"Malignant" Left Ventricular Hypertrophy Identifies Subjects at High Risk for Progression to Asymptomatic Left Ventricular Dysfunction, Heart Failure, and Death: MESA (Multi-Ethnic Study of Atherosclerosis)

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Background—As heart failure (HF)-associated morbidity and mortality continue to escalate, enhanced focus on prevention is increasingly important. "Malignant" left ventricular (LV) hypertrophy (LVH): LVH combined with an elevated cardiac biomarker reflecting either injury (high-sensitivity cardiac troponin T), or strain (amino-terminal pro-B-type natriuretic peptide) has predicted accelerated progression to HF. We sought to determine whether malignant LVH identified community-dwelling adults initially free of cardiovascular disease at high risk of asymptomatic decline in LV ejection fraction or a clinical cardiovascular event.

Methods and Results—A total of 4985 of 6814 individuals without prevalent cardiovascular disease underwent baseline cardiac magnetic resonance for LVH in combination with measurement of plasma high-sensitivity cardiac troponin T and amino-terminal pro-B-type natriuretic peptide as part of MESA (Multi-Ethnic Study of Atherosclerosis) and were subsequently divided into 4 groups: (1) No LVH, no elevated biomarkers (n=2206; 44.3%); (2) No LVH, ≥1 elevated biomarkers (n=2275; 45.7%); (3) LVH, no elevated biomarkers (n=153; 3.0%); and (4) LVH, ≥1 elevated biomarkers (malignant LVH; n=351; 7.0%). Cardiac magnetic resonance was repeated 10 years later (n=2831) for assessment of LV ejection fraction <50%. Median follow-up was 12.2 years. Malignant LVH was associated with 7.0-, 3.5-, and 2.6-fold adjusted increases in incidence of HF, cardiovascular death, and asymptomatic LV dysfunction, respectively, versus group 1. New-onset HF was predominately HF with reduced ejection fraction (9.5-fold increase).

Conclusions—Malignant LVH is predictive of progression to asymptomatic LV dysfunction, HF (particularly HF with reduced ejection fraction), and cardiovascular death. Consequently, malignant LVH represents a high-risk phenotype among individuals without known cardiovascular disease, which should be targeted for increased surveillance and more-aggressive therapies. (*J Am Heart Assoc*. 2018;7:e006619. DOI: 10.1161/JAHA.117.006619.)

Key Words: heart failure • left ventricular dysfunction • left ventricular hypertrophy • mortality • N-terminal pro-B-type • troponin T

As the population continues to age, increasingly the first episode of symptomatic cardiovascular disease (CVD) manifests in the form of heart failure (HF).[1] For the primary prevention of HF, there are challenges in the identification of novel risk factors outside the "traditional" factors that also apply to atherosclerotic disease, attributed to the heterogeneous nature of HF progression among asymptomatic individuals. However, preliminary evidence suggests that a multimodality cardiac-specific biomarker approach has potential to differentiate risk beyond

traditional risk factors or a single modality, such as imaging or blood tests alone.[2]

Left ventricular (LV) hypertrophy (LVH) is determined by noninvasive measurement by multiple modalities. Whereas patients with LVH represent a risk group for adverse outcomes, progression to reduced LV systolic function, let alone major adverse cardiac events, occurs in a minority.[3] Recent studies by our group have demonstrated that presence of LVH in conjunction with elevated soluble biomarkers for myocardial injury (high-sensitivity cardiac troponin T; hs-cTnT) and hemodynamic stress (amino-terminal pro–B-type natriuretic peptide; NT-proBNP) can identify a "malignant" phenotype of LVH more likely to progress to HF or death in both middle-aged and older individuals.[2,4]

In the current study, we seek to further elucidate incident HF and cardiovascular mortality risk as well as to determine whether this intermediate "malignant" LVH phenotype, characterized by elevated cardiac-specific biomarkers, leads to progression to asymptomatic reduced LV ejection fraction (LVEF) across a spectrum of age in a contemporary, racially and ethnically diverse, community-based population free of

known CVD. Application of a multimodality approach to identify patients at the highest risk for incident asymptomatic and symptomatic heart failure with reduced ejection fraction (HFrEF) while LVEF is still preserved may have significant potential for early therapeutic interventions.

Methods

Data Access

The full data set is stored at the MESA Data Coordinating Center at the University of Washington (Seattle, WA). It is available for verification of these results with approval from the MESA Publications and Presentations committee.

Study Population

The MESA (Multi-Ethnic Study of Atherosclerosis) study has been previously described.[5] In short, 6814 American men and women, ranging from 45 to 84 years of age and comprising 4 self-reported ethnicities (non-Hispanic white, black, Hispanic, and Chinese), free of known CVD at baseline, were enrolled and gave informed consent. The study was approved by the institutional review boards of participating centers. The measurement of hs-cTnT and NT-proBNP for this ancillary study was approved by the University of Maryland Baltimore institutional review board.

The study sample for this analysis included all MESA participants with a complete cardiac magnetic resonance (CMR) at visit 1 (baseline), and with nonmissing cardiac-specific biomarker measures (n=4985; Figure 1). For the subanalysis of incident asymptomatic reduced LVEF (defined as <50%), we further restricted the analysis to those participants with a CMR at visit 5 (≈10 years after baseline), who also remained free of interim HF and coronary heart disease, and who had an LVEF ≥50% at baseline (n=2831).

Biomarker Assay Measurements

hs-cTnT and NT-proBNP were measured in EDTA plasma previously unthawed or unthawed once that was collected at baseline in the MESA cohort (2000–2002) and measured as previously described on the Cobas e601 (Roche Diagnostics, Indianapolis, IN).[6] NT-proBNP was measured in a total of 6791 (99.6%) and hs-cTnT in 6783 (99.5%) participants.

