE 2 Risk of Incident HF, by LVH and Initial Biomarker Level

LVH by Echocardiography	Tertile of NT-proBNP	Hazard Ratios (95% CI) Unadjusted	Risk-Factor Adjusted*
None	1	1.00	1.00
	2	1.22 (0.96–1.50)	1.22 (0.97–1.52)
	3	2.03 (1.64–2.50)	1.94 (1.56–2.41)
Yes	1	1.87 (1.20–2.91)	1.71 (1.10–2.67)
	2	2.52 (1.69–3.76)	2.07 (1.38–3.10)
	3	4.42 (3.28–5.94)	3.78 (2.78–5.15)
LVH by Echocardiography	**Tertile of hs-cTnT**	**Unadjusted**	**Risk-Factor Adjusted***
None	1	1.00	1.00
	2	1.69 (1.36–210)	1.36 (1.09–1.69)
	3	2.75 (2.23–3.38)	2.07 (1.67–2.56)
Yes	1	2.62 (1.80–3.81)	2.31 (1.58–3.36)
	2	2.20 (1.41–3.44)	1.70 (1.08–2.66)
	3	5.88 (4.37–7.90)	3.86 (2.84–5.26)

Interaction of LVH with NT-proBNP ($p = 0.5$) and hs-cTnT ($p = 0.6$). *Risk-factor adjusted: age, race, sex, smoking, hypertension, diabetes, coronary heart disease, body mass index, eGFR <60 ml/min/1.73 m^2, LVEF <45%, and RWT.

CI = confidence interval; HF = heart failure; NT-proBNP = N-terminal pro-B-type natriuretic peptide; other abbreviations as in Table 1.

FIGURE 2 Rate of Incident HFrEF, by LVH and Tertile of NT-proBNP or hs-cTnT



NT-proBNP tertiles stratified by age and gender, as described in "Statistical Analysis". HFrEF defined as EF<45% based on clinical echocardiograms or other cardiac imaging performed within 30 days of the HF event.

hs cTnT tertiles stratified by age and gender, as described in "Statistical Analysis". HFrEF defined as EF<45% based on clinical echocardiograms or other cardiac imaging performed within 30 days of the HF event.

(A) NT-proBNP; **(B)** hs-cTnT. HFrEF ascertained as described in the Methods section as incident HF with LVEF <45% based on clinical echocardiograms or other cardiac imaging performed within 30 days of the HF event and expressed as number of incident events per 100 person-years. The study sample was divided into age- and sex-specific tertiles of each biomarker, as described in the Methods section. EF = ejection fraction; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; other abbreviations as in Figure 1.

had eccentric LVH and 84 had concentric LVH. Prevalence of LVH was 8.6%, 10.9%, and 18.1% ($p < 0.001$) across 1st, 2nd and 3rd NT-proBNP tertiles and 8.5%, 11.9%, and 19.3%, ($p < 0.001$) across 1st, 2nd and 3rd hs-cTnT tertiles, respectively. Hypertension was present in 74% of those with LVH and 55% of those without.

Table 1 shows baseline clinical and echocardiographic characteristics, stratified by hs-cTnT and presence of LVH. Those with greater hs-cTnT were older, more likely to be male, and more likely to have diabetes, abnormal LVEF, eGFR <60 ml/min/1.73 m^2, and higher blood pressure and body mass index. Similar trends across hs-cTnT were noted for those with and without LVH. Among subjects without LVH, those with higher NT-proBNP were less likely to be African American and more likely to have coronary heart disease, eGFR <60 ml/min/1.73 m^2, abnormal LVEF, and higher blood pressure and lower body mass index (Online Table 1). Similar trends, although typically not significant, were observed among those with LVH. Correlations of NT-proBNP and hs-cTnT with LVMI at baseline were only modest ($\rho = 0.12$ and $\rho = 0.21$, respectively).

