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Left Ventricular Dilation and Incident Congestive Heart Failure in Asymptomatic Adults without Cardiovascular Disease. MESA

Joseph Yeboah, MD, MS^{a,b}, David A. Bluemke, MD^c, W Gregory Hundley, MD^a, Carlos J Rodriguez, MD, MPH^{a,b}, Joao A C Lima, MD^d, and David M Herrington, MD, MHS^{a,b}

^aDepartment of Internal Medicine / Cardiology, Wake Forest University School of Medicine, Winston – Salem NC

^bDepartment of Epidemiology and Prevention, Wake Forest School of Medicine, Winston-Salem, NC

^cNational Institutes of Health Clinical Center, Bethesda, MD

^dDepartment of Cardiology and Radiology, Johns Hopkins University, Baltimore, MD

Abstract

Background—Limited data exist on the association between LV dilation/remodeling and incident heart failure (HF), especially in adults without prior myocardial infarction and valvular heart disease. We assessed the association between left ventricular (LV) dilation and remodeling, and incident heart failure in a multi ethnic cohort

Methods—4974 of 6814 participants in the Multi-Ethnic Study of Atherosclerosis (MESA) had cardiac magnetic resonance imaging and complete data. Kaplan-Meier (KM) and Cox proportional hazard analyses were used to assess the association between LV end diastolic diameter (LVEDD) and adjudicated HF.

Results—During the 12 years of follow up (mean 9.4 years), 177(3.6%) HF events occurred, 126(71.2%) HFref and 51(28.8%) HFpef. LV dilation (LVEDD >52mm or >95th percentile) was associated with HF in univariate [HR (95%CI): 1.21(1.08 – 1.46) p=0.007] and multivariable Cox models [HR (95%CI): 1.28(1.09–1.57) p=0.01] adjusting traditional risk factors, medication use, LV ejection fraction (LVEF) and interim MI. We found a significant multiplicative interaction between LVEDD and LV ejection fraction in our full multivariable models. Participants with dilated LV and normal ejection fraction had increase risk [HR (95%CI):2.22(1.46–3.37), p=0.006] and those with dilated LV and decreased ejection fraction having the worse prognosis [HR

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Address correspondence and reprints to Joseph Yeboah, MD, MS, Department of Internal Medicine/Cardiology, Wake Forest School of Medicine, Medical Center Blvd., Winston-Salem, NC 27157., Phone: 336 716 7015., Fax: 336 716 9188., jyeboah@wakehealth.edu.

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(95%CI): 7.35(2.36 – 22.85), $p=0.0006$] compared with normal size LV and normal ejection fraction. High proportion of participants with LV dilation had eccentric remodeling; a risk factor for HF. Concentric hypertrophy also a risk factor for HF was common in normal LV group.

Conclusion—LV dilation predicts incident HF independent of risk factors, LV EF and interim MI

Keywords

left ventricular dilation; left ventricular remodeling; heart failure; risk factors; left ventricular ejection fraction

Introduction

Heart failure is a major cause of morbidity and mortality (1). Damage to the left ventricle (LV) is often associated with remodeling (2). Current data suggests that LV remodeling (dilation) is a precursor of clinical heart failure (HF) and mortality in individuals who have had a myocardial infarction (3, 4). Using M-mode echocardiography, the Framingham Heart Study (FHS) also showed that LV dilation was associated with increased risk for clinical heart failure in Caucasians without myocardial infarction (MI) (5). In the FHS, greater LV dimension predicted incident HF better than fractional shortening (a surrogate for LV ejection fraction) and LV mass (5). However, the FHS used M-mode echocardiography, an imaging modality which is rarely used in clinical practice today and has also been shown to over or underestimate LV parameters (6). Furthermore, the ethnically homogeneous population in the FHS limits the applicability of this data to current population. Thus, the association between LV dilation - assessed using current imaging modalities- and incident HF in individuals without clinical cardiovascular disease (including myocardial infarction) remains unclear.