CMR Imaging and Image Analysis

CMR images were acquired in 5004 participants at exam 1 (2000–2002) for measures of LV mass and function as previously described.[5,7] At exam 5 (2010–2012), 3015 participants underwent a second CMR. There were 2981
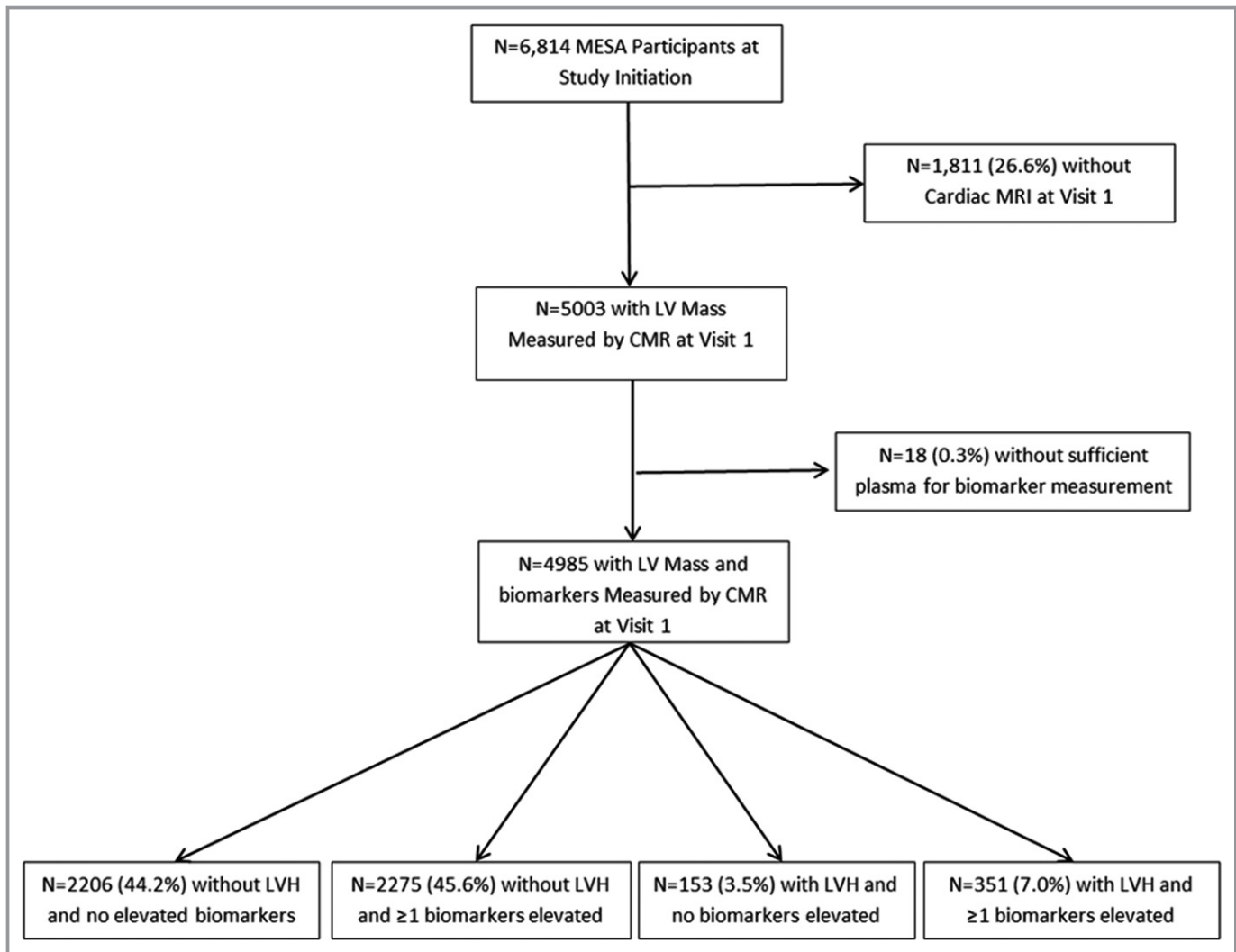
Figure 1. Flow diagram for inclusion of MESA participants in the present analysis. CMR indicates cardiac magnetic resonance; LV, left ventricular; LVH, left ventricular hypertrophy; MESA, The Multi-Ethnic Study of Atherosclerosis; MRI, magnetic resonance imaging.

participants with exams at both time points. To account for the different pulse magnetic resonance imaging sequences and subsequent variances in measurements, correction equations were used to convert fast gradient echo magnetic resonance imaging pulse sequence measurements (exam 1) into steady-state free precession measurements (exam 5) for longitudinal measurement analyses.[8]

Clinical Follow-up and Cohort Surveillance

MESA study clinical event endpoints for this analysis included incident HF and cardiovascular mortality. Events were adjudicated by the MESA study group as previously described.[5,7] Specifically, incident HF was ascertained by participant interview at annual study visits and all hospitalizations were reviewed. Expert reviewers classified potential HF events as definite, probable, or absent. Probable HF required the presence of typical symptoms, a physician-assigned HF

diagnosis, and the receipt of HF treatment. Definite HF additionally required 1 or more objective criteria for decompensated HF (such as pulmonary edema and systolic or diastolic dysfunction or dilated left ventricle on cardiac imaging). For the purposes of this analysis, events adjudicated as probable or definite HF were considered as the primary outcome. Incident HF events were further categorized as HFrEF or heart failure with preserved ejection fraction (HFpEF) based on an LVEF threshold of <50% as measured at the time of the HF event. Cardiovascular mortality was defined as death related to atherosclerotic heart disease, cerebrovascular disease, other atherosclerotic CVD, and other CVD death.

Candidate Covariates

Clinical characteristics and cardiovascular risk factors used as covariates were obtained from the MESA baseline examination and included: age, sex, race/ethnicity, smoking status

(current, former, or never), systolic and diastolic blood pressure, use of antihypertensive medications, height, weight, lipid levels, diabetes mellitus, and glomerular filtration rate,[5] the latter estimated from serum creatinine using the CKD-EPI equation.[9]

Primary Predictor Variable

LV mass index was calculated by dividing LV mass (measured by CMR at exam 1) by estimated body surface area. LV mass index values above the sex-specific 95th percentile of MESA participants without hypertension were considered to represent LVH, corresponding to cut-off values of 85.3 g/m^2 for women and 107.8 g/m^2 among men.[10] High hs-cTnT and NT-proBNP levels were defined as the upper tertile for each biomarker, stratified by age (per decade). The rationale for age stratification was the large difference in hs-cTnT and NT-proBNP distribution by age. Participants were categorized on the basis of LVH and elevated biomarkers into 4 groups: (1) No LVH, no elevated biomarkers; (2) No LVH, ≥1 elevated biomarkers; (3) LVH, no elevated biomarkers; and (4) LVH, ≥1 elevated biomarkers ("malignant" LVH).

Statistical Analysis

Baseline characteristics were compared across 4 subgroups as defined above using chi-squared tests for categorical variables, 1-way ANOVA for continuous variables, and Kruskall–Wallis test for skewed continuous variables.

Cumulative risk of incident HF, cardiovascular mortality, HFrEF, and HFpEF were estimated for each LVH-biomarker subgroup using the Kaplan–Meier method and compared with the log-rank test. Adjusted associations between the LVH-biomarker subgroups and these 4 outcomes were estimated using separate Cox proportional hazard models. Follow-up time was defined as time from baseline visit to incident HF or cardiovascular mortality, with censoring on noncardiovascular death or last date of observation (December 31, 2013 or last known follow-up). For models of HFrEF and HFpEF, the primary outcome was defined as the HF subtype of interest, with censoring on HF of other subtypes (including those with unknown LVEF). Adjustment was made for the candidate confounder variables described above. Comparison of the estimated hazard ratios (HRs) for malignant LVH versus nonmalignant LVH for each outcome was performed using appropriate contrast functions. Additive interaction between LVH and elevated biomarkers on risk of HF and cardiovascular death was quantified using the relative excess risk attributed to interaction as previously described; relative excess risk attributed to interaction >0 indicates that the joint effect of LVH and elevated biomarkers is greater than that predicted from the sum of individual effects.[11] Sensitivity analyses were performed explicitly modeling the competing risk with noncardiovascular mortality using the Fine-Gray method.[12] Additional sensitivity analyses were performed to compare the associations of LVH-biomarker groups with incident HF among older (≥65 years) versus middle-aged adults; formal interaction of LVH-biomarker group by age was tested with multiplicative terms.