ASSOCIATION OF LVH AND BASELINE CARDIAC BIOMARKER LEVELS WITH INCIDENT HF. A total of 643 incident HF events occurred during a median 13.1 years (interquartile range: 7.1 to 18.0) of follow-up. The rate of incident HF varied markedly between those with and without LVH ($p < 0.001$) and by tertile of NT-proBNP and hs-cTnT ($p < 0.001$ for both) (Figures 1A and 1B, respectively). Those participants with LVH and in the highest NT-proBNP tertile were more than 4 times as likely to have incident HF compared with those without LVH and in the lowest NT-proBNP tertile (Table 2) (hazard ratio [HR]: 4.42; 95% CI: 3.28 to 5.94). Adjustment for demographic factors, comorbidity, RWT, and LVEF attenuated this association only modestly (HR: 3.78; 95% CI: 2.78 to 5.15). In contrast, those with LVH, but in the lowest NT-proBNP tertile, were only at 1.71 (95% CI: 1.10 to 2.67) times the risk of incident

TABLE 3 Risk of HFrEF, by LVH and Initial Biomarker Level

LVH by Echocardiography	Tertile of NT-proBNP	Hazard Ratios (95% CI)	
		Unadjusted	Risk-Factor Adjusted*
None	1	1.00	1.00
	2	1.03 (0.64–1.65)	1.00 (0.62–1.62)
	3	1.74 (1.11–2.21)	1.66 (1.05–2.62)
Yes	1	1.03 (0.64–1.65)	0.93 (0.28–3.04)
	2	3.49 (1.72–70.6)	2.92 (1.42–5.99)
	3	6.48 (3.82–10.97)	5.06 (2.89–8.86)
LVH by Echocardiography	**Tertile of hs-cTnT**	**Unadjusted**	**Risk-Factor Adjusted***
None	1	1.00	1.00
	2	2.30 (1.42–3.73)	1.77 (1.08–2.89)
	3	3.64 (2.29–5.80)	2.62 (1.62–4.21)
Yes	1	2.70 (1.12–6.51)	2.19 (0.90–5.32)
	2	3.38 (1.40–8.14)	2.65 (1.10–6.46)
	3	12.94 (7.5–22.23)	7.83 (4.43–13.83)

Interaction of LVH with NT-proBNP tertiles ($p = 0.07$) and hs-cTnT tertiles ($p = 0.4$). *Risk-factor adjusted: Adjustment covariates same as for Table 2.

HFrEF = heart failure with reduced ejection fraction; other abbreviations as in Tables 1 and 2.

HF compared with those without LVH, after adjustment. Those participants with LVH and the highest tertile of hs-cTnT were at approximately 6 times higher risk of HF compared with those without LVH and in the lowest hs-cTnT tertile (HR: 5.88; 95% CI: 4.37 to 7.90) (Table 2). This association was attenuated only moderately after adjustment for potential confounders (adjusted HR: 3.86; 95% CI: 2.84 to 5.26).

Similar results were observed when LVMI was used in place of LVH (Online Table 2). Compared with those in the lowest tertiles of LVMI and biomarker levels, those in the highest tertile of LVMI and biomarkers had 3.4 (NT-proBNP) and 3.3 times (hs-cTnT) the risk of incident HF, after adjustment for potential confounders. In a competing risks model accounting for all-cause mortality, the associations found in Table 2 were only slightly attenuated and all remained significant (Online Table 3). Among those with LVH, additional adjustment for residual differences in LVMI did not change the associations of either biomarker with incident HF ($\Delta\beta$ <5% for both markers). Among those with LVH, the addition of hs-cTnT or NT-proBNP (as continuous variables) significantly increased model discrimination, and the addition of hs-cTnT significantly improved risk reclassification for incident HF at 10 years when added to traditional risk factors, LVEF, and RWT (Online Table 4).