In this study, we report the association between LV end diastolic diameter by cardiac magnetic resonance (CMR) in individuals without baseline clinical cardiovascular disease and incident HF over a mean of 8.5 years in the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods

Study Population and Data Collection

A detailed study design for MESA has been published elsewhere (7). In brief, MESA is a prospective cohort study begun in July 2000 to investigate the prevalence, correlates, and progression of subclinical CVD in individuals without known CVD at baseline. The cohort included 6814 women and men aged 45–84 years old recruited from 6 US communities (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles County, CA; northern Manhattan, NY; and St. Paul, MN). MESA participants were 38% white ($n = 2624$), 28% black ($n = 1895$), 22% Hispanic ($n = 1492$) and 12% Chinese ($n = 803$). Individuals with a history of physician-diagnosed MI, angina, heart failure, stroke or transient ischemic attack, or who had undergone an invasive procedure for CVD (coronary artery bypass graft, angioplasty, valve replacement, pacemaker placement or other vascular surgeries) were

excluded. This study was approved by the Institutional Review Boards of each study site and written informed consent was obtained from all participants.

Demographics, medical history, anthropometric and laboratory data for this study were obtained at the first MESA examination (July 2000 to August 2002). Current smoking was defined as having smoked a cigarette in the last 30 days. Diabetes mellitus was defined as fasting glucose ≥ 126 mg 100 ml^{-1} or the use of hypoglycemic medications. Use of antihypertensive and other medications was based on the review of prescribed medication containers. Resting blood pressure was measured three times participants who were seated; the average of the second and third readings was recorded. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg or use of medication prescribed for hypertension. Body mass index was calculated as weight (kg)/height² (m²). Total and high-density lipoprotein cholesterol were measured from blood samples obtained after a 12-h fast. Low-density lipoprotein cholesterol was estimated by the Friedewald equation (8). Interim myocardial infarction is defined as adjudicated MI (definite or probable) which occurred in participants during the follow-up period. In MESA, reviewers classified MI as definite, probable, or absent, based primarily on combinations of symptoms, ECG, and cardiac biomarker levels. In most cases, definite or probable MI required either abnormal cardiac biomarkers (2 times upper limits of normal) regardless of pain or ECG findings; evolving Q waves regardless of pain or biomarker findings; or a combination of chest pain, and ST-T evolution or new LBBB, and biomarker levels 1–2 times upper limits of normal

Cardiac Magnetic Resonance (CMR)

Consenting participants underwent CMR imaging a median of 16 days after the baseline evaluation; 95% were completed by 11 weeks after the baseline examination. Participation in the CMR exam was voluntary. All imaging was done with a four-element phased-array surface coil positioned anteriorly and posteriorly, electrocardiographic gating, and brachial artery blood pressure monitoring (9). Imaging consisted of fast gradient echo cine images of the LV with time resolution < 50 ms. Functional parameters and mass were determined by volumetric imaging. Imaging data were read using MASS software (version 4.2, Medis Leiden, the Netherlands) at a single reading center by trained readers blinded to risk factor information. Papillary muscles were included in the LV volumes. LV end-diastolic volume and LV end-systolic volume were calculated using Simpson's rule (the summation of areas on each separate slice multiplied by the sum of slice thickness and image gap). LVEF was calculated as LV stroke volume/LV end-diastolic volume $\times 100$.

The interobserver variability in estimating LV parameters were: LVEF (5.1%, 95% CI 3.6, 6.7) and intraobserver variability in estimating LV parameters were: LV mass (6.3 gm, 95% CI, 5.17, 7.38); LVEF (3.9%, 95% CI, 3.06, 4.72) (10). For LV end diastolic diameter, the left ventricular area at the mid ventricular short axis level was first determined by the contour method indicated above. The average diameter at this level was calculated as diameter = square root (area)/ π . Because normal CMR values for LVEDD have not been defined, we adopted the American Society of Echocardiography (ASE) (11) criteria for dilated LV (LV end diastolic diameter greater than 52mm). In addition, we defined LV

dilation as LVEDD > 95th percentile from the MESA cohort. In order to make our results comparable to prior published data (12, 13), LV systolic dysfunction (LVSD) was defined as participants with LVEF <50%.