For the analysis of new systolic dysfunction, the frequency of a new LVEF <50% among those without interim HF between the initial and follow-up CMR was compared across LVH-biomarker subgroups using the chi-squared test. Logistic regression was used to estimate the odds ratios for new systolic dysfunction by LVH-biomarker subgroup, adjusting for baseline LVEF and for the same set of potential confounding risk factors described above. The analyses were performed with StataSE (v12.1; StataCorp LP, College Station, TX).

Results

Study Population

Among 6814 MESA participants enrolled at baseline, a CMR interpretable for LV mass index was completed in 5003 (73.4%). Of these, both hs-cTnT and NT-proBNP were measured on 4985 (99.6%). These participants were included in the analysis. LVH was present among 504 (10.1%), of whom n=351 (69.6%) also had ≥1 biomarker in the upper tertile based on age. Baseline characteristics among the 4 subgroups characterized by LVH and biomarker levels are shown in Table 1. The study sample was 48% male and had a mean (SD) age of 61.5 (10.1) years. Overall, 11.6% of the population was diabetic; 35% was on an at least 1 antihypertensive medication. The mean LVEF was 62.4% (6.2). Baseline median [interquartile range] hs-cTnT and NT-proBNP levels were 4.9 [<3.0, 7.1] ng/L and 51.5 [23.0, 103.4] pg/mL, respectively. Significant differences between subgroups were observed with regard to age, sex, race, diabetes mellitus status, blood pressure, antihypertensive medication, estimated glomerular filtration rate, history of smoking, low-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and LVEF.

Incident HF Events and Cardiovascular Deaths

Participants were followed for a median of 12.2 years, during which there were 177 definite or probable incident HF events and 141 cardiovascular deaths. Cumulative hazard curves for incident HF for the 4 subgroups are shown in Figure 2A. Increased incidence of HF was observed in all 3 subgroups compared with those without LVH or an elevation of a biomarker, but the increase was most dramatic in participants with LVH and elevation of ≥1 biomarker (unadjusted HR, 11.28; 95% confidence interval [CI], 7.29–17.44); this

Table 1. Characteristics of Study Participants, by LVH-Biomarker Group

	No LVH, No Biomarker Elevated	No LVH, ≥1 Biomarker Elevated	LVH, No Biomarker Elevated	LVH, ≥1 Biomarker Elevated	P Value
N	2206	2275	153	351	
Age, y	61.0 (10.1)	61.6 (10.1)	60.7 (9.8)	64.2 (10.3)	<0.001
Male	1041 (47.2%)	1126 (49.5%)	46 (30.1%)	162 (46.2%)	<0.001
Race/ethnicity					
White	751 (34.0%)	1061 (46.6%)	33 (21.6%)	103 (29.4%)	<0.001
Chinese-American	397 (18.0%)	226 (9.9%)	5 (3.3%)	24 (6.8%)	
Black	547 (24.8%)	536 (25.4%)	61 (39.9%)	135 (38.5%)	
Hispanic	511 (23.2%)	452 (19.9%)	54 (35.3%)	89 (25.4%)	
Diabetes mellitus					
Normal	1703 (77.3%)	1732 (76.3%)	98 (64.1%)	221 (63.0%)	<0.001
IFG	297 (13.5%)	267 (11.8%)	21 (13.7%)	60 (17.1%)	
Untreated DM	54 (2.5%)	50 (2.2%)	7 (4.6%)	11 (3.1%)	
Treated DM	149 (6.8%)	221 (9.7%)	27 (17.7%)	59 (16.8%)	
SBP, mm Hg	121.8 (18.4)	125.3 (21.4)	136.3 (22.7)	144.0 (25.4)	<0.001
DBP, mm Hg	71.3 (9.5%)	71.3 (10.4)	75.7 (10.2)	76.9 (12.6)	<0.001
Hypertension medication	621 (28.2%)	856 (37.6%)	77 (50.3%)	204 (58.3%)	<0.001
Smoking					
Never	1196 (54.3%)	1126 (49.6%)	76 (50.0%)	159 (45.7%)	<0.001
Former	751 (34.1%)	866 (38.2%)	42 (27.6%)	122 (35.1%)	
Current	254 (11.5%)	278 (12.3%)	34 (22.4%)	67 (19.3%)	
LDL-C	119.6 (31.3)	115.3 (30.8)	117.1 (28.6)	114.0 (33.6)	<0.001
HDL-C	50.2 (14.2)	52.2 (15.6)	52.2 (15.4)	50.9 (15.2)	<0.001
Triglycerides, mg/dL	114 [78, 163]	109 [76, 159]	101 [78, 159]	105 [79, 169]	0.6
eGFR, mL/min per 1.73 m^2	80.3 (14.5)	76.3 (16.3)	85.1 (16.1)	75.9 (19.7)	<0.001
eGFR <60 mL/min per 1.73 m^2	159 (7.2%)	368 (16.2%)	9 (5.9%)	71 (20.2%)	<0.001
hs-cTnT, ng/L	3.22 [<3.0, 4.47]	6.1 [3.24, 9.30]	3.41 [<3.00, 4.91]	8.54 [4.98, 13.44]	
NT-proBNP, pg/mL	31.7 [15.4, 53.6]	79.0 [41.1, 146.9]	33.7 [18.2, 49.6]	148.0 [67.7, 311.7]	
LVEF, %	62.6 (5.6)	62.6 (6.0)	62.8 (6.2)	60.1 (9.0)	<0.001
LV mass, g					
Men	156.3 (26.9)	167.7 (30.5)	227.8 (22.2)	243.5 (34.1)	<0.001
Women	117.3 (20.9)	118.8 (21.5)	166.0 (21.2)	172.0 (30.0)	<0.001

DBP indicates diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; hs-cTnT, high-sensitivity troponin T; IFG, impaired fasting glucose; LDL, low-density lipoprotein; LV, left ventricular; LVEF, left ventricular ejection fraction; LVH, LV hypertrophy; NT-proBNP, amino-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure.