LVH, CARDIAC BIOMARKERS, AND INCIDENCE OF HFrEF VERSUS HFpEF. Among incident HF events, 215 (33.4%) had documented preserved ejection fraction (EF), 150 (23.3%) had reduced EF, and 278 (43%) had no documented EF at the time of incident HF diagnosis. Among those with incident HFrEF, 37 (24.7%) had LVH at baseline. The rate of incident HF with HFrEF differed significantly by tertile of NT-proBNP among those without ($p = 0.01$) and with ($p = 0.001$) LVH (Figure 2A). The absolute difference in HFrEF rates by NT-proBNP tertile was greater among those with LVH. Similar results were noted for tertiles of hs-cTnT, with a markedly greater risk of HFrEF among those with LVH and the highest tertile of hs-cTnT (Figure 2B). After adjustment for potential confounders, those participants with LVH in the highest tertile of NT-proBNP had a 5-fold greater risk of incident HFrEF (HR: 5.06; 95% CI: 2.89 to 8.86) (Table 3), and those with LVH in the highest tertile of hs-cTnT were at 7.8 times the risk of incident HFrEF versus those without LVH in the lowest hs-cTnT level tertile (HR: 7.83; 95% CI: 4.43 to 13.83).

Among those with incident HFpEF, 32 (15.0%) had LVH at baseline. Rate of incident HFpEF also differed significantly by tertile of NT-proBNP level among those without ($p = 0.003$) and with ($p = 0.02$) LVH (Figure 3A). After adjustment for potential confounders, those with LVH and in the highest tertile of NT-proBNP were at approximately 3-fold greater risk of HFpEF compared with those without LVH and with the lowest NT-proBNP (HR: 3.11; 95% CI: 1.80 to 5.37) (Online Table 5). Similar results were observed for hs-cTnT and LVH with regard to risk of HFpEF (Figure 3B, Online Table 5).

LVH, CHANGE IN BIOMARKER LEVELS, AND INCIDENT HF. A total of 1,474 subjects had complete measures of change in biomarkers and complete LV mass measures on the 1994 to 1995 echocardiogram, and were without HF, myocardial infarction, or eGFR <30 ml/min/1.73 m^2. Of these, 193 (13.1%) had LVH.

Participants with LVH and a significant increase of NT-proBNP or hs-cTnT level had markedly higher rates of incident HF (Online Figures 2A and 2B) ($p < 0.001$ for both biomarkers) compared with those without LVH and with stable or declining biomarker levels. After adjustment for baseline NT-proBNP and risk factors, there remained an approximately 3-fold increased risk for incident HF when NT-proBNP level increased in those with LVH (Table 4). In contrast, those with LVH but without an increasing NT-proBNP level were not at significantly greater risk of incident HF. Compared with those with stable or declining hs-cTnT without LVH, those with LVH and an increase in hs-cTnT level were at a 3.1-fold greater

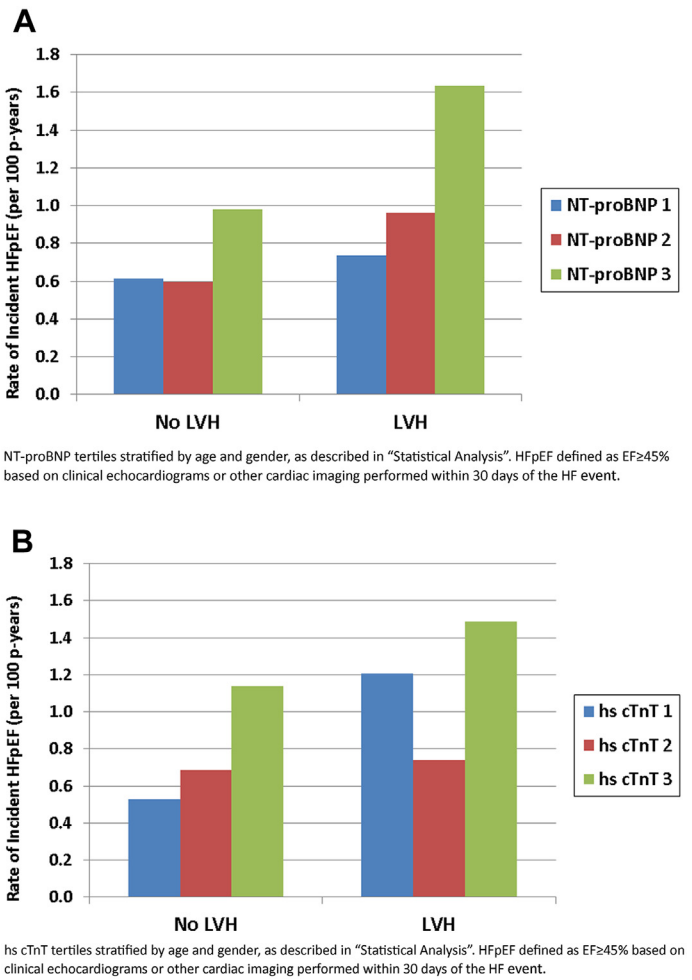
risk of incident HF, after adjustment for baseline hs-cTnT and risk factors. Similar results were observed using LVMI in place of LVH (Online Table 6). In sensitivity analyses, we examined whether the relationship between change in biomarkers and incident HF among those with LVH was explained by residual differences in LVM between those with and without biomarker increases. Among those with LVH, significant increases of NT-proBNP or hs-cTnT were associated with markedly greater HF risk even after additional adjustment for LVMI (as a continuous variable).