Ascertainment of Outcomes

Outcomes in MESA are adjudicated by a committee which includes a cardiologist, a cardiovascular physician-epidemiologist and a neurologist. Reviewers/ adjudicators classified incident HF as definite, probable, or absent. Definite or probable HF required heart failure symptoms, such as shortness of breath or edema; probable HF required HF diagnosed by a physician and patient receiving medical treatment for HF. Definite HF required one or more other criteria, such as pulmonary edema/congestion by chest X-ray; poor LV function by cardiac imaging; or echocardiography evidence of LV diastolic dysfunction. Participants who had only a physician diagnosis of HF and no other evidence were classified as “no HF”. Individuals with adjudicated definite or probable HF were used in our analysis. Documented left ventricular ejection fraction at HF diagnosis was also collected during the adjudication process and was used to classify the HF as systolic (LVEF <50%) and diastolic (≥ 50%) heart failure.

Statistical Analysis

Demographic characteristics of participants with and without LV dilation are reported as mean ± SD for continuous variables and as frequency or percentages for categorical variables during the MESA baseline exam. LV end diastolic diameter was introduced into models as continuous variables and also as a categorical variable (dilated LV as defined by ASE). LV end diastolic volume was introduced into models as continuous variable. The cohort was also categorized into 4 groups based on the presence or absence of LV dilation and LV systolic dysfunction.

LV remodeling was assessed by the unadjusted LV mass/LV end diastolic volume ratio [Mass to Cavity ratio (M-C)]. The M-C ratio, a conceptual equivalent of the relative wall thickness, is used in geometric classification of LV architecture by echocardiography. An abnormal M-C ratio was defined as M-C ratio greater than sex-specific 95% percentile in this cohort. Abnormal LV mass (high LV mass) was also defined as LV mass (LVM) greater than 95% sex -specific percentile in this cohort. LV remodeling was then classified into patterns of eccentricity: normal (normal LVM, normal M-C ratio), concentric remodeling (normal LVM, high M-C ratio), eccentric Hypertrophy (high LVM, normal M-C ratio), and concentric hypertrophy (high LVM, high M-C ratio) (14, 15).

Kaplan-Meier analyses and log rank test were used to explore the association between LV dilation/ 4 categories of LV dilation and LV systolic dysfunction combination and incident HF. Cox proportional hazard analysis was also used to assess the association between LV dilation and incident HF in unadjusted and adjusted models adjusting for covariates including age, gender, race/ethnicity, diabetes mellitus, body mass index (BMI), height, systolic blood pressure, diastolic blood pressure, cigarette smoking status, blood pressure medication use (ACE inhibitors or beta blockers), statin use, LV ejection fraction, interaction term(LV end diastolic diameter *LV ejection fraction) and interim MI. These

covariates were chosen based on their associations in the present study and also in prior publications. The extended Cox model, which used the time-dependent variable approach, was used to test for the proportionality assumption. The above analysis was repeated in participants with normal left ventricular systolic function (i.e. LV ejection fraction $\geq 50\%$). A 2-tailed value of $P < 0.05$ was considered significant. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

5004 participants underwent cardiac CMR during the MESA baseline examination. Of these 4974 had no significant valvular disease, complete data and therefore were included in this analysis. After a mean of 9.4 years (maximum of 12 years), 177 (3.6%) incident HF cases occurred (2.7% of whites, 0.9% of Chinese, 3.04% of African Americans and 2.18% of Hispanics). 46(26%) cases were adjudicated as definite HF and 131(74%) cases as probable HF. 126(71.2%) had reduced left ventricular ejection fraction (HFref) and 51(28.8%) had preserved ejection fraction (HFpef) at HF diagnosis.

