Radiology

ORIGINAL RESEARCH • CARDIAC IMAGING

Left Ventricular Mass at MRI and Long-term Risk of Cardiovascular Events: The Multi-Ethnic Study of Atherosclerosis (MESA)

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Background: Few data exist on the long-term risk prediction of elevated left ventricular (LV) mass quantified by MRI for cardiovascular (CV) events in a contemporary, ethnically diverse cohort.

Purpose: To assess the long-term impact of elevated LV mass on CV events in a prospective cohort study of a multiethnic population in relationship to risk factors and coronary artery calcium (CAC) score.

Materials and Methods: The Multi-Ethnic Study of Atherosclerosis, or MESA (*ClinicalTrials.gov*: NCT00005487), is an ongoing prospective multicenter population-based study in the United States. A total of 6814 participants (age range, 45–84 years) free of clinical CV disease at baseline were enrolled between 2000 and 2002. In 4988 participants (2613 [52.4%] women; mean age, 62 years ± 10.1 [standard deviation]) followed over 15 years for CV events, LV mass was derived from cardiac MRI at baseline enrollment by using semiautomated software at a central core laboratory. Cox proportional hazard models, Kaplan-Meier curves, and *z* scores were applied to assess the impact of LV hypertrophy.

Results: A total of 290 participants had hard coronary heart disease (CHD) events (207 myocardial infarctions [MIs], 95 CHD deaths), 57 had other CV disease–related deaths, and 215 had heart failure (HF). LV hypertrophy was an independent predictor of hard CHD events (hazard ratio [HR]: 2.7; 95% confidence interval [CI]: 1.9, 3.8), MI (HR: 2.8; 95% CI: 1.8, 4.0), CHD death (HR: 4.3; 95% CI: 2.5, 7.3), other CV death (HR: 7.5; 95% CI: 4.2, 13.5), and HF (HR: 5.4; 95% CI: 3.8, 7.5) ($P < .001$ for all end points). LV hypertrophy was a stronger predictor than CAC for CHD death, other CV death, and HF (*z* scores: 5.4 vs 3.4, 6.8 vs 2.4, and 9.7 vs 3.2 for LV hypertrophy vs CAC, respectively). Kaplan-Meier analysis demonstrated an increased risk of CV events in participants with LV hypertrophy, particularly after 5 years.

Conclusion: Elevated left ventricular mass was strongly associated with hard coronary heart disease events, other cardiovascular death, and heart failure over 15 years of follow-up, independent of traditional risk factors and coronary artery calcium score.

Left ventricular (LV) hypertrophy has been identified as an independent risk factor for subsequent cardiovascular events, including heart failure (HF), coronary heart disease (CHD), and stroke (1–9). Regression of LV hypertrophy through medical treatment leads to a reduction in cardiovascular events (10–13). In the Losartan Intervention for Endpoint reduction in hypertension, or LIFE, trial of more than 8000 participants with hypertension, regression of LV hypertrophy through medical therapy was associated with fewer hospitalizations for HF, fewer sudden cardiac deaths, and fewer major adverse cardiovascular events over approximately 5 years (10–12). In a meta-analysis of four studies with 1064 study participants with hypertension, Verdecchia et al (13) reported that regression of LV hypertrophy was associated with reduction of cardiovascular events by 59% compared with persistent or new development of LV hypertrophy. However, we also now recognize that coronary artery calcium (CAC) score, obtained with noncontrast CT, functions to integrate multiple risk factors for cardiovascular disease, CHD, and HF (6,14,15). In this contemporary context, the role of LV hypertrophy has not been examined, to our knowledge.

Prior studies primarily used electrocardiography (ECG) (7,9) or M-Mode and two-dimensional (2D)

Abbreviations

CAC = coronary artery calcium, CHD = coronary heart disease, CI = confidence interval, ECG = electrocardiography, HF = heart failure, HR = hazard ratio, LV = left ventricle, MESA = Multi-Ethnic Study of Atherosclerosis, MI = myocardial infarction

Summary

Left ventricular hypertrophy was strongly associated with hard coronary heart disease events (death and myocardial infarction) over 15 years of follow-up in a contemporary ethnically diverse cohort, after adjustment for traditional risk factors and coronary artery calcium.

Key Results

- Left ventricular hypertrophy quantified by using MRI was an independent predictor of hard coronary heart disease events (hazard ratio [HR]: 2.7), including myocardial infarction (HR: 2.8) and coronary artery disease–related death (HR: 4.3), other cardiovascular disease–related death (HR: 7.5), and heart failure (HR: 5.4) ($P < .001$ for all end points).
- For risk of long-term cardiovascular events, left ventricular hypertrophy was a stronger predictor than CT coronary artery calcium score for coronary artery disease–related death, other cardiovascular disease–related death, and heart failure (z scores: 5.4 vs 3.4, 6.8 vs 2.4, and 9.7 vs 3.2 for left ventricular hypertrophy vs coronary artery calcium score, respectively).

echocardiography (2–5,8) to identify LV hypertrophy. Currently, cardiovascular MRI is widely accepted as the standard of reference for quantification of LV mass (16). For 4967 participants in the Multi-Ethnic Study of Atherosclerosis (MESA) who underwent MRI and ECG, it has already been reported that various ECG criteria had low (approximately 20%) sensitivity for LV hypertrophy (17). Echocardiography-defined LV mass is based on an assumed LV geometry that may not be present in LV hypertrophy (18). MRI-derived LV mass is more precise and accurate compared with LV mass measurements based on M-Mode and 2D echocardiography-derived equations (16,19–21).