An additional analysis was done to determine the risk of HFrEF and HFpEF based on an increase in biomarker level and the presence or absence of LVH. Compared with individuals without LVH and with no increase in NT-proBNP levels, an increase in NT-proBNP among those with LVH was associated with an adjusted HR of 3.46 (95% CI: 1.56 to 7.65) for HFrEF but no significant increase in the risk for HFpEF (**Table 5**, Online Table 7, respectively). Likewise, compared with individuals without LVH and with no increase in hs-cTnT, an increase in hs-cTnT in the subgroup with LVH was associated with an adjusted HR of 6.95 (95% CI: 3.07 to 15.72) for HFrEF but no increase in the risk for HFpEF (**Table 5**, Online Table 7, respectively).

DISCUSSION

Among community-dwelling older adults without prior HF or myocardial infarction, the HF risk associated with LVH was heterogeneous and strongly influenced by baseline levels and changes in NT-proBNP and hs-cTnT, biomarkers of subclinical hemodynamic stress and myocardial injury, respectively. Unique to this study was our finding that baseline biomarker elevation appeared to associate with increased risk for progression to HFrEF to a greater extent than HFpEF among those with LVH. The stratification of risk for progression to HFrEF was even more powerful when evaluating longitudinal change in cardiac-specific biomarker levels. For example, an increase of >50% in hs-cTnT level in combination with LVH was associated with an approximately 7-fold adjusted greater risk of HFrEF, whereas the same combination of both LVH and an increasing hs-cTnT conferred no increased risk for HFpEF. By following longitudinal change, each subject can in effect act as his/her own control, allowing characterization of the dynamic processes that result in progression from asymptomatic structural heart disease to symptomatic HF.

FIGURE 3 Rate of Incident HFpEF, by LVH and Tertile of NT-proBNP or hs-cTnT



(A) NT-proBNP; **(B)** hs-cTnT. HFpEF ascertained as described in the Methods section as incident HF with LVEF ≥45% based on clinical echocardiograms or other cardiac imaging performed within 30 days of the HF event and expressed as number of incident events per 100 person-years. The study sample was divided into age- and sex-specific tertiles of each biomarker, as described in the Methods section. HFpEF = heart failure with preserved ejection fraction; other abbreviations as in **Figures 1 and 2**.

The implications of our findings are potentially 2-fold. First, this study provides clinical data to support a recently proposed paradigm that identifies distinct pathophysiologies for HFrEF and HFpEF (24). Second, the results of this study may provide a rationale to develop and test a preventive strategy using cardiac-specific biomarkers and cardiac imaging to identify asymptomatic older adults at highest risk for progression to HFrEF. Although HFrEF and HFpEF often present with similar signs and symptoms, there has been debate as to the degree of commonality of

TABLE 4 Risk of Incident HF, by LVH and Change in Biomarkers (N = 1,474)