(502 (10.1%) participants had LV dilation (defined as LVEDD $> 52\text{mm}$) and 4477 had normal LV diameter. Using LVEDD $> 95^{\text{th}}$ percentile, 267 (5.4%) participants had dilated LV. 0.3% of participants had dilated LV and LV systolic dysfunction (DLVDEF), 1.4% had normal LV size and LV systolic dysfunction (NSDEF), 9.8% had dilated LV and normal LV systolic function (DLVNEF) and 88.5% had normal LV size and normal LV systolic function (NSNEF). Table 1 shows the demographic characteristics and CV risk factor profile of participants with and without LV dilation. Participants with LV dilation were younger, more likely to be males, have higher BMI and taller than those with normal LV size.

As expected a relatively higher percentage of participants with dilated LV had eccentric hypertrophy compared with the normal LV group. A smaller percentage of the dilated LV group had concentric remodeling and only one had concentric hypertrophy (Table 1). 112(2.5%) of participants with no remodeling (normal), 41(20.2%) of those with eccentric hypertrophy, 6(3.1%) of those with concentric remodeling and 18 (26.5%) of those with concentric hypertrophy at baseline developed adjudicated HF during the follow up exam.

56 out of the 177 participants, who developed adjudicated HF during the follow up, also developed myocardial infarction. 42(75%) were adjudicated as systolic heart failure while 14(25%) were adjudicated as diastolic heart failure.

LV End Diastolic Diameter and Incident HF

In the Kaplan Meier analysis (Figure 1), participants with LV dilation had an increased risk for incident HF compared with those with normal LV size (Log rank Chi sq. 22.6, $p < 0.0001$). Participants with DLVDEF had the worst event-free survival, followed by NSDEF and DLVNEF compared with NSNEF (Figure 2; Log rank for each comparison < 0.01).

LV end diastolic diameter (per unit SD) was associated with increased risk for incident HF in the univariate and multivariable models (Table 2). Similarly, LV dilation (defined as

either LVEDD >52mm or LVEDD > 95th percentile) was also associated with increased risk for incident HF in univariate and multivariable models (Table 2). A multiplicative interaction term between LV end diastolic diameter and LV ejection fraction was significant in the full model [Chi square = 19.0, $p < 0.0001$]. In the full multivariable model with NSNEF as the reference group: participants with DLVNEF had an increased risk [hazard ratio (95%CI): 2.22(1.46–3.37), $p=0.006$], participants with NSDEF had an increased risk [HR (95%CI): 3.16(1.54 – 6.49), $p=0.001$] and participants with DLVDEF had an increased risk [HR(95%CI): 7.35(2.36 – 22.85), $p=0.0006$]. The wider confidence interval for the DLVDEF is due to the relatively small number of participants with this CMR characteristic in this relatively healthy cohort during the MESA baseline exam. LVEDD and LV geometry were not associated with incident HF in multivariable models when the above analyses was stratified by gender or race due to the significant reduction in power in the stratified analyses.

When the analysis was limited to participants with normal LV systolic function at the MESA baseline examination, LV dilation was also associated with increased risk for incident HF in both univariate and multivariable models (Table 3).

LV End Diastolic Diameter and Incident Definite HF

46 HF events that occurred were adjudicated as definite by MESA. LV dilation (LVEDD >52mm) was associated with incident HF in univariate and full models [hazard ratio (95%CI): 2.81(1.43 – 5.56), $p=0.002$ and 3.98(1.87 – 8.46), $p=0.0003$ respectively]. LV end diastolic diameter (per unit SD) was also associated with increased risk in univariate and full models [hazard ratio (95%CI): 1.30(0.98 – 1.70), $p=0.06$ and 1.42(1.05 – 1.91), $p=0.02$ respectively]. When the analysis was limited to participants with normal LV systolic function (LVEF >50%) at the baseline exam (# cases = 42), LV dilation (LVEDD>52mm) was associated with HF in univariate and multivariable models [hazard ratio (95%CI): 2.48(1.19 – 5.18), $p=0.015$ and 3.63(1.60 – 8.28), $p=0.002$ respectively]. The association between LVEDD (per unit SD) and HF was not significant [hazard ratio (95%CI): 1.16(0.89 – 1.56), $p=0.316$ and 1.28(0.92 – 1.79), $p=0.14$ respectively].