To date, prior studies have evaluated the relationship of cardiovascular risk to LV mass over 4–7 years of follow-up (1,4,5,8,22). The objective of our study was therefore to assess the long-term cardiovascular risk of LV hypertrophy in a contemporary, ethnically diverse cohort. We hypothesized that baseline LV mass is predictive of cardiovascular events over long-term follow-up in MESA after adjustment for traditional cardiovascular risk factors.

Given the widespread integration of CAC scoring in clinical practice, the relationship of elevated LV mass to CAC score was also explored. MRI was used as the standard of reference for LV mass measurement.

Materials and Methods

The MESA study was approved by the institutional review boards of each of the participating field sites in the United States (Wake Forest University, Winston-Salem, NC; Columbia University, New York City, NY; Johns Hopkins University, Baltimore, Md; University of Minnesota, Minneapolis, Minn; Northwestern University, Evanston, Ill; and University of California, Los Angeles, Calif), and all participants provided written informed consent. All sites were compliant with the Health Insurance Portability and Accountability Act.

Study Sample

The design of MESA (*ClinicalTrials.gov:* NCT00005487) has been previously described (23). In brief, MESA is an ongoing population-based longitudinal cohort study initiated in July 2000. A total of 6814 participants were recruited from six U.S. communities (Baltimore City and Baltimore County, Md; Chicago, Ill; Forsyth County, NC; Los Angeles County, Calif; Northern Manhattan and the Bronx, New York City, NY; and St Paul, Minn) and four different ethnicities (white, black, Hispanic, and Chinese). At baseline, study participants were between the age of 45 and 84 years and were free of clinically recognized cardiovascular disease. A total of 4999 participants also underwent cardiac MRI at baseline to determine LV mass and volumes.

To date, multiple studies have been published on the MESA cohort. However, to our knowledge, the long-term relationship between LV mass and cardiovascular events has not been assessed or reported.

Risk Factor Measures

MESA participants underwent an extensive evaluation, including clinical history, physical examination, laboratory testing, and anthropometric measurements. Information regarding demographics, smoking history (defined as current, former, or never), current medication (including lipid-lowering, hypoglycemic, and antihypertensive drugs), and physician diagnosis of hypertension and diabetes was obtained by standard questionnaires.

Weight was measured to the nearest 0.5 kg, and height was measured to the nearest 0.1 cm. Body surface area was calculated as $0.20247 \cdot [\text{height (m)}^{(0.725)}] \cdot [\text{weight (kg)}^{(0.425)}]$, and body mass index was calculated as weight in kilograms divided by height in meters squared. Resting blood pressure was measured three times in seated participants; the average of the last two measurements was used in analysis.

Total cholesterol, high-density lipoprotein cholesterol, and glucose levels were measured from blood samples obtained after a 12-hour fast. Diabetes was defined as a fasting glucose level of 126 mg/dL or greater or the use of hypoglycemic medication. Impaired fasting glucose was defined as a fasting glucose level of 100–125 mg/dL (24). (Glucose levels can be converted from milligrams per deciliter to millimoles per liter by multiplication by 0.055.) Hypertension was defined as a systolic blood pressure of 140 mm Hg or greater, a diastolic blood pressure of 90 mm Hg or greater, or the self-reported use of antihypertensive medications (25).

Imaging Assessment

The CAC score in Agatston units was derived from either cardiac-gated electron-beam CT or multidetector CT (26). LV mass and LV volumes were assessed by using MRI with 1.5-T imaging units (Avanto and Espree, Siemens Medical Systems, Erlangen, Germany; and Signa HD, GE Healthcare, Milwaukee, Wis), as described previously (27). In brief, a stack of short-axis images covering the entire LV was acquired by using a cine fast gradient-echo sequence with temporal resolution less than or equal to 40 msec. LV mass was calculated at end

diastole as the sum of the myocardial area (difference between endocardial and epicardial contour) times the section thickness plus the intersection gap multiplied by the specific gravity of myocardium (1.05 g/mL).

Assessment of Events

Adjudication of events has been published in detail previously (1). After baseline examination, participants were followed with five periodic in-person MESA study examinations and with telephone interviews every 9–12 months to obtain data regarding hospital admissions, cardiovascular outpatient diagnosis, and deaths. Copies of death certificates and medical records of hospitalizations were requested to ascertain cardiovascular events and mortality. According to prespecified criteria and blinded to all data collected on the participants during examinations and follow-up calls, end point classification was performed by two independent physicians from the MESA study events committee using MESA study criteria. In instances of disagreement, a final decision was made by the entire events committee.

Hard CHD events included definite and probable myocardial infarction (MI) and definite coronary artery disease–related death. Diagnosis of MI was based on clinical criteria (chest pain), ECG criteria, and cardiac biomarker levels, as described previously (1). Criteria for definite coronary artery disease–related death were in-hospital death due to MI, out-of-hospital death with a documented MI within 28 days, chest pain within 72 hours before death, or a history of CHD and the absence of a known nonatherosclerotic or noncardiac cause of death. Other cardiovascular death was defined as cardiovascular-related death not due to stroke and adjudicated to not be atherosclerotic in origin (eg, death due to pulmonary embolism, arrhythmia, or cardiomyopathy). Criteria for HF included a diagnosis of HF by a physician and medical treatment for HF (probable HF), or definite HF which also required pulmonary edema by radiography or a dilated ventricle, or poor LV function or evidence of LