Journal of the American College of Cardiology Vol. 61, No. 2, 2013

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2012.10.012

Biomarkers of Chronic Cardiac Injury and Hemodynamic Stress Identify a Malignant Phenotype of Left Ventricular Hypertrophy in the General Population

Ian J. Neeland, MD,* Mark H. Drazner, MD, MSc,* Jarett D. Berry, MD, MS,* Colby R. Ayers, MS,*† Christopher deFilippi, MD,‡ Stephen L. Seliger, MD, MS,§ Vijay Nambi, MD, PhD,‖ Darren K. McGuire, MD, MHSc,*† Torbjørn Omland, MD, PhD, MPH,¶# James A. de Lemos, MD*

Dallas, Texas; Baltimore, Maryland; Houston, Texas; and Lørenskog and Oslo, Norway

Objectives The goal of this study was to determine if biomarkers of subclinical myocardial injury and hemodynamic stress identify asymptomatic individuals with left ventricular hypertrophy (LVH) at higher risk for heart failure (HF) and death.

Background The interaction between LVH, low but detectable cardiac troponin T (cTnT), and elevated N-terminal pro–B-type natriuretic peptide (NT-proBNP) on cardiovascular (CV) outcomes in the general population is unknown.

Methods Participants in the Dallas Heart Study without clinical HF, LV dysfunction, or chronic kidney disease underwent measurement of LV mass by magnetic resonance imaging (MRI), cTnT by highly sensitive assay, and NT-proBNP analysis (n = 2,413). Subjects were stratified according to LVH and by detectable cTnT (≥3 pg/ml) and increased NT-proBNP (>75th age- and sex-specific percentile) levels. For each analysis, participants were categorized into groups based on the presence (+) or absence (–) of LVH and biomarker levels above (+) or below (–) the predefined threshold.

Results Nine percent of participants were LVH+, 25% cTnT+, and 24% NT-proBNP+. Those LVH+ and cTnT+ and/or NT-proBNP+ (n = 144) were older and more likely to be male, with a greater risk factor burden and more severe LVH compared with those who were LVH+ biomarker– ($p < 0.01$ for each). The cumulative incidence of HF or CV death over 8 years among LVH+ cTnT+ was 21% versus 1% (LVH– cTnT–), 4% (LVH– cTnT+), and 6% (LVH+ cTnT–) ($p < 0.0001$). The interactions between LVH and cTnT ($p_{interaction} = 0.0005$) and LVH and NT-proBNP ($p_{interaction} = 0.014$) were highly significant. Individuals who were LVH+ and either cTnT+ or NT-proBNP+ remained at >4-fold higher risk for HF or CV death after multivariable adjustment for CV risk factors, renal function, and LV mass compared with those who were LVH– biomarker–.

Conclusions Minimal elevations in biomarkers of subclinical cardiac injury and hemodynamic stress modify the association of LVH with adverse outcomes, identifying a malignant subphenotype of LVH with high risk for progression to HF and CV death. (J Am Coll Cardiol 2013;61:187–95) © 2013 by the American College of Cardiology Foundation

From the *Department of Internal Medicine, Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, Texas; †Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, Texas; ‡Division of Cardiology, University of Maryland, Baltimore, Maryland; §Division of Nephrology, Department of Medicine, University of Maryland, Baltimore, Maryland; ‖Division of Atherosclerosis and Vascular Medicine, Baylor College of Medicine and Center of Cardiovascular Prevention, Methodist DeBakey Heart and Vascular Center, Houston, Texas; ¶Department of Cardiology, Division of Medicine, Akershus University Hospital, Lørenskog, Norway; and the #Center for Heart Failure Research and K.G. Jebsen Cardiac Research Centre, University of Oslo, Oslo, Norway. This work was supported by Award Number T32HL007360 from the National Heart, Lung, and Blood Institute to Dr. Neeland, the Donald W. Reynolds Foundation, and by National Institutes of Health/National Center for Advancing Translational Sciences grant number UL1RR02498. Biomarker measurements were supported by investigator-initiated grants from Roche Diagnostics. Dr. Nambi is the monitor for study sponsored by Anthera; a former member of "virtual advisory board" for Roche; and has research collaboration without financial support with General Electric and Tomtec. Dr. Seliger has received consulting income from Roche Diagnostics. Dr. deFilippi has received consulting income from Roche Diagnostics; honoraria from Roche Diagnostics and Siemens Healthcare Diagnostics; and research grant support from Siemens Healthcare Diagnostics. Dr. McGuire has received consulting income from Tethys Bioscience. Dr. Omland has received speakers' honoraria from Abbott Diagnostics, Siemens Healthcare Diagnostics, and Roche Diagnostics; and research grant support from Abbott Diagnostics and Roche Diagnostics through Akershus University Hospital. Dr. de Lemos has received research grant support from Roche Diagnostics and Abbott Diagnostics; and consulting income from Tethys Bioscience. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received August 16, 2012; revised manuscript received September 25, 2012, accepted October 9, 2012.

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Abbreviations and Acronyms

BSA = body surface area
CI = confidence interval
cTnT = cardiac troponin T
CV = cardiovascular
ECG = electrocardiogram
eGFR = estimated glomerular filtration rate
HF = heart failure
HR = hazard ratio
LV = left ventricular
LVEF = left ventricular ejection fraction
LVH = left ventricular hypertrophy
MRI = magnetic resonance imaging
NT-proBNP = N-terminal pro–B-type natriuretic peptide

Left ventricular (LV) hypertrophy (LVH), most commonly due to chronic hypertensive heart disease, is associated with substantial morbidity and mortality, including the development of heart failure (HF) and death from cardiovascular (CV) disease (1,2). LVH develops in response to chronic pressure and volume overload and may ultimately progress to pathological systolic or diastolic dysfunction and symptomatic HF (3). Maladaptive LV remodeling plays a central role in the transition from asymptomatic LVH to clinical HF and results from cardiomyocyte injury and tissue fibrosis (4), as well as increased diastolic wall stress and neurohormonal activation (5).