LV Size, LV Ejection Fraction and Interim Myocardial Infarction in Heart Failure Cases (N=177)

The 37 participants with dilated LV at baseline who developed HF during follow up (Group A) had a mean (SD) LVEF of 61.0% (11.4) at baseline and 38.5 % (13.0) at HF diagnosis. 9(24.3%) had an adjudicated MI during the follow up. 32 (86.5%) were systolic heart failure and 5(13.5%) were diastolic heart failure. The 140 participants with normal LV size at baseline who developed HF during the follow up (Group B) had a mean (SD) LVEF of 63.9 % (12.1) at baseline and 43.0 % (15.6) at HF diagnosis. 47(33.5%) had an adjudicated MI during the follow up period. 94(67.1%) were systolic heart failure while 46(32.9%) were diastolic heart failure. There was no significant difference in MI rate (Chi square = 1.16, $p=0.28$), LV ejection fraction at baseline and baseline number of LVSD (Chi square= 0.88, $p=0.35$) between group A and B. However a significantly higher proportion of group A developed LV systolic dysfunction (LVEF <50%) at HF diagnosis compared with group B (Chi square = 5.4, $p=0.02$).

Discussion

We sought to determine whether LV dilation is an independent predictor of incident HF in MESA participants. These individuals were asymptomatic community dwelling adults, and were free of clinical cardiovascular diseases (including valvular heart disease) at baseline. Our data show that LV dilation is an independent predictor of incident HF after adjusting for risk factors including LV ejection fraction and interim MI.

The myocardium has been shown to remodel when it is injured (2). Pfeffer et al showed in a series of experiments that after MI, there is outward remodeling of the LV myocardium and hence LV dilation (3). Such LV dilation precedes clinical symptoms of heart failure and has been the target for therapies such as ACE inhibitors, ARB's and aldosterone antagonists (16–18). Although the myocardial responses to injuries other than infarction are varied, in one report of individuals without history of MI, LV dilation was an independent predictor of incident HF (5). The present study supports this earlier observation. In addition, our study suggests that the association between LV dilation and incident HF also exist in individuals with normal LV ejection fraction.

Reduced LV systolic function is an independent predictor of incident HF (19). Hence current guidelines recommend preventive therapy to individuals with asymptomatic LV systolic dysfunction (LVEF <50%) to reduce their progression to clinical HF (20). Our data suggests that even for people with normal LV systolic function, LV dilation is an independent predictor of incident HF. This finding needs replication in other cohorts but provides a potential additional target population for preventive therapy aimed at reducing the prevalence of heart failure in our communities.

The present study also shows an interaction between LV dilation and LV ejection fraction for incident HF in asymptomatic community dwelling adults. Using participants with normal LV size (end diastolic diameter) and normal LV systolic function as the reference, participants with the highest risk for incident HF were those with LV dilation and LV systolic dysfunction, followed by those with normal LV size but LV systolic dysfunction and those with LV dilation and normal LV systolic function (Figure 2). This graded risk remained significant in our full multivariable Cox models. A significant number of participants in the present study who had eccentric hypertrophy during the baseline exams also developed heart failure compared with those with concentric remodeling or hypertrophy. Thus, the type of remodeling that accompanies myocardial injury may be important in determining the degree of the risk for HF.