HR was significantly greater than the risk associated with LVH without elevated biomarkers. Associations were largely similar after adjustment for demographics, risk factors, and baseline LVEF (HR, 6.99; 95% CI, 3.68–9.74; Table 2). Results were also similar when regression models accounted for the competing risk of noncardiovascular death (Table S1). Cumulative risk of cardiovascular death was significantly higher in participants with LVH and elevation of ≥1 biomarker (adjusted HR, 3.48; 95% CI, 2.14–5.65; Figure 2B; Table 2), with greater risk for those with LVH and elevated versus nonelevated biomarkers. There was a significant additive interaction between LVH and ≥1 elevated biomarkers on risk of incident HF (relative excess risk attributed to interaction=3.45; 95% CI, 0.25, 6.65; P=0.035) and cardiovascular death (relative excess risk attributed to interaction=3.11; 95% CI, 1.23, 5.00; P=0.001).
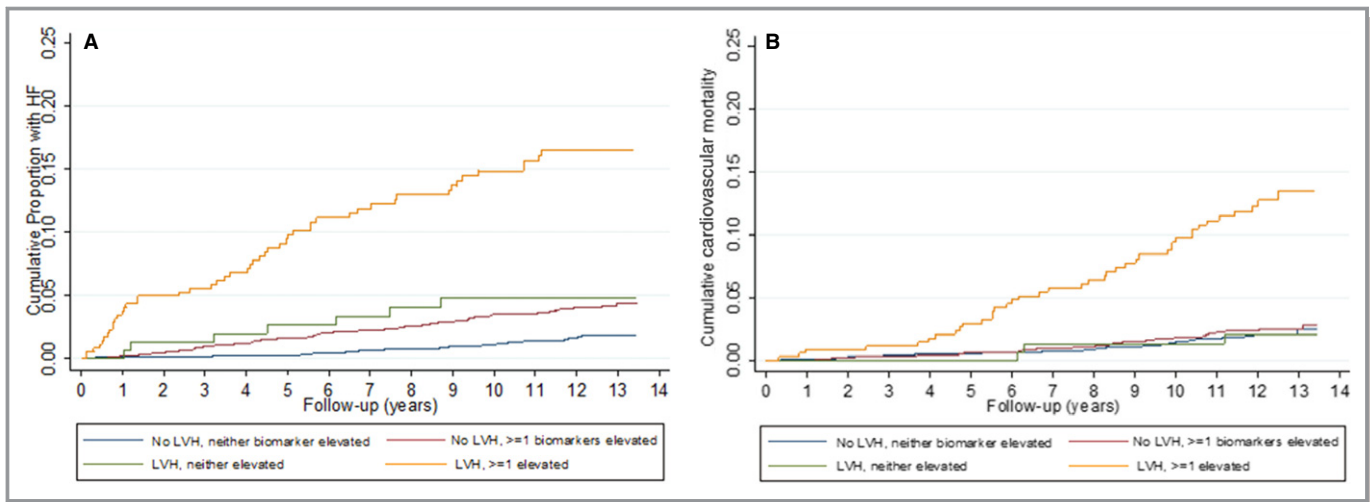
Figure 2. A, Cumulative incidence of HF, by LVH-biomarker group. Kaplan–Meier curve depicting cumulative risk of HF among: (1) No LVH, no elevated biomarker; (2) No LVH, ≥1 elevated biomarker; (3) LVH, no elevated biomarker; and (4) LVH, ≥1 elevated biomarker groups over median follow-up period of 12 years. HF indicates heart failure; LVH, left ventricular hypertrophy. B, Cumulative cardiovascular death, by LVH-biomarker group. Kaplan–Meier curve depicting cumulative risk of cardiovascular mortality among: (1) No LVH, no elevated biomarker; (2) No LVH, ≥1 elevated biomarker; (3) LVH, no elevated biomarker; and (4) LVH, ≥1 elevated biomarker groups over median follow-up period of 12 years. HF indicates heart failure; LVH, left ventricular hypertrophy.

Among those with incident HF a determination of HFrEF was made in 87 (49.2%), HFpEF in 72 (40.6%), and unknown LVEF in 18 (10.2%). Incident HFrEF was relatively common in participants with ≥1 elevated biomarker level and LVH, occurring in 10.6% (95% CI, 7.6–14.8) at 10 years. This translated into a nearly 24-fold increment in unadjusted risk and 9.5-fold greater adjusted risk compared with those with neither LVH nor an elevated biomarker level (Figure 3A; Table 2). The groups with either LVH or ≥1 elevated biomarker level also had a significant increased risk of HFrEF, but to a significantly ($P<0.05$) lesser extent than the group with the combination of the 2. In contrast, incident HF attributed to HFpEF was qualitatively less differentiated based on the presence of LVH and/or an elevated biomarker level (Figure 3B). Once adjusted, only the group with LVH combined with an elevated biomarker level remained at significantly higher risk of HFpEF compared with those without LVH or an elevated biomarker level (HR=2.73 [95% CI, 1.23–6.04]), although this risk was not significantly different from the risk associated with LVH without elevated biomarkers.

Cumulative Risk of HF by Age, Sex, and Race/Ethnicity

Of the 177 HF events, 125 (73.5%) occurred in participants aged ≥65 years. A subgroup analysis based on age is presented in Table S2. The combination of LVH and biomarkers markedly differentiated the risk of incident HFrEF in older adults. For example, in the absence of LVH and elevation of a biomarker level, the incidence of HFrEF is only 0.6 in

1000 patient-years, which is comparable to middle-aged adults with similar characteristics (0.3 in 1000 patient-years). In contrast, older adults with both LVH and an elevated cardiac biomarker level (n=173 [8.5%]) have an incidence rate of 15.2 HFrEF events per 1000 patient-years (adjusted HR, 23.2; 95% CI, 8.78–61.32) versus those with neither LVH nor an elevated biomarker. However, there was no significant interaction by age for incident HF ($P=0.96$) nor cardiovascular death ($P=0.3$).

Adjusted HRs for incident HF and HFrEF were greater for men with LVH and ≥1 elevated biomarker compared with women with the same findings. Men with LVH and ≥1 elevated biomarker had an approximately 32-fold increased risk of HFrEF compared with a 4-fold increased risk for women when compared with those without LVH or an elevated biomarker level (Table S3). There was significant interaction based on sex for all incident HF ($P=0.02$). Despite qualitatively greater differences among men than women for differentiation of cardiovascular mortality risk, there was no significant interaction based on sex ($P=0.2$). In addition, no significant interaction was found for risk of incident HF or cardiovascular mortality across the four represented races/ethnicities (data not shown).