Although clearly a risk factor for HF and CV death, the natural history of LVH is heterogeneous, with a progressive course in some individuals but an uncomplicated course in many others. Identification of biological pathways that contribute to the transition from LVH to clinical HF, and biomarkers that accurately represent these pathways, may help to identify individuals at high risk for adverse outcomes and to develop therapeutic targets to prevent disease transition. Biomarkers of myocardial injury and neurohormonal activation due to hemodynamic stress may therefore play key roles in defining the transition from asymptomatic LVH to clinical HF (6–8).

Cardiac troponin T (cTnT) and N-terminal pro–B-type natriuretic peptide (NT-proBNP) are released from cardiac myocytes in response to a variety of pathological stimuli, including increased LV wall stress and hypertrophy, and are markers of cardiac injury and ventricular wall stress (9,10). Both biomarkers have been shown to associate strongly with incident HF (11,12) and mortality (13,14) in the general population; however, the impact of minimally elevated circulating levels of cTnT and NT-proBNP among individuals with LVH is unknown. Our goal was to test the hypothesis that biomarker evidence of subclinical myocardial injury and hemodynamic stress could identify asymptomatic individuals with LVH at higher risk for transition to HF and CV death.

Methods

Study population. The Dallas Heart Study (DHS) is a multiethnic, probability-based, population cohort study of Dallas County adults in which deliberate oversampling of African-Americans was performed. Detailed methods of the DHS have been described previously (15). Briefly, between 2000 and 2002, a total of 3,072 subjects completed the 3 DHS visits, including a detailed in-home survey, laboratory testing, and imaging studies. Participants were then followed up for the occurrence of predefined clinical events and death. For the current study, we excluded participants with an LV ejection fraction (LVEF) <40%, estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2, and those with prevalent clinical HF (defined by self-report of "congestive heart failure, an enlarged heart, a weak heart, or cardiomyopathy") at baseline, yielding a final sample size of 2,413. Participants provided written informed consent, and the protocol was approved by the institutional review board of University of Texas Southwestern Medical Center.

Biomarker, imaging, and body composition measurements. Detailed methods describing measurements of cTnT by using a highly sensitive assay (Elecsys-2010 Troponin T hs STAT, Roche Diagnostics, Indianapolis, Indiana) and NT-proBNP (Elecsys, Roche Diagnostics) in the DHS have been published previously (14,16). The lowest concentrations within the analytical measurement range of the assays were 3 pg/ml and 5 pg/ml for cTnT and NT-proBNP, respectively. Cardiac magnetic resonance imaging (MRI) was performed by using a 1.5-T system (Intera, Philips Medical Systems, Best, the Netherlands). LV mass, wall thickness, end-diastolic and end-systolic volumes, and LVEF were calculated from short-axis sequences. LV concentricity was defined as the ratio of LV mass to end-diastolic volume (17).

Fat-free mass was measured with dual-energy x-ray absorptiometry (Delphi W scanner, Hologic, Inc., Bedford, Massachusetts, and Discovery software [version 12.2]) (18). Body mass index was calculated as weight (kilograms)/height (meters)^2 based on weight and height measured at study entry. Body surface area (BSA) was calculated by using the method of Tikuisis et al. (19). Twelve-lead electrocardiograms (ECG) were recorded at 25 mm/s and 1 mV/cm standardization, with a sampling rate of 0.5 kHz, by using the Marquette 12SL ECG analysis program version 229 (GE Marquette Medical Systems, Milwaukee, Wisconsin). Voltage measurements were obtained electronically by using median voltages from an aligned group of all beats from each lead. Two DHS investigators blinded to demographic and clinical information reviewed each ECG to verify the computer-identified parameters and to provide a clinical interpretation.

Definitions. LVH was defined as LV mass/BSA ≥89 g/m^2 in women and ≥112 g/m^2 in men, based on a phenotypically normal subpopulation of the DHS cohort, as previously described (17). As a sensitivity analysis, LVH was also defined by indexing LV mass to height$^{2.7}$ (LV mass/height$^{2.7}$ ≥39 g/$m^{2.7}$ [women] and ≥48 g/$m^{2.7}$ [men]) and fat-free mass (LV mass/fat-free mass ≥3.7 g/kg [both men and women]). Analyses of LVH according to the Sokolow-Lyon ECG criteria, defined as the sum of the S-wave amplitude in lead V_1 plus the maximum R-wave amplitude

in V_5 or V_6 ≥3.5 mV (35 mm) or aVL R-wave amplitude ≥1.1 mV (11 mm) (20), were also performed.

cTnT was characterized as elevated if equal to or above the limit of blank of the assay (3 pg/ml). The limit of blank corresponds to the lowest cTnT concentration within the analytical measurement range of the assay. NT-proBNP was defined as increased if above the age- and sex-specific 75th percentile of the population (using 5 age categories with cutoffs of 35, 40, 50, and 60 years). The NT-proBNP threshold at the 75th percentile was selected to yield a similar proportion of individuals characterized with elevated NT-proBNP as with detectable cTnT. Both thresholds were prospectively defined based on prior studies (14,21).