LVH by Echocardiography	Increase in NT-proBNP	% of LVH Subgroup	Hazard Ratios (95% CI) Baseline-Adjusted	Risk-Factor Adjusted*
None	No	1,046 (81.7%)	1.00	1.00
	Yes	235 (18.3%)	1.51 (1.14–2.00)	1.33 (0.99–1.80)
Yes	No	129 (66.8%)	1.39 (0.97–1.99)	1.22 (0.83–1.78)
	Yes	64 (33.2%)	3.56 (2.46–5.15)	2.90 (1.98–4.27)
LVH by Echocardiography	**Increase in hs-cTnT**	**% of LVH Subgroup**	**Baseline-Adjusted**	**Risk-Factor Adjusted***
None	No	1,062 (82.9%)	1.00	1.00
	Yes	219 (17.1%)	2.15 (1.63–2.84)	1.88 (1.40–2.50)
Yes	No	144 (74.6%)	1.71 (1.23–2.39)	1.51 (1.06–2.16)
	Yes	49 (25.4%)	4.27 (2.85–6.38)	3.08 (2.03–4.67)

Baseline-adjusted: Adjusted for baseline biomarker concentration. Interaction of LVH with increase in NT-proBNP: (p = 0.04) and in hs-cTnT (p = 0.8). *Risk-factor adjusted: Adjusted for baseline biomarker level, age, race, sex, smoking, hypertension, diabetes, coronary heart disease, body mass index, LVEF <45%, eGFR <60 ml/min/1.73 m^2, and RWT.

Abbreviations as in Tables 1 and 2.

pathophysiology between HFrEF and HFpEF (25). Our findings provide support to the contention that if HFpEF is preceded by myocyte cell hypertrophy, it is without cell death, whereas HFrEF, although potentially preceded by hypertrophy, is also associated with progressive myocyte death and increased wall stress (24,26). This hypothesis is supported by the differences in HF prediction associated with longitudinal change in biomarker levels, which may reflect not only the background milieu of cardiovascular risk factors but also the pace of asymptomatic myocyte loss and increasing wall stress.

TABLE 5 Risk of Incident HFrEF, by LVH and Change in Biomarker Levels (N = 1,474)

LVH by Echocardiography	Increase in NT-proBNP	% of LVH Subgroup	Hazard Ratios (95% CI) Baseline-Adjusted	Risk-Factor Adjusted
None	No	1,046 (81.7%)	1.00	1.00
	Yes	235 (18.3%)	1.17 (0.60–2.29)	1.14 (0.55–2.35)
Yes	No	129 (66.8%)	2.08 (1.07–4.06)	1.99 (0.97–4.08)
	Yes	64 (33.2%)	4.77 (2.36–9.77)	3.46 (1.56–7.65)
LVH by Echocardiography	**Increase in hs-cTnT**	**% of LVH Subgroup**	**Baseline-Adjusted**	**Risk-Factor Adjusted**
None	No	1,062 (82.9%)	1.00	1.00
	Yes	219 (17.1%)	2.65 (1.45–4.86)	2.48 (1.29–4.77)
Yes	No	144 (74.6%)	2.87 (1.53–5.39)	2.21 (1.08–4.54)
	Yes	49 (25.4%)	6.94 (3.22–14.96)	6.95 (3.07–15.72)

Cell values are HRs (95% CI) from Cox proportional hazards models. HRs adjusted for baseline biomarker level, age, race, sex, smoking, hypertension, diabetes, coronary heart disease, body mass index, eGFR <60 ml/min/1.73 m^2, RWT, and LVEF <45%. Interaction between LVH and change in NT-proBNP: p = 0.5. Interaction between LVH and change in hs-cTnT: p = 0.7.

Abbreviations as in Tables 1 to 3.

We have previously shown that changes in NT-proBNP and hs-cTnT were associated with incident HF and cardiovascular death (16,17). In support of the concept that myocyte loss—reflected in increases of these biomarkers—is critical to the progression of symptomatic HF, we also demonstrated in older adults with initial low levels of hs-cTnT and NT-proBNP and a normal LVEF that an increase in 1 or both biomarkers was associated with an increased incidence of progression to asymptomatic reduced LVEF (27). Histologic findings from myocardial biopsies also support evidence of greater myocyte cell loss in those with HFrEF compared with HFpEF (28). In contrast, HFpEF was associated with greater myocyte hypertrophy versus HFrEF irrespective of the extent of collagen deposition (28).