Most of the adjudicated HF in the MESA cohort were heart failure with reduced ejection fraction (HFref). This is contrary to current literature that heart failure with preserved ejection fraction (HFpef) and HFref have equal incidence/ prevalence in the general population. This may be explained by the fact that a significantly high proportion of MESA participants with eccentric remodeling and concentric hypertrophy developed HF during the follow up period compared with normal (no remodeling) and concentric remodeling. However a significantly high proportion of the participants with concentric hypertrophy had an adjudicated MI, a diagnosis which would have brought these participants in contact with

healthcare practitioners for preventive therapy, during the follow up period. Thus screening for eccentric remodeling, a significant proportion of who have dilated LV and therefore could be captured by screening for dilated LV, in the general population may also identify high risk individuals for preventive therapy.

The strengths of this study include the large sample size, long duration of follow-up, adjudicated outcomes, use of cardiac CMR, the multi-ethnic cohort and the fact that unlike other studies, all participants were free of clinical cardiovascular disease including valvular heart disease at baseline. However, MESA is an observational study; although we adjusted for most covariates in our adjusted models, our results may still have been influenced by residual confounding. Other cardiac CMR data (e.g. left atria size and structure) likely to influence the development of HF are not currently available in MESA. Inclusion of such data and a more comprehensive analysis of the MESA cardiac CMR data may further inform risk prediction of these outcomes in this population. We used the ASE criteria for dilated LV in this analysis, although our approach for measuring LV end diastolic diameter using cardiac CMR is slightly different from the ASE recommendation in echocardiography. However similar associations were observed in our sensitivity analysis (defining LV dilation as LVEDD >95th percentile) and when LV end diastolic diameter was used as a continuous variable in our models. The LV ejection fraction at diagnosis of HF were reported and the imaging modalities used for the assessment was not uniform. Lastly, our results may not be applicable to populations such as professional athletes, marathon runners and others whose LV is known to dilate as an adaptation to their vigorous exercise activities.

Conclusion

In a multi-ethnic cohort of adults who were free of clinical cardiovascular disease at baseline, LV dilation predicts incident HF independent of risk factors, left ventricular ejection fraction and interim MI. A significant proportion of individuals with LV dilation have eccentric remodeling, a marker that appears to be a risk marker for HFref. LV dilation and eccentric remodeling may be an additional target for preventive therapies aimed at reducing the prevalence of clinical HF.

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Highlights

1. Reduced LV function remain the only proven target for primary HF prevention
2. Dilated LV is a predictor of HF
3. Dilated LV or eccentric LV remodeling maybe a target for primary HF prevention.

Figure 1. Kaplan Meier curves showing the event-free survival for participants with and without dilated left ventricle (LV) for incident heart failure in the Multi Ethnic Study of Atherosclerosis (MESA)

Figure 2.

Kaplan Meier curves showing the event-free survival for participants with normal left ventricular size (NS) and normal left ventricular ejection fraction (NEF), dilated left ventricle (DLV) and NEF, NS and decreased LV ejection fraction (DEF), DLV and DEF for incident heart failure in the Multi Ethnic Study of Atherosclerosis (MESA)

Table 1

Demographic characteristics of participants with and without left ventricular (LV) dilation per the American Society of Echocardiography guidelines in MESA.