Race/ethnicity, history of CV diseases, and smoking status were self-reported. Detailed descriptions of variable definitions for hypertension, hypercholesterolemia, and low high-density lipoprotein cholesterol have been previously described by using conventional clinical definitions (22). Presence of the metabolic syndrome was defined and Framingham 10-year CVD risk estimates were calculated according to the National Cholesterol Education Program's Adult Treatment Panel III report (23). GFR was estimated by using the Modification of Diet in Renal Disease equation (24).

Outcomes. The primary outcome was the composite of incident HF or CV death. Incident HF was defined as first hospitalization for systolic or diastolic HF as determined through: 1) a detailed health survey regarding interval CV events administered by the Data Coordinating Center during annual calls to study subjects; and/or 2) for subjects providing informed consent (>90%), quarterly tracking for hospital admissions using the Dallas–Fort Worth Hospital Council Data Initiative database, which includes all hospital admission data for 70 of 72 hospitals in the Dallas–Fort Worth area. Primary clinical source documents were collected and reviewed for all suspected nonfatal CV events (including myocardial infarction and HF) and were independently adjudicated by a blinded endpoint committee. Systolic HF was defined as a clinical diagnosis of symptomatic HF in the setting of an LVEF <50% or documentation of a "depressed or low" LVEF. Diastolic HF was defined as a clinical diagnosis of symptomatic HF in the setting of an LVEF ≥50% or documentation of a "preserved or normal" LVEF. Death events were ascertained through December 31, 2009, from the National Death Index and classified as CV if the primary cause was related to the cardiovascular system according to the International Statistical Classification of Diseases, 10th Revision codes I00–I99 (25).

Statistical analysis. For each analysis, participants were categorized into groups based on the presence (+) or absence (–) of LVH and biomarker levels above (+) or below (–) the predefined threshold. Baseline characteristics were compared between those without LVH, those with LVH but without elevated biomarkers, and those with LVH and elevated biomarkers by using chi-square tests for dichotomous variables and Wilcoxon rank sum tests for continuous variables. The cumulative incidence of the primary outcome among groups with LVH− biomarker−, LVH− biomarker+, LVH+ biomarker−, and LVH+ biomarker+ was estimated by using time-to-event analysis, and Kaplan-Meier curves were constructed and compared by using the log-rank test. Cox proportional hazards models were used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the primary outcome among each group after conditions of proportionality were confirmed. Interaction terms were included in the unadjusted models to determine if qualitative interactions between LVH, cTnT, and NT-proBNP were present. Multivariable models were used to adjust for age, sex, African-American race, diabetes, hypertension, prior CV disease, smoking, body mass index, eGFR, and LV mass/BSA. Shrinkage coefficients were tested for each multivariable model to ensure against model overfitting. Sensitivity analyses were performed by using a 5-pg/ml threshold to define detectable cTnT and defining LVH by using LV mass indexed to $height^{2.7}$ and fat-free mass, and also according to the Sokolow-Lyon ECG criteria. Exploratory analyses were performed by comparing outcomes among those with LVH and 0, 1, or 2 elevated biomarkers.

For all statistical testing, a 2-sided p value <0.05 was considered statistically significant. All statistical analyses were performed by using SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina).

Results

Prevalence and univariable associations of LVH phenotypes. Among the 2,413 participants meeting study criteria (mean age 44; 56% women; 48% African-American), 223 (9.2%) had LVH, 590 (24.5%) had detectable cTnT (cTnT+), and 584 (24.2%) had a NT-proBNP value >75th percentile (NT-proBNP+). The correlation between cTnT and NT-proBNP among all study participants was not significant (Spearman's rho = 0.03, p = 0.14); however, among the subgroup with detectable cTnT, NT-proBNP was weakly correlated with cTnT (Spearman's rho = 0.14, p = 0.001). Among those with LVH, 35.4% had no biomarker elevation, 20.2% were cTnT+ only, 18.8 % were NT-proBNP+ only, and 25.6% were both cTnT+ and NT-proBNP+. The frequency of LVH with cTnT+ was highest in African-American men (12%), with sequentially lower rates seen in African-American women (4%), Caucasian men (2%), and Caucasian women (1%), respectively.

Baseline characteristics are presented in Table 1. Compared with both those without LVH and those with LVH but without detectable cTnT, participants with LVH and detectable cTnT were older, more likely to be male and African American, with more hypertension, diabetes, metabolic syndrome, prior CVD, and lower eGFR (p < 0.05 for each). In addition, compared with LVH+ cTnT– individuals, those LVH+ cTnT+ had greater LV mass and wall thickness, a higher LV concentricity index, and higher

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Table 1 Baseline Characteristics of the Study Population