Risk of HF by Specific Soluble Cardiac Biomarker and Alternate Cutoffs Combined With LVH

Combining LVH and the presence of an elevated hs-cTnT level identifies a higher risk for incident HF compared with LVH and an elevated NT-proBNP level (12.5 versus 6.8 HF events/

Table 2. Risk of Incident HF, Cardiovascular Death, and HF Subtype by LVH-Biomarker Subgroup

	Unadjusted	Demographic-Adjusted*	Risk Factor–Adjusted†	RF+LVEF–Adjusted‡
Outcome	Hazard Ratio (95% Confidence Interval)			
Heart failure				
No LVH, no biomarker elevated	Reference	Reference	Reference	Reference
No LVH, ≥1 biomarker elevated	2.49 (1.68, 3.71)	2.24 (1.50, 3.35)	2.11 (1.40, 3.18)	2.10 (1.39, 3.17)
LVH, no biomarker elevated	3.01 (1.33, 6.80)	3.38 (1.48, 7.68)	2.80 (1.21, 6.47)	2.74 (1.12, 6.32)
LVH, ≥1 biomarker elevated	11.28 (7.29, 17.44)	9.55 (6.13, 14.87)	7.37 (4.57, 11.87)*	6.99 (3.68, 9.74)*
Cardiovascular death				
No LVH, no biomarker elevated	Reference	Reference	Reference	Reference
No LVH, ≥1 biomarker elevated	1.20 (0.80, 1.79)	1.08 (0.73, 1.62)	0.99 (0.65, 1.50)	0.97 (0.64, 1.47)
LVH, no biomarker elevated	0.99 (0.31, 3.17)	1.05 (0.32, 3.39)	0.95 (0.29, 3.12)	0.91 (0.28, 3.00)
LVH, ≥1 biomarker elevated	6.52 (4.25, 10.01)	5.12 (3.31, 7.92)	4.05 (2.52, 6.51)§	3.48 (2.14, 5.65)§
HFrEF				
No LVH, no biomarker elevated	Reference	Reference	Reference	Reference
No LVH, ≥1 biomarker elevated	3.40 (1.73, 6.65)	2.95 (1.50, 5.77)	2.68 (1.36, 5.30)	2.61 (1.32, 5.16)
LVH, no biomarker elevated	5.33 (1.70, 16.75)	5.75 (1.82, 18.23)	4.98 (1.55, 16.03)	4.67 (1.45, 15.02)
LVH, ≥1 biomarker elevated	23.58 (11.9, 46.5)	18.99 (9.56, 37.74)	14.54 (7.01, 30.16)§	9.53 (4.52, 20.12)‖
HFpEF				
No LVH, no biomarker elevated	Reference	Reference	Reference	Reference
No LVH, ≥1 biomarker elevated	1.74 (1.02, 2.98)	1.59 (0.92, 2.73)	1.55 (0.89, 2.71)	1.55 (0.88, 2.70)
LVH, no biomarker elevated	2.09 (0.62, 6.99)	2.33 (0.68, 7.92)	1.83 (0.52, 6.39)	1.83 (0.52, 6.49)
LVH, ≥1 biomarker elevated	4.07 (1.96, 8.44)	3.45 (1.65, 7.24)	2.63 (1.19, 5.79)‖	2.73 (1.23, 6.04)‖

HF indicates heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; RF, risk factors.

Adjustment covariates: *Age, race, sex. †Demographics and: systolic and diastolic blood pressure, antihypertensive medications, weight, height, LDL-C, HDL-C, triglycerides, diabetes mellitus, smoking, and estimated glomerular filtration rate. ‡Risk factors and LVEF by baseline cardiac magnetic resonance.

§Significant difference (P<0.05) comparing LVH with elevated biomarker to LVH without elevated biomarker.

‖No significant difference comparing LVH with elevated biomarker to LVH without elevated biomarker levels.

1000 patient-years; *P*=0.009). The highest incidence rate of HF occurred in the presence of LVH and both biomarkers being elevated (25.0 HF events per 1000 patient-years; Table S4). However, in a fully adjusted model, these differences in incident HF risk were no longer significantly different between subgroups defined by elevations in individual versus both cardiac-specific biomarkers.

We also evaluated hs-cTnT by using non-age-based tertile values for the MESA cohort. As anticipated, once adjusted for age, the HR for both cardiovascular death and HF were similar to the age-based tertiles (Table S5), with significantly greater risk of both outcomes for LVH with elevated biomarkers compared with LVH alone. The age-based upper tertile values for hs-cTnT and NT-proBNP are shown in Table S6.

Progression to an Asymptomatic Abnormal LVEF

An evaluation for incident LVEF <50% in participants without interim HF or coronary heart disease events was examined in 2831 participants who underwent baseline and follow-up CMR with a baseline LVEF ≥50%. There were a total of 109 participants with new asymptomatic abnormal LVEF over 10 years. There was a progressively greater incidence of new abnormal LVEF across the 4 subgroups, with the lowest incidence (3.1%) in those without LVH nor elevated biomarkers and greatest incidence (7.4%) in those with LVH and ≥1 elevated biomarker (*P*=0.04 across subgroups). After adjustment, those with LVH and an elevated level of ≥1 biomarker had a more than 2.5-fold greater odds of progression to an abnormal LVEF compared with asymptomatic participants without LVH nor an elevated biomarker level (adjusted OR, 2.58; 95% CI, 1.20–5.56; Figure 4; Table S7).

Discussion

Among community dwelling adults free of CVD, the presence of LVH and a modest elevation of 1 of 2 cardiac specific biomarker levels identified a marked increased risk of new-
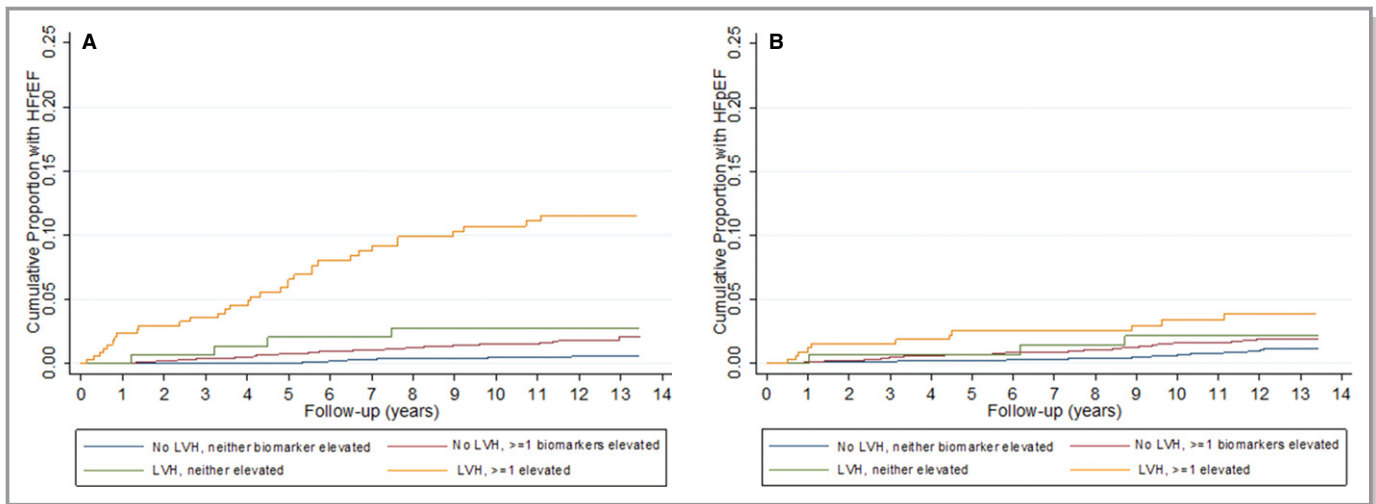
Figure 3. A, Cumulative risk of HFrEF, by LVH-biomarker group. Kaplan–Meier curve depicting cumulative risk of HFrEF among: (1) No LVH, no elevated biomarker; (2) No LVH, ≥1 elevated biomarker; (3) LVH, no elevated biomarker; and (4) LVH, ≥1 elevated biomarker groups over median follow-up period of 12 years. B, Cumulative risk of HFpEF, by LVH-biomarker group. Kaplan–Meier curve depicting cumulative risk of HFpEF among: (1) No LVH, no elevated biomarker; (2) No LVH, ≥1 elevated biomarker; (3) LVH, no elevated biomarker; and (4) LVH, ≥1 elevated biomarker groups over median follow-up period of 12 years. HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVH, left ventricular hypertrophy.