Variable	Dilated Left Ventricle(>52mm) (N = 507) Mean± SD	Normal Left Ventricle (N = 4467) Mean ±SD	P value
Age (yrs)	58.9 ±9.9	61.8± 10.1	<0.001
Male gender (%)	358(70.6)	2009(45.0)	<0.0001
Race/Ethnicity (%)			0.11
Caucasian	226(44.6)	1715(38.4)	
Chinese	33(6.5)	616(13.8)	
African American	137(27.0)	1148(25.7)	
Hispanic	111(21.9)	995(22.1)	
BMI (Kg/m ²)	29.0± 4.9	27.6 ±4.9	<0.001
Blood Pressure(mmHg)			
Systolic	124.4± 19.3	125.6 ±21.5	0.254
Diastolic	72.5± 9.8	71.8 ±10.4	0.214
Cholesterol (mg/dl)			
Total	194.8 ±36.4	189.8 ±35.3	0.003
LDL	117.2 ±31.3	117.6 ±31.3	0.739
Triglycerides	121.2 ±71.1	132.4 ±86.5	0.005
Cigarette Smoking (%)			0.311
Never	245(48.3)	2310(51.8)	
Former	192(37.9)	1582(35.6)	
Current	70(13.8)	561(12.6)	
Diabetes mellitus (%)	46(9.1)	526(11.9)	0.196
Height(cm)	172.5± 9.7	165.7 ±9.7	<0.001
HMG CoA reductase use (%)	62(12.2)	660(14.8)	0.122
BP medication use (%)	147(29.0)	1407(31.5)	0.249
ACE I use	56(11.0)	508(11.3)	0.756
ARB use	13(2.6)	150(3.4)	0.321
Beta Blocker use	43(8.5)	391(8.8)	0.778
LV end diastolic diameter(mm)	55.4± 3.8	43.7± 4.7	<0.0001
LV ejection fraction (%)	66.1± 7.5	69.3 ±7.3	<0.001
LV systolic dysfunction (<50%)	15 (3.0)	70 (1.6)	0.01
LV Remodeling			

Variable	Dilated Left Ventricle(>52mm) (N = 507) Mean± SD	Normal Left Ventricle (N = 4467) Mean ±SD	P value
M-C Ratio	1.06± 0.19	1.18 ±0.25	<0.0001
Types of Remodeling			
Normal(no remodeling)	451(88.9)	4084(91.4)	
Eccentric hypertrophy	52(10.3)	136(3.6)	
Concentric remodeling	3(0.6)	189(4.2)	
Concentric hypertrophy	1(0.2)	59(1.3)	

M-C indicates mass-cavity ratio, ACE I indicates Angiotensin converting enzyme inhibitor, ARB indicates angiotensin receptor blocker

Table 2

Hazard Ratios (95%CI) of left ventricular dilation parameters for incident heart failure (# of events = 177) a mean of 9.4 years of follow up in univariate and multivariable Cox models in the total cohort (N=4974)

Variables	Univariate Hazard Ratio(95%CI)	P value	Multivariable ** Hazard Ratio (95%CI)	P value
LV End Diastolic Diameter (mm) *	1.21(1.08 – 1.46)	0.007	1.28(1.09–1.57)	0.01
Dilated LV(>52mm)	2.44(1.58 – 3.76)	<0.0001	2.54(1.59 – 4.04)	0.0008
Dilated LV (> 95 th percentile)	2.72(1.61 – 4.60)	0.0009	2.41(1.40 – 4.20)	0.002

* Continuous variables were standardized (variable/unit SD)

** Adjusted for age, gender, race/ethnicity, BMI, height, SBP, DBP, cigarette smoking, diabetes mellitus, BP medication use, statin use, LV ejection fraction, LV end diastolic diameter*LV ejection fraction, and interim myocardial infarction.

Table 3

Hazard Ratios (95%CI) of left ventricular dilation parameters for incident heart failure (# of events = 149) after a mean of 9.4 years of follow up in univariate and multivariable Cox models in subcohort with normal left ventricular ejection fraction (N=4889).

Variables	Univariate Hazard Ratio(95%CI)	P value	Multivariable** Hazard Ratio(95%CI)	P value
LV End Diastolic Diameter(mm)*	1.15(0.96 – 1.35)	0.07	1.13(0.96 – 1.35)	0.15
Dilated LV (>52mm)	2.55(1.73 – 3.76)	<0.0001	2.28(1.48 – 3.50)	0.002
Dilated LV(>95 th percentile)	2.62(1.47 – 4.68)	0.001	2.30(1.24 – 4.24)	0.008

* Continuous variables were standardized (variable/unit SD)

** Adjusted for age, gender, race/ethnicity, BMI, height, SBP, DBP, cigarette smoking, diabetes mellitus, BP medication use, statin use, LV ejection fraction, LV end diastolic diameter*LV ejection fraction and interim myocardial infarction.