Variable	No LVH (n = 2,190)	LVH		LVH	
		cTnT– (n = 121)	cTnT+ (n = 102)	NT-proBNP– (n = 124)	NT-proBNP+ (n = 99)
Age (yrs)	43 (36, 51)	43 (37, 50)	51 (45, 59)*†	45 (38, 53)	49 (42, 56)*‡
Male (%)	43.7	31.4	68.6*†	45.2	52.5
Race (%)					
Caucasian	35.8	16.5	14.7*	14.5	17.2*
African-American	45.0	76.9	78.4*	78.2	76.8*
Hispanic	17.0	5.0	6.9*	5.6	6.1*
Other	2.1	1.7	0.0	0.0	0.0
Hypertension (%)	27.3	65.8	76.8*	64.2	79.2*
Systolic BP (mm Hg)	120 (111, 130)	138 (123, 156)	151 (134, 167)*†	139 (123, 153)	154 (132, 170)*‡
Diastolic BP (mm Hg)	76 (71, 83)	84 (78, 95)	87 (79, 94)*	83 (77, 93)	89 (80, 100)*‡
Diabetes (%)	8.5	14.0	30.4*†	20.2	23.2*
Hypercholesterolemia (%)	13.1	11.6	15.7	13.7	13.1
Low HDL cholesterol (%)	39.4	38.0	38.2	38.7	37.4
Metabolic syndrome (%)	31.8	42.1	58.8*†	50.8	48.5*
Current smoking (%)	24.7	49.6	29.4†	36.3	45.5*
Prior CHD (%)	1.6	1.7	10.8*†	3.2	9.1*
Prior CVD (%)	2.9	5.0	15.7*†	4.0	17.2*‡
Framingham 10-year CVD risk estimate ≥6 (%)	16.6	24.0	52.9*†	31.5	44.4*
Estimated GFR (ml/min per 1.73 m^2)	97.1 (85.3, 111.4)	103.9 (91.1, 116.3)	93.5 (80.3, 108.6)*†	98.3 (86.4, 115.1)	97.6 (83.9, 112.2)
Body mass index (kg/m^2)	29.1 (25.2, 33.9)	29.0 (25.5, 34.7)	31.0 (26.3, 35.7)*	29.7 (26.4, 34.9)	29.5 (25.2, 35.4)
LV mass/BSA (g/m^2)	77.5 (68.7, 88.0)	103.7 (93.1, 116.9)	119.4 (108.2, 129.0)*†	108.7 (94.6, 117.7)	119.8 (101.1, 130.0)*‡
LV wall thickness (mm)	11.2 (10.2, 12.3)	13.5 (12.3, 14.5)	14.6 (13.7, 16.4)*†	13.9 (13.0, 15.1)	14.3 (12.9, 15.4)*
LV ejection fraction (%)	73.3 (68.4, 77.7)	71.7 (65.6, 75.9)	70.5 (61.9, 76.0)*	71.8 (66.3, 75.6)	70.5 (62.8, 76.3)*
LV end-diastolic volume/BSA (ml/m^2)	50.6 (44.7, 57.0)	55.6 (49.0, 62.8)	58.1 (48.6, 68.1)*	54.9 (47.6, 62.1)	58.4 (50.1, 68.7)*‡
LV end-systolic volume/BSA (ml/m^2)	13.4 (10.6, 16.7)	16.1 (12.5, 20.2)	16.1 (12.9, 22.9)*	15.1 (12.3, 20.2)	17.3 (13.1, 23.0)*‡
Concentricity (g/ml)	1.5 (1.4, 1.7)	1.9 (1.7, 2.1)	2.0 (1.8, 2.5)*†	1.9 (1.7, 2.3)	1.9 (1.7, 2.3)*
cTnT (pg/ml)	<3.0 (<3.0, <3.0)	<3.0 (<3.0, <3.0)	7.4 (5.1, 10.9)*†	<3.0 (<3.0, 4.8)	4.1 (<3.0, 9.7)*‡
NT-proBNP (pg/ml)	26.4 (12.6, 52.9)	35.5 (13.1, 85.5)	71.0 (25.9, 194.0)*†	20.1 (9.4, 39.4)	127 (86.2, 257.7)*‡

Values are median (25%, 75% percentile) or proportion (%) where indicated. *$p < 0.05$ versus no LVH group. †$p < 0.05$ versus LVH+ cTnT– group. ‡$p < 0.05$ versus LVH+ NT-proBNP– group.
(+) = presence; (–) = absence; BP = blood pressure; BSA = body surface area; CHD = coronary heart disease; cTnT = cardiac troponin T; CVD = cardiovascular disease; GFR = glomerular filtration rate; HDL = high density lipoprotein; LV = left ventricular; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro–B-type natriuretic peptide.

levels of NT-proBNP. Generally similar findings were seen when LVH+ NT-proBNP+ individuals were compared with LVH+ NT-proBNP– individuals, with the exception that larger LV end-diastolic and end-systolic volumes, rather than wall thickness and concentricity, were associated with increased NT-proBNP.

Associations of LVH phenotypes with HF and CV death. During a median follow-up period of 8.1 (interquartile range 7.6 to 8.6) years, the primary outcome of HF or CV death occurred in 65 (2.7%) participants, including 28 HF events (1.36 per 1,000 person-years) and 37 CV deaths (1.80 per 1,000 person-years). Among those who developed HF or died of CV causes, 63.1% were men and 78.5% were African-American. Of those with incident HF, 65.2% had systolic HF and 34.8% had diastolic HF, with a median LVEF at the time of diagnosis of 30% (interquartile range 20 to 36) and 55% (interquartile range 55 to 70), respectively; 20% of those with systolic HF and 25% with diastolic HF had a myocardial infarction during the study interval.