onset HF and high cardiovascular mortality. This finding persisted across a broad spectrum of age in a contemporary multiethnic, community-based cohort. For the outcome of incident HF (particularly HFrEF) and cardiovascular mortality, the presence of LVH with a modest elevation of ≥1 biomarker significantly differentiated an often markedly higher risk than LVH alone. Furthermore, we found there was a significant additive interaction between LVH and cardiac-specific biomarker levels for the risk of incident HF and cardiovascular death. There are novel findings in this study of the MESA cohort that build upon our past work in the Dallas Heart Study and the Cardiovascular Health Study, where we first coined

the term "malignant" LVH.[2,4] First, we differentiated that malignant LVH is a potent risk factor for HFrEF, qualitatively more so than for HFpEF, across a spectrum of age in participants without known CVD. This finding suggests that biochemical measures of myocyte loss and strain may best predict a process of adverse remodeling (represented by HFrEF) and, to a lesser extent, a process of progressive fibrosis (represented by HFpEF). This may also be attributed to the fact that HFpEF reflects both cardiac and noncardiac factors that play variable roles across a heterogeneous group of patients. We found a significant interaction with sex and the presence of malignant LVH for the risk of incident HF, particularly HFrEF, with a 32-fold increased risk in men versus those with neither LVH nor an elevated biomarker. No such interaction was observed across race/ethnicity based on the presence of malignant LVH. Second, we provide insight into the pathophysiology of hypertrophy coupled with biochemical evidence of low-level injury or strain by showing a 2.5-fold greater risk of decline to an asymptomatic abnormal LVEF over 10 years compared with those with neither baseline feature. This supports the concept that hypertrophy can be associated with accelerated myocyte cell loss, replacement fibrosis, and adverse remodeling.[13] The pathophysiological differences between sex for progression to HF symptoms in the presence of LVH and ≥1 elevated biomarker level are not certain, but men in the MESA study have almost a 6-fold higher risk for the presence of CMR defined replacement fibrosis compared with women.[14] We also noted that, after adjustment, neither cardiac-specific biomarker nor the combination of the 2 was superior for prediction of incident HF,

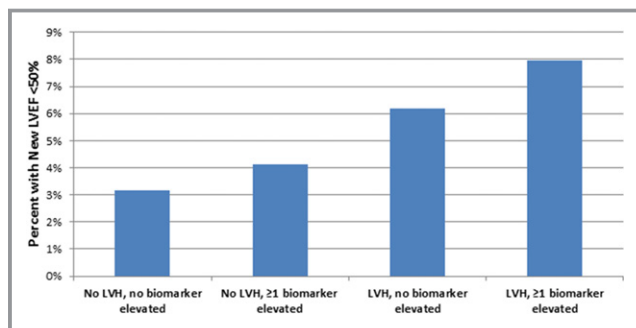**Figure 4.** Incidence of new-onset asymptomatic LV dysfunction by LVH-biomarker group over 10 years. Bar graph depicts incidence of new LVEF <50% in patients with initial LVEF >50% among: (1) No LVH, no elevated biomarker; (2) No LVH, ≥1 elevated biomarker; (3) LVH, no elevated biomarker; and (4) LVH, ≥1 elevated biomarker group. LVEF indicates left ventricular ejection fraction; LVH, left ventricular hypertrophy.

suggesting significant overlap in pathophysiology represented by these biomarkers for identifying LVH patients at highest risk and that measurement of both NT-proBNP and hs-cTnT should be considered to identify those with malignant LVH.

The implications of our study are multifold. Stage B HF is defined as the presence of structural heart disease in the absence of symptoms of HF and represents the tip of the iceberg compared with the morbidity, mortality, and cost associated with stage C disease.[15,16] Currently, routine cardiac imaging to screen for LVH is not recommended, attributed, in part, to the observation that the progression of LVH to symptomatic HF is heterogeneous.[17] Malignant LVH defines a subgroup of LVH patients, representing 7% of MESA participants, by definition free of known CVD, and independent of the presence of hypertension, who may potentially benefit from increased surveillance. Surveillance with biomarkers has some precedence, previously being efficacious among primary care patients in a randomized, controlled trial of BNP monitoring.[18] We show that combining LVH with biomarker elevation identifies participants at a 2.5- to 4-fold greater risk than just biomarker elevation alone.

Our finding that malignant LVH has strong predisposition for HFrEF over HFpEF is of particular importance and makes a compelling case to consider this multimodality cardiac-specific risk stratification. HF has a heterogeneous etiology with near equivalent incidences of HFpEF and HFrEF.[19] Unfortunately, the lack of effective treatment strategies for HFpEF, combined with the lack of clinical and echocardiographic characteristics allowing for differentiation of progression to HFpEF versus HFrEF, makes it difficult to identify patients who are most likely to derive benefit from a specific intervention in the absence of a low LVEF. Low LVEF is infrequent in an asymptomatic community-based population, making screening for it an unattractive strategy.[20] Consequently, the finding that malignant LVH is more strongly predictive of HFrEF than LVH without elevated biomarkers, but is not significantly more predictive of HFpEF, may allow for both earlier and more-appropriate initiation of the multiple therapeutic modalities, which have demonstrated efficacy in HFrEF (but not HFpEF).[21,22] A prospective study is needed to determine whether the same medical therapies (renin-angiotensin aldosterone system inhibitors and beta-blockers) that have efficacy for reducing progression to symptomatic HF in patients with asymptomatic LV systolic dysfunction would also have comparable efficacy in patients with malignant LVH. Recently, it has been suggested that it is possible to subgroup HFpEF into different phenotypes using machine learning or other algorithms.[23,24] It remains to be determined whether the malignant LVH phenotype may be also able to identify specific patient phenotypes that would be at greater risk to progress to HFpEF among the overall heterogeneous HFpEF cohort. The converse is that the absence of LVH and lower levels of both biomarker, representing 44.3% of the MESA population, identifies a subgroup at a reassuring low-risk for progression to HF even in those with advanced age.