LVH SUBTYPE AND HF RISK. LVH is a well-known structural intermediary in the progression of hypertension to HF (3,14). However, the progression of LVH to an abnormal LVEF or symptomatic HF is heterogeneous and cannot be explained on the basis of hypertension alone (3). In other cohorts, dividing LVH into concentric versus eccentric subtypes only moderately differentiated participants at increased risk of HFpEF versus HFrEF (10). This lack of prognostic utility may be secondary to the current 2-tiered classification of LVH, which does not account for the presence or absence of LV dilation (29). In the current study, we did not find that NT-proBNP or hs-cTnT was associated with RWT or greater LV mass in those with LVH, nor was there a difference in HFrEF or HFpEF risk by LVH subtype. Overall, our findings suggest that risk stratification among those with LVH may be better achieved by biochemical phenotyping compared with stratification by RWT.

CLINICAL IMPLICATIONS. Current guidelines for hypertension and appropriateness criteria for cardiac imaging do not recommend screening for LVH in hypertensive patients or differentiating treatment on the basis of its presence (6,30). This is in large part based on the low positive predictive value of LVH for HF and no obvious change in treatment strategy based on its identification. However, we and others have previously identified that elevated levels of cardiac-specific biomarkers in the presence of LVH stratifies these subjects with particularly high-risk HF (5,31). With extension of this finding in the present study that now identifies HFrEF as a primary sequela of elevated or increasing cardiac-specific biomarker levels in the presence of LVH in older adults, specific therapies could be considered.

In asymptomatic patients with reduced LVEF, angiotensin-converting enzyme (ACE) inhibitors reduce the progression to symptomatic HF and along with beta-blockers remain a class I indication for treatment (8). In patients with LVH and systolic hypertension, an angiotensin receptor blocker (ARB) was superior to beta-blockers to prevent a variety of cardiovascular outcomes, including HF (4). Further implicating the activation of the renin-angiotensin-aldosterone system as an upstream mechanism resulting in biochemical measures of myocyte loss and progression to HFrEF are findings from the HOPE (Heart Outcomes Prevention Evaluation) study in patients with normotensive vascular risk, in whom a higher dose of ramipril prevented a decrease in LVEF and increase in LV dimensions compared with a low-dose or placebo (32). We suggest that our findings provide a basis for identifying older adults who could be targeted for HF prevention with renin-angiotensin-aldosterone system antagonism irrespective of whether they have hypertension. Furthermore, even many patients with hypertension may not be treated with an ACE inhibitor or ARB, and if they are treated, the doses can be low and there may be benefit to upward titration.

For example, by testing a biomarker strategy to modify care, the STOP-HF (Saint Vincent's Screening To Prevent Heart Failure) trial found that intensifying management in primary care patients with at least 1 cardiovascular risk factor based on mild elevations in brain natriuretic peptide (BNP) resulted in a trend toward reduced new-onset HF (33). These results were in large part driven by differences in the use of ACE inhibitors and ARBs in patients with a known BNP >50 pg/ml, compared with the control group with a BNP value >50 pg/ml for which the values were unknown to the clinician or patient. Further refining this strategy by evaluating for LVH and measuring NT-proBNP or hs-cTnT could identify a high-risk cohort for progression to HFrEF in which specific therapies may be beneficial. A pilot and feasibility study of this approach for primary HF prevention is currently being developed. Lifestyle interventions also may be efficacious, as we have shown in a randomized pilot study that 1 year of physical activity in previously sedentary older adults significantly blunts an increase in hs-cTnT level (34). Greater attention to medical and lifestyle interventions could reduce progression to symptomatic HF in this high-risk cohort with LVH and elevated or increasing cardiac-specific biomarker levels.

STUDY LIMITATIONS. LV mass measures were missing in approximately one third of participants, with missing measures more likely among older male subjects and those with cardiovascular risk factors (12). This differential lack of LV mass data may have led to biased estimates of the association with incident HF. However, the fact that these associations persisted after adjustment for demographics and risk factors, and are consistent with our prior findings in younger adults with LVH, suggests these associations are robust. Biomarkers were missing in an additional 25% of participants; as previously reported (16,17), those with complete biomarker measurements differed modestly from those with missing measurements, which also could have introduced bias. We only measured 2 biomarkers, and other biomarkers may have better prognostic utility for HFpEF. Last, measures of LVEF at incident HF were incomplete and not adjudicated by a core echocardiography laboratory, which may have biased the results of associations with HF subtype. However, on the basis of the large number of events with point-of-care echocardiograms, it is unlikely that the robust differences in the prediction of HFrEF versus HFpEF based on biomarkers and LVH would be nullified. Finally, no statistical adjustments to the type I error rate were made for multiple testing, and we cannot exclude a false-positive finding.

CONCLUSIONS

LVH, as measured by echocardiography, was present in a substantial minority of older adults, particularly in those with elevated levels of NT-proBNP and hs-cTnT. The presence of LVH and elevated or increasing biomarker levels, independent of risk factors and subclassification of LVH, identified participants at high risk for new-onset HF, particularly HFrEF. These findings identify a cohort of community-dwelling individuals who may ultimately benefit from careful follow-up and consideration of specific medical and lifestyle interventions to prevent progression to symptomatic HF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: LVH has long been an electrocardiogram and imaging biomarker of risk for incident HF and cardiovascular death. Baseline levels and upward trajectories of highly sensitive blood-based cardiac-specific biomarkers of cardiac injury (troponin T) and strain (NT-proBNP) recently have been shown to predict similar outcomes. The combination of either biomarker with imaging evidence of LVH identifies older adults at particularly high risk for developing HFrEF, suggesting that the cardiac-specific biomarkers identify a "malignant" subtype of hypertrophy.

TRANSLATIONAL OUTLOOK: LVH is a heterogeneous process at a cellular level. Mildly elevated levels of biomarkers of cardiac injury and strain likely identify ongoing subclinical myocyte cell death, potentially through a process of apoptosis rather than ischemic necrosis. Further studies are needed to determine whether this subclinical process can be interrupted through pharmacological or lifestyle interventions.

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, et al. Heart Disease and stroke statistics—2014 update: a report from the American Heart Association. Circulation 2014;129:e28–292.

2. Lieb W, Xanthakis V, Sullivan LM, et al. Longitudinal tracking of left ventricular mass over the adult life course: clinical correlates of short- and long-term change in the Framingham Offspring Study. Circulation 2009;119:3085–92.

3. Drazner MH. The progression of hypertensive heart disease. Circulation 2011;123:327–34.

4. Kjeldsen SE, Dahlof B, Devereux RB, et al. Effects of losartan on cardiovascular morbidity and mortality in patients with isolated systolic hypertension and left ventricular hypertrophy: a Losartan Intervention for Endpoint Reduction (LIFE) substudy. JAMA 2002;288:1491–8.

5. Neeland IJ, Drazner MH, Berry JD, et al. Biomarkers of chronic cardiac injury and hemodynamic stress identify a malignant phenotype of left ventricular hypertrophy in the general population. J Am Coll Cardiol 2013;61:187–95.

6. Douglas PS, Garcia MJ, Haines DE, et al. 2011 appropriate use criteria for echocardiography. J Am Soc Echocardiogr 2011;24:229–67.

7. Owan TE, Hodge DO, Herges RM, et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006; 355:251–9.

8. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013;128:e240–319.

9. De Keulenaer GW, Brutsaert DL. Systolic and diastolic heart failure are overlapping phenotypes within the heart failure spectrum. Circulation 2011; 123:1996–2005.

10. Ho JE, Lyass A, Lee DS, et al. Predictors of new-onset heart failure: differences in preserved versus reduced ejection fraction. Circ Heart Fail 2013;6:279–86.

11. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: design and rationale. Ann Epidemiol 1991;1:263–76.

12. Gardin JM, Siscovick D, Anton-Culver H, et al. Sex, age, and disease affect echocardiographic left ventricular mass and systolic function in the free-living elderly. The Cardiovascular Health Study. Circulation 1995;91: 1739–48.

13. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:450–8.

14. Aurigemma GP, Gottdiener JS, Shemanski L, et al. Predictive value of systolic and diastolic function for incident congestive heart failure in the elderly: the Cardiovascular Health Study. J Am Coll Cardiol 2001;37:1042–8.

15. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification. Eur J Echocardiol 2006;7:79–108.

16. deFilippi CR, Christenson RH, Gottdiener JS, et al. Dynamic cardiovascular risk assessment in elderly people. The role of repeated N-terminal pro-B-type natriuretic peptide testing. J Am Coll Cardiol 2010;55:441–50.

17. deFilippi CR, de Lemos JA, Christenson RH, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. JAMA 2010;304:2494–502.

18. Giannitsis E, Kurz K, Hallermayer K, et al. Analytical validation of a high-sensitivity cardiac troponin T assay. Clin Chem 2010;56:254–61.

19. Ives DG, Fitzpatrick AL, Bild DE, et al. Surveillance and ascertainment of cardiovascular events. The Cardiovascular Health Study. Ann Epidemiol 1995;5:278–85.

20. Breslow N. Covariance analysis of censored survival data. Biometrics 1974;30:89–99.

21. Pencina MJ, D'Agostino RB Sr., D'Agostino RB Jr., et al. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–72.

22. Leening MJ, Vedder MM, Witteman JC, Pencina MJ, Steyerberg EW. Net reclassification improvement: computation, interpretation, and controversies: a literature review and clinician's guide. Ann Intern Med 2014;160:122–31.

23. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496–509.

24. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol 2013; 62:263–71.

25. Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. Circulation 2011;123: 2006–13.

26. Gonzalez A, Ravassa S, Beaumont J, et al. New targets to treat the structural remodeling of the myocardium. J Am Coll Cardiol 2011;58:1833–43.

27. Glick D, deFilippi CR, Christenson R, et al. Long-term trajectory of two unique cardiac biomarkers and subsequent left ventricular structural pathology and risk of incident heart failure in community-dwelling older adults at low baseline risk. J Am Coll Cardiol HF 2013;1:353–60.

28. van Heerebeek L, Borbely A, Niessen HW, et al. Myocardial structure and function differ in systolic and diastolic heart failure. Circulation 2006;113: 1966–73.

29. Khouri MG, Peshock RM, Ayers CR, et al. A 4-tiered classification of left ventricular hypertrophy based on left ventricular geometry: the

Dallas Heart Study. Circ Cardiovasc Imaging 2010;3:164–71.

30. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507–20.

31. Olsen MH, Wachtell K, Nielsen OW, et al. N-terminal brain natriuretic peptide predicted cardiovascular events stronger than high-sensitivity C-reactive protein in hypertension: a LIFE substudy. J Hypertens 2006;24:1531–9.

32. Lonn E, Shaikholeslami R, Yi Q, et al. Effects of ramipril on left ventricular mass and function in cardiovascular patients with controlled blood pressure and with preserved left ventricular ejection fraction: a substudy of the Heart Outcomes Prevention Evaluation (HOPE) Trial. J Am Coll Cardiol 2004;43:2200–6.

33. Ledwidge M, Gallagher J, Conlon C, et al. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. JAMA 2013;310:66–74.

34. deFilippi CR, de Lemos J, Newman AB, et al. Initiation of moderate physical activity reduces progression of subclinical cardiac injury in previously sedentary older adults: results from a randomized pilot study of exercise intervention. Circulation 2013;128:A16937.

KEY WORDS epidemiology, heart failure, left ventricular hypertrophy, natriuretic peptides, troponin T

APPENDIX For supplemental tables and figures, please see the online version of this article.