The cumulative incidence of HF or CV death was 20.6% in the LVH+ cTnT+ group compared with 1.1% (LVH– cTnT–), 3.9% (LVH– cTnT+), and 5.8% (LVH+ cTnT–) (log-rank $p < 0.0001$) (Fig. 1A). Among those who were LVH+ NT-proBNP+, the primary outcome occurred in 20.2% compared with 1.5% (LVH– NT-proBNP–), 2.5% (LVH– NT-proBNP+), and 6.5% (LVH+ NT-proBNP–) (log-rank $p < 0.0001$) (Fig. 1B). Although only 6% of the study population had LVH with cTnT+ and/or NT-proBNP+, these individuals accounted for approximately 40% of all HF or CV death events. The crude HR with 95% CI for the primary outcome was 22.6 (95% CI 12.1 to 42.5) for LVH+ cTnT+ and 15.5 (95% CI 8.6 to 28.0) for LVH+ NT-proBNP+ participants compared with those who were LVH– cTnT– and LVH– NT-proBNP–, respectively (Table 2). Highly significant statistical interactions were observed both between LVH and detectable cTnT ($p_{interaction}=0.0005$) and between LVH and elevated NT-proBNP ($p_{interaction} = 0.014$) for the primary outcome. Interactions remained significant after including each biomarker as a continuous variable ($p_{interaction} = 0.026$ for LVH-cTnT and $p_{interaction} = 0.044$ for LVH-NT-proBNP). Findings were consistent across subgroups defined by age, sex, race, ejec-

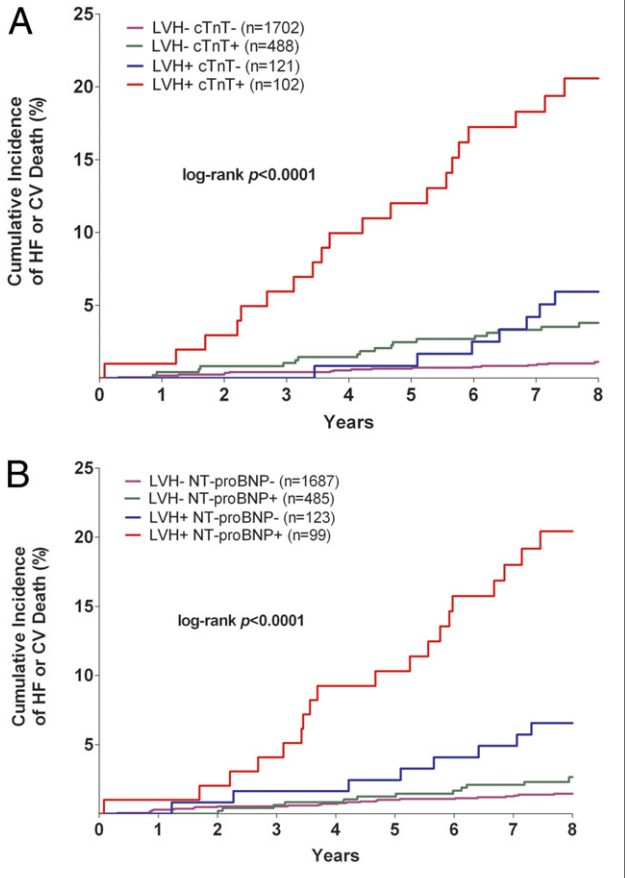

Figure 1 **Kaplan-Meier Curves for Incident HF or CV Death**

Unadjusted Kaplan-Meier curves for incident heart failure (HF) or cardiovascular (CV) death stratified by the presence (+) or absence (–) of left ventricular hypertrophy (LVH) and detectable cardiac troponin T **(A)** or increased N-terminal pro–B-type natriuretic peptide (NT-proBNP) **(B)**. cTnT = cardiac troponin T.

tion fraction, and comorbidities (Online Fig. 1) and for both individual components of the composite outcome (Fig. 2). Results were also insensitive to the use of height$^{2.7}$ or fat-free mass as the indexing variable for LV mass and to use of a 5-pg/ml threshold to define detectable cTnT (data not shown).

Detectable cTnT was associated with a higher risk for HF or CV death across sex-specific tertiles of LV mass, with the largest effect seen among those with the highest LV mass ($p < 0.0001$ for cTnT+ vs. cTnT– in tertile 3, Fig. 3A), consistent with the statistical interaction reported earlier. In addition, the presence of LVH was associated with a marked increase in the risk for HF or CV death across the entire spectrum of cTnT levels ($p < 0.001$ for each) (Fig. 3B), with the greatest effect seen at cTnT levels >14 pg/ml (the previously reported 99th percentile value for the assay in normal controls).

Among the subgroup of individuals with LVH, the presence of detectable cTnT was associated with a >4-fold increase in the risk of the composite outcome (crude HR 4.2 [95% CI 1.8 to 9.8]) compared with those who were LVH+ cTnT–. Similar findings were seen for the LVH+ NT-proBNP+ group compared with those who were LVH+ NT-proBNP– (crude HR 3.5 [95% CI 1.5 to 7.9]). In exploratory analyses restricted to those with LVH, graded associations were also seen between the number of elevated biomarkers and the incidence of HF or CV death. The primary outcome occurred in 5.1% of those with LVH and normal biomarkers, 8.1% of those with LVH and either cTnT+ or NT-proBNP+, and 29.8% of those with LVH and both cTnT+ and NT-proBNP+ (log-rank $p < 0.0001$) (Fig. 4).

In multivariable analyses adjusting for age, sex, African-American race, diabetes, hypertension, CV disease, smoking, body mass index, eGFR, and LV mass/BSA, LVH with cTnT+ or NT-proBNP+ remained strongly associated with incident HF or CV death compared with individuals who were LVH– and cTnT– or NT-proBNP–, respectively (adjusted HR 4.3 [95% CI 1.7 to 11.1] for LVH+ cTnT+ and adjusted HR 4.5 [95% CI 1.7 to 11.8] for LVH+ NT-proBNP+) (Table 2). Results were insensitive to substitution of systolic blood pressure (as a contin-