Limitations

Our findings should be interpreted in the setting of several methodological limitations. With regard to CMR, it should be noted that no CMR was available in ≈30% of the MESA cohort and that generally patients without CMR were older and less healthy. We recognize that detection of LVH with CMR, though accurate would be limited by both cost and accessibility. Our past work has shown that detection of LVH by ECG and echocardiography combined with these same biomarkers also detects a malignant LVH that identifies individuals at much higher risk for progression to HF hospitalization and death.[2,4] The current analysis in MESA with a later second CMR exam provided the opportunity to also accurately show the progression of an asymptomatic decline in LVEF in addition to clinical events. Although we did not observe that malignant LVH was more strongly associated with HFpEF than LVH alone (in contrast to HFrEF), this may have represented a type II error and does not provide conclusively inference that malignant LVH is more predictive of HFrEF. Furthermore, it should be emphasized that only 2 biomarkers were included in our analysis and that other biomarkers may have better prognostic utility for both HF and, in particular, HFpEF. It should be noted that measurements of LVEF during sentinel HF events were incomplete and not adjudicated by a core echocardiography laboratory, which may have biased the results of associations with a specific HF subtype.

Conclusions

Malignant LVH as measured by CMR defined LVH in combination with elevation of soluble cardiac biomarkers for myocardial injury (hs-cTnT), and myocardial hemodynamic stress (NT-proBNP) was associated with an increased incidence of asymptomatic LV dysfunction, HF (specifically HFrEF), and cardiovascular mortality among a contemporary multiethnic cohort of middle- to older-aged individuals without prevalent CVD. These findings define a subpopulation, without symptomatic CVD, who may benefit from enhanced surveillance and intervention to prevent progression to symptomatic HF and death.

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SUPPLEMENTAL MATERIAL

Table S1. Rates of Incident HF, by LVH-biomarker subgroup, accounting for competing risk of non-CV mortality.

Outcome	Unadjusted	Demographic-adjusted[*]	Risk factor-adjusted[†]	RF + LVEF-adjusted[‡]
	Hazard Ratio (95% Confidence Interval)			
Heart Failure				
No LVH, no biomarker elevated	Reference	Reference	Reference	Reference
No LVH, ≥1 biomarkers elevated	2.46 (1.66, 3.66)	2.19 (1.46, 3.26)	2.08 (1.39, 3.11)	2.08 (1.39, 3.11)
LVH, no biomarker elevated	3.01 (1.33, 6.81)	3.35 (1.46, 7.70)	2.79 (1.19, 6.56)	2.68 (1.16, 6.17)
LVH, ≥1 biomarker elevated	10.56 (6.82, 16.34)[§]	8.43 (5.38, 13.21)[§]	6.36 (3.86, 10.49)[∥]	5.14 (3.11, 8.48)

§ Significant difference (p<.05) comparing LVH with elevated biomarker to LVH without elevated biomarker

∥ No significant difference comparing LVH with elevated biomarker to LVH without elevated biomarker levels

CV=cardiovascular; HF=heart failure; LVEF=left ventricular ejection fraction; LVH=left ventricular hypertrophy.

Adjustment Covariates:

* Age, race, sex

† Demographics and: systolic and diastolic blood pressure, anti-hypertensive medications, weight, height, LDL-C, HDL-C, triglycerides, diabetes, smoking, and estimated glomerular filtration rate.

‡ Risk factors and Left Ventricular Ejection Fraction by baseline cardiac magnetic resonance.

Table S2. Risk of Incident HF and HF subtype, by LVH-biomarker and age subgroup.

Heart Failure	<65 (N=2933)		≥65 (N=2052)	
	Incidence Rate (/1000pyrs)	Adjusted* Hazard Ratios	Incidence Rate (/1000pyrs)	Adjusted* Hazard Ratios
No LVH, no biomarker elevated	0.7 (0.5, 1.2)	Reference	2.5 (1.6, 3.7)	Reference
No LVH, ≥1 biomarker elevated	1.4 (1.0, 2.12)	1.56 (0.73, 3.35)	6.7 (5.3, 8.6)	2.45 (1.49, 3.97)
LVH, no biomarker elevated	1.8 (0.5, 7.4)	1.44 (0.30, 6.89)	8.1 (3.4, 19.5)	3.98 (1.47, 10.79)
LVH, ≥1 biomarker elevated	9.1 (5.6, 14.6)	5.24 (2.15, 12.77)	23.9 (17.0, 33.6)	8.22 (4.61, 14.65)
HFrEF				
No LVH, no biomarker elevated	0.3 (0.1, 0.8)	Reference	0.6 (0.3, 1.4)	Reference
No LVH, ≥1 biomarker elevated	0.8 (0.4, 1.3)	1.44 (0.49, 4.18)	2.8 (1.9, 4.1)	4.01 (1.62, 9.91)
LVH, no biomarker elevated	0.9 (0.1, 6.5)	1.50 (0.17, 13.42)	4.9 (1.6, 15.1)	11.24 (2.70, 46.71)
LVH, ≥1 biomarker elevated	6.9 (4.0, 11.9)	6.97 (2.17, 22.41)	15.2 (9.9, 23.3)	23.20 (8.78, 61.32)
CV Death				
No LVH, no biomarker elevated	0.6 (0.3, 1.1)	Reference	3.3 (2.4, 4.6)	Reference
No LVH, ≥1 biomarker elevated	0.5 (0.3, 1.0)	0.56 (0.21,1.56)	4.4 (3.3, 6.0)	1.12 (0.70, 1.79)
LVH, no biomarker elevated	0.9 (0.1, 6.1)	0.96 (0.12, 7.92)	3.0 (0.8, 12.1)	0.92 (0.22, 3.95)
LVH, ≥1 biomarker elevated	5.7 (3.3, 10.1)	3.77 (1.34, 10.61)	16.8 (11.6, 24.4)	3.96 (2.28, 6.87

HF=heart failure; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; LVH=left ventricular hypertrophy;

*Adjustment Covariates: Age, race,sex, systolic and diastolic blood pressure, anti-hypertensive medications, weight, height, LDL-C, HDL-C, triglycerides, diabetes, smoking, and estimated GFR.

CV=cardiovascular; HF=heart failure; HFrEF=heart failure with reduced ejection fraction.

Table S3. Risk of Incident HF, CV Death, and HFrEF, among men and women.