Table 2 **Unadjusted and Multivariable-Adjusted Associations of LVH**

Model	LVH– cTnT–*	Hazard Ratio (95% CI) LVH– cTnT+	LVH+ cTnT–	LVH+ cTnT+	p Value for interaction
Model 1 (unadjusted)	1.00	3.7 (2.0, 7.1)	5.5 (2.8, 13.1)	22.6 (12.1, 42.5)	0.0005
Model 2	1.00	1.8 (0.9, 3.9)	2.8 (1.1, 7.0)	6.2 (2.8, 13.7)	
Model 3	1.00	1.9 (0.9, 4.0)	2.0 (0.7, 5.7)	4.3 (1.7, 11.1)	
	LVH– NT-proBNP–*	**LVH– NT-proBNP+**	**LVH+ NT–proBNP–**	**LVH+ NT-proBNP+**	
Model 1 (unadjusted)	1.00	1.7 (0.8, 3.3)	4.5 (2.0, 9.9)	15.5 (8.6, 28.0)	0.014
Model 2	1.00	2.2 (1.0, 4.5)	2.4 (1.1, 5.6)	6.0 (3.0, 11.8)	
Model 3	1.00	2.1 (1.0, 4.4)	2.0 (0.8, 5.3)	4.5 (1.7, 11.8)	

Model 1 was unadjusted; Model 2 was adjusted for age, sex, African-American race, diabetes, hypertension, prior CVD, smoking, body mass index, and estimated GFR; Model 3 was adjusted for Model 2 plus LV mass/BSA. *Referent.

Abbreviations as in Table 1.

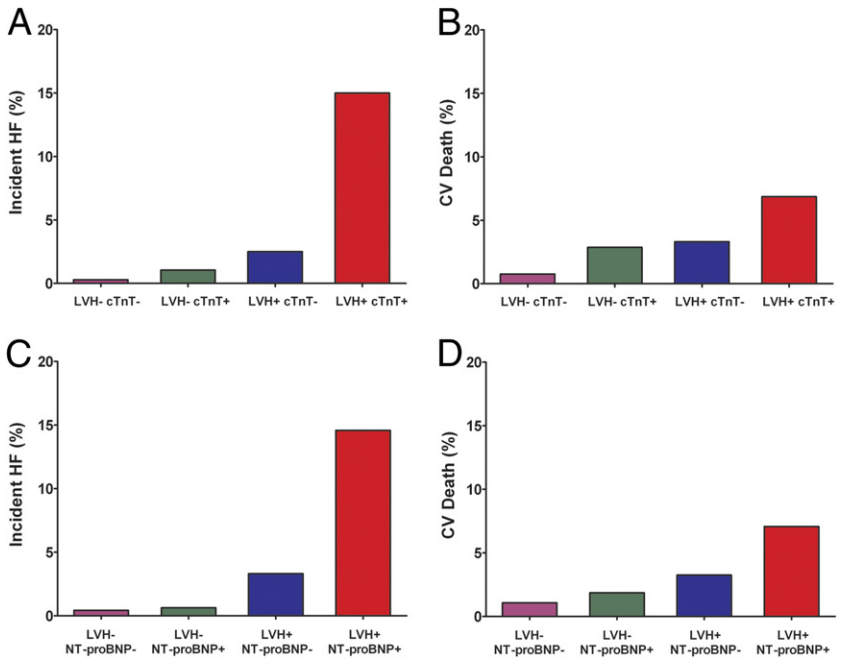

Figure 2 **Incidence of HF and CV Death Stratified According to Biomarker Group**

Incidence of HF and CV death stratified according to the presence (+) or absence (–) of LVH and detectable cTnT **(A and B)** or increased NT-proBNP **(C and D)** levels. Abbreviations as given in Figure 1.

uous measure) for hypertension status in the multivariable model.

Replacing MRI definitions of LVH with electrocardiographic LVH criteria. Using the Sokolow-Lyon ECG criteria, 215 (8.9%) participants had LVH, of whom 35.8% were cTnT+ and 32.9% NT-proBNP+. The primary outcome occurred in 16.9% who were ECG LVH+ cTnT+ compared with 1.3% (ECG LVH– cTnT–), 5.3% (ECG LVH– cTnT+), and 2.9% (ECG LVH+ cTnT–) (log-rank $p < 0.0001$) (Online Fig. 2A). Among those who were ECG LVH+ NT-proBNP+, the primary outcome occurred in 15.7% compared with 1.6% (ECG LVH– NT-proBNP–), 4.1% (ECG LVH– NT-proBNP+), and 4.2% (ECG LVH+ NT-proBNP–) (log-rank $p < 0.0001$) (Online Fig. 2B). Significant interactions were observed between ECG LVH and both cTnT ($p_{interaction} = 0.013$) and NT-proBNP ($p_{interaction} = 0.017$) for the primary outcome. Associations remained significant after multivariable adjustment, with an adjusted HR of 3.2 (95% CI 1.4 to 7.6) for ECG LVH+ cTnT+ and an adjusted HR 3.4 (95% CI 1.5 to 7.9) for ECG LVH+ NT-proBNP+ compared with ECG LVH– biomarker–groups (Online Table 1).

Discussion

In a representative population-based sample of US adults without HF, we report substantial heterogeneity in the clinical phenotype of LVH, with a very high risk of HF or CV death observed among individuals who have LVH with concomitant biomarker evidence of subclinical myocardial injury or neurohormonal activation due to hemodynamic stress, and a more benign course among those with LVH but without elevated biomarkers. Although high-risk phenotypes with LVH and biomarker elevation were observed in fewer than 6% of the population at baseline, such individuals represented approximately 40% of HF or CV death events during follow-up. Moreover, these associations were independent of traditional CV risk factors and renal function, and were consistent across subgroups defined according to age, sex, race, and baseline LVEF. The findings were insensitive to indexing methods for LVH and performed similarly when LVH was defined by using ECG criteria, suggesting that simple and inexpensive strategies may be available to identify this high-risk group. Importantly, the observations are not explained simply by higher LV mass among those with abnormal cTnT or NT-proBNP because the findings were also robust to further adjustment for precise MRI measurements of LV mass. Based on these findings, small elevations in cTnT and NT-proBNP may be pathophysiological indicators of adverse remodeling on the pathway from LVH to clinical HF and not merely surrogate markers for more severe LVH.

Increasing evidence suggests that circulating biomarkers of cardiac injury and neurohormonal activation provide biological insight into chronic CV disease in the population. Studies have demonstrated that cTnT is detectable by using a highly sensitive assay in >90% of patients with chronic

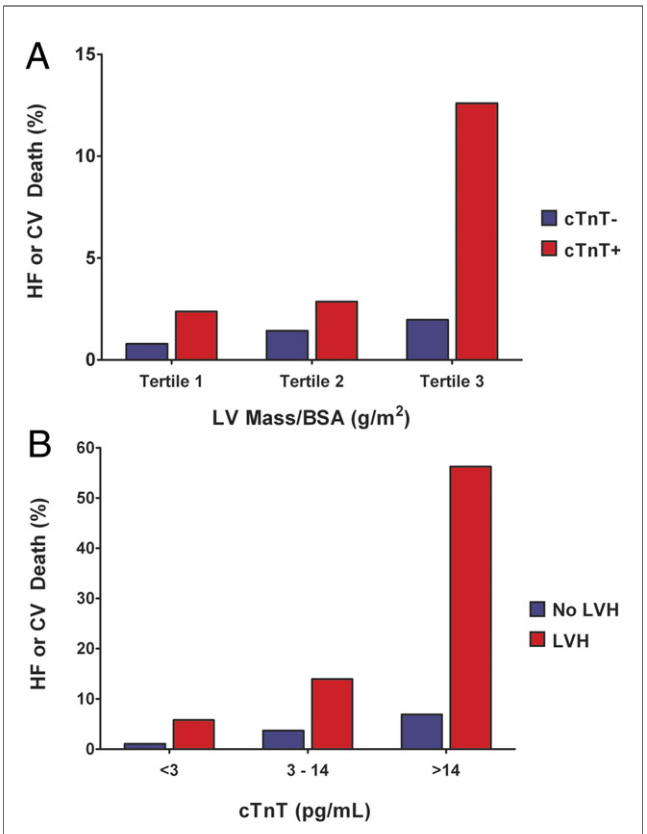

Figure 3 **Incidence of HF or CV Death**

(A) Incidence of HF or CV death by tertile of left ventricular (LV) mass stratified according to detectable or undetectable cTnT. **(B)** Incidence of HF or CV death according to cTnT level stratified by the presence or absence of LVH. BSA = body surface area; other abbreviations as in Figure 1.

stable coronary artery disease (26) or ambulatory HF (27) and in 25% to 67% of middle-aged adults in the general population (12,14). The concentration of NT-proBNP also varies widely in the population, with the highest levels among those of older age and female sex (28). LVH has been shown to be an independent determinant of circulating cTnT and NT-proBNP levels in stable, ambulatory populations (29–31). In our study, the prevalence of cTnT+ and NT-proBNP+ was twice as high among those with LVH compared with those without, and higher levels of both markers were associated with more severe LVH. Notably, within the population with LVH, structural changes associated with cTnT included increased LV wall thickness and concentricity; in contrast, NT-proBNP associated with increased LV end-diastolic and end-systolic volumes. These findings, along with the observation that cTnT and NT-proBNP were weakly correlated with each other in our study, support the notion that each biomarker may reflect partially overlapping but nonredundant pathways through which LVH can transition to clinical HF.

LVH is independently associated with adverse CV outcomes, including HF and death. Each 50-g increment in echocardiographically assessed LV mass was associated with a 73% increased risk of CV death among men and a 112% increased risk among women in the Framingham Heart Study (2) and a 50% increased risk of developing systolic HF in the Cardiovascular Health Study (1). Although interval myocardial infarction is an important contributor to the transition from LVH with a normal LVEF to a reduced LVEF, our findings raise the possibility that chronic subclinical myocardial injury may mediate the progression from concentric LVH to LV systolic dysfunction in some individuals without myocardial infarction. In addition, given that much of the progression to HF occurred among those with preserved LVEF, our findings also suggest that cardiac injury and hemodynamic stress may be important in the transition from LVH to diastolic HF.

The interaction between LVH and cTnT and NT-proBNP has not been previously described. Investigators from the PEACE (Prevention of Events with Angiotensin-Converting Enzyme Inhibition) trial demonstrated that each unit increase in cTnT (measured by using a highly sensitive assay) was associated with a >2-fold risk of HF among patients with stable coronary artery disease and normal LVEF, independent of NT-proBNP levels (26). Similar associations have been observed in ambulatory cohorts representative of the general population, where very low concentrations of cTnT (measured by using a highly sensitive assay) and NT-proBNP confer independent prognostic information with regard to HF, as well as CV and all-cause mortality (12,14,32). However, data on patient subgroups with LVH are lacking. Our study provides robust evidence for effect modification of the association between LVH and HF and CV death by both cTnT and NT-proBNP, as highly significant interaction terms were seen. In addition, although only exploratory, we found an absolute 25% increase in the risk for HF or CV death among those with LVH and elevation in both biomarkers com-