	Men		Women	
Heart Failure	Incidence Rate*	Adjusted HR (95% CI)	Incidence Rate	Adjusted HR (95% CI)
No LVH, no biomarker elevated	1.4 (0.8, 2.2)	Reference	1.4 (0.9, 2.2)	Reference
No LVH, ≥1 biomarker elevated	4.4 (3.4, 5.8)	2.62 (1.48, 4.63)	2.4 (1.7, 3.4)	1.64 (0.89, 3.04)
LVH, no biomarker elevated	10.0 (4.2, 24.1)	8.95 (3.20, 25.06)	1.7 (0.4 , 6.6)	0.63 (0.14, 2.84)
LVH, ≥1 biomarker elevated	24.7 (17.7, 34.4)	14.15 (7.39, 27.10)	8.2 (4.9, 13.6)	3.27 (1.53, 7.00)
Test of Interaction	p=.02			
CV Death				
No LVH, no biomarker elevated	1.9 (1.3, 2.8)	Reference	1.5 (1.0, 2.3)	Reference
No LVH, ≥1 biomarker elevated	2.4 (1.7, 3.4)	1.13 (0.64, 2.00)	1.7 (1.0 2.5)	0.82 (0.43, 1.56)
LVH, no biomarker elevated	1.8 (0.3, 13.0)	1.24 (0.16, 9.42)	1.6 (0.4, 6.3)	0.53 (0.12, 2.35)
LVH, ≥1 biomarker elevated	16.1 (11.0, 23.5)	8.93 (4.7, 16.9)	6.3 (3.6, 10.8)	1.60 (0.73, 3.53)
Test of Interaction	p=0.2			
HFrEF				
No LVH, no biomarker elevated	0.4 (0.2, 1.0)	Reference	0.5 (0.2, 1.0)	Reference
No LVH, ≥1 biomarker elevated	2.1 (1.5, 3.1)	3.96 (1.50, 10.46)	0.9 (0.5, 1.6)	1.61 (0.58, 4.45)
LVH, no biomarker elevated	6.0 (1.9, 18.7)	14.86 (3.47, 63.71)	0.8 (0.1, 5.9)	0.75 (0.08, 6.83)
LVH, ≥1 biomarker elevated	19.0 (13.1, 27.8)	31.7 (11.45, 87.86)	3.8 (1.8, 8.0)	4.04 (1.20, 13.59)

Test of Interaction	p=.07

* Per 1000 patient years

CV=cardiovascular; HF=heart failure; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; LVEF=left ventricular ejection fraction; LVH=left ventricular hypertrophy;

Table S4. Rates of Incident HF, by LVH and elevation in each biomarker.

	Rate of Incident HF (/1000 patient years)	Unadjusted HRs	Adjusted[*] HRs
No LVH, no biomarker elevated	1.4 (1.0, 1.9)	Reference	Reference
No LVH, >1 biomarker elevated	3.4 (2.7, 4.2)	2.49 (1.68, 3.71)	2.13 (1.41, 3.21)
LVH, no biomarker elevated	4.1 (2.0, 8.6)	3.01 (1.34, 6.80)	2.81 (1.21, 6.48)
LVH, elevated hs-cTnT only	12.5 (6.7, 23.3)	9.21 (4.55, 18.65)	6.90 (3.33, 14.28)
LVH, elevated NT-proBNP only	6.8 (3.4, 13.6)	5.00 (2.32, 10.81)	5.68 (2.54, 12.69)
LVH, >1 biomarker elevated	25.0 (17.7, 35.3)	18.35 (11.3, 29.8)	8.37 (4.86, 14.42)[†]

HF=heart failure; HR=hazard ratio; hs-cTnT= highly sensitive cardiac troponin T; LVH=left ventricular hypertrophy; NT-proBNP= amino-terminal pro B-type natriuretic peptide

* Adjustment Covariates: Age, race, sex, demographics and: systolic and diastolic blood pressure, anti-hypertensive medications, weight, height, LDL-C, HDL-C, triglycerides, diabetes, smoking, and estimated GFR.

† No significant difference between this subgroup and those with LVH and only 1 elevated biomarker.

Table S5. Association of LVH-biomarker with incident HF and CV death (non-age-based biomarker tertiles).

Outcome	Unadjusted	Demographic-adjusted[*]	Risk factor-adjusted[†]	RF + LVEF-adjusted[‡]
	Hazard Ratio (95% Confidence Interval)			
CV Death				
No LVH, no biomarker elevated (N=3985, 78.7%)	Reference	Reference	Reference	Reference
No LVH, ≥1 biomarker elevated (N=560, 11.2%)	5.31 (3.54, 7.96)	2.17 (1.39, 3.38)	2.25 (1.33, 3.80)	2.14 (1.28, 3.61)
LVH, no biomarker elevated (N=325, 6.5%)	2.51 (1.34, 4.66)	2.62 (1.40, 4.92)	1.07 (0.32, 3.48)	1.04 (0.32, 3.36)
LVH, ≥1 biomarker elevated (N=179, 3.6%)	15.23 (9.85, 23.54)	7.42 (4.70, 11.72)	4.73 (3.10, 7.21)§	4.10 (2.66, 6.32)§
Heart Failure				
No LVH, no biomarker elevated	Reference	Reference	Reference	Reference
No LVH, ≥1 biomarker elevated	7.65 (5.35, 10.94)	4.16 (2.78, 6.22)	4.73 (3.17, 7.04)	4.52 (3.04, 6.73)
LVH, no biomarker elevated	4.09 (2.47, 6.77)	4.40 (2.64, 7.33)	2.37 (1.07, 5.26)	2.32 (1.05, 5.13)
LVH, ≥1 elevated	18.95 (12.59, 28.50)§	11.92 (7.7, 18.4)§	6.56 (4.43, 9.70)§	5.38 (3.60, 8.04)§

§ Significant difference (p<.05) comparing LVH with elevated biomarker to LVH without elevated biomarker

Adjustment Covariates:

* Age, race, sex

† Demographics and: systolic and diastolic blood pressure, anti-hypertensive medications, weight, height, LDL-C, HDL-C, triglycerides, diabetes, smoking, and estimated glomerular filtration rate.

‡ Risk factors and Left Ventricular Ejection Fraction by baseline cardiac magnetic resonance.

Table S6. Age-specific cut-points of hs-cTnT and NT-proBNP which define elevated biomarkers.

Age Range (years)	hs-cTnT (ng/L)	NT-proBNP (pg/mL)
45-54	4.70	48.3
55-64	5.45	66.0
65-74	7.18	104.8
75-85	10.19	175

hs-cTnT= highly sensitive cardiac troponin T; NT-proBNP= amino-terminal pro B-type natriuretic peptide

Table S7. Odds of new LVEF<50% at follow-up CMR, by initial LVH-biomarker group.

	Unadjusted	Demographic-adjusted[*]	Risk factor-adjusted[†]
No LVH, <1 biomarker elevated	Reference	Reference	Reference
No LVH, >1 biomarker	1.31 (0.86, 1.99)	1.23 (0.81, 1.88)	1.22 (0.79, 1.88)
LVH, <1 biomarker	2.00 (0.77, 5.21)	2.03 (0.76, 5.39)	2.06 (0.75, 5.62)
LVH, >1 elevated biomarker	2.64 (1.32, 5.26)[‡]	2.54 (1.25, 5.17)[‡]	2.58 (1.20, 5.56)[‡]

‡ No difference in odds of new LVEF<50% compared to LVH without elevated biomarkers

Adjustment Covariates:

* Age, race, sex

† Demographics and: systolic and diastolic blood pressure, anti-hypertensive medications, weight, height, LDL-C, HDL-C, triglycerides, diabetes, smoking, estimated GFR, and initial LVEF

CMR=cardiac magnetic resonance imaging; LVEF=left ventricular ejection fraction; LVH=left ventricular hypertrophy