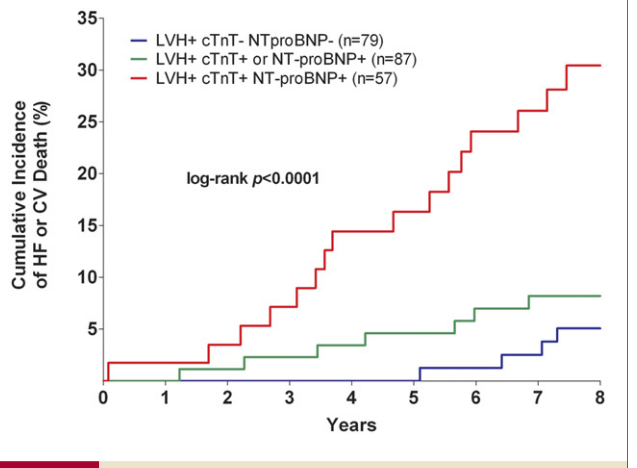

Figure 4 **Unadjusted Kaplan-Meier Curves for Incident HF or CV Death**

Data from individuals with LVH stratified according to number of elevated biomarkers. Abbreviations as in Figure 1.

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pared with those with LVH alone. These findings suggest that not only do cardiac injury and neurohormonal activation independently confer an adverse prognosis among individuals with LVH, but they likely reflect ongoing processes that act synergistically to contribute to the transition from asymptomatic LVH to clinical HF. Future studies evaluating associations of these biomarkers with imaging-based assessments of cardiac remodeling in individuals with LVH are needed.

Clinical and therapeutic implications. African-American individuals have an increased prevalence of LVH and are at increased risk for HF and CV death compared with other racial/ethnic groups (17). Although the associations of cTnT, NT-proBNP, and LVH on HF and CV death were consistent across race/ethnicity subgroups in this study (Online Fig. 1), it is important to note that African-American men had the highest proportion of LVH and detectable cTnT within the study cohort and that the majority of the events occurred among this subgroup. A particularly notable finding is that African-American women were more likely than Caucasian men to have the LVH+ cTnT+ phenotype. Given that African-Americans are 8 times as likely to have hypertension as an antecedent to clinical HF (33) and 2 to 3 times more likely to have LVH (17) compared with Caucasians, our findings may contribute to understanding the biological mechanisms underpinning the disproportionate burden of HF and CV death among African-Americans.

Preliminary observations suggest that levels of both cTnT (34) and NT-proBNP (35), as well as the subsequent risk for death and HF associated with elevations in these biomarkers, may be modifiable. Given the extraordinarily high risk observed in the subgroups with LVH and abnormal biomarkers, early identification and targeted treatments to modify this malignant phenotype represent an important clinical and research priority, with particular implications for African-American individuals.

Currently, screening for LVH in the population is performed most extensively with ECG, although the prevalence of ECG LVH varies significantly according to age, sex, race, and ECG criteria used. ECG criteria systematically underestimate the true prevalence of LVH by MRI, with ECG LVH prevalence ranging between 0.6% (2) and 4.9% (36) compared with an MRI prevalence of 7.7% (37) in the Multi-Ethnic Study of Atherosclerosis and 9.2% in the current study. Despite systematic misclassification by ECG of a significant proportion of participants as not having LVH, the finding of an interaction between LVH and cTnT and NT-proBNP was maintained, such that those with ECG-defined LVH and elevated cardiac biomarkers had an absolute increased risk for HF or CV death of >11% compared with those with ECG-defined LVH but without elevated biomarkers. These findings suggest that biomarkers may be used to subphenotype those with ECG-defined LVH, identifying individuals at particularly high risk for transition to cardiac failure and death. The clinical implications of this approach require further prospective study.

Study strengths and limitations. Strengths of the current study include use of both advanced cardiac MRI imaging and standard ECG criteria to define LVH, the assessment of cardiac injury by using a novel, highly sensitive troponin assay, and longitudinal follow-up in a well-validated prospective cohort. In addition, the large proportion of African-American patients included in our study population allows robust examination of outcomes in this important subgroup. Several limitations also merit comment. First, the number of HF and CV death events was relatively small despite the large sample size, due to the low-risk general population sample studied. For this reason, our findings are preliminary and should be primarily considered in light of their pathophysiological, rather than clinical, implications. Further study is required to validate these observations in larger populations with LVH and long-term follow-up. Second, extrapolation to older populations from our relatively young cohort should not be made because older populations have higher cTnT (32) and NT-proBNP levels, and different thresholds may be needed to explore potential interactions with LVH. Third, the prognostic differences between LVH with elevation in a single biomarker compared with both biomarkers should be considered hypothesis-generating given the relatively low number of participants and events modeled in these groups.

Conclusions

Elevated circulating levels of cTnT and NT-proBNP identified a malignant LVH phenotype in the general population, reflecting chronic cardiac injury and hemodynamic stress that may contribute to the transition from asymptomatic LVH to clinical HF. Highly significant interactions were observed between LVH and both cTnT and NT-proBNP, as individuals with LVH and elevated biomarkers had an extremely high risk for HF or CV death over 8 years of follow-up. These findings suggest that circulating cTnT and NT-proBNP may identify a subpopulation of those with LVH in need of aggressive prevention and treatment to improve CV outcomes.

Reprint requests and correspondence: Dr. James A. de Lemos, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, MC 8830, Dallas, Texas 75390. E-mail: james.delemos@utsouthwestern.edu.

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Key Words: heart failure ■ left ventricular hypertrophy ■ natriuretic peptides ■ troponin.

APPENDIX

For supplementary figures and table on the study results, please see the online version of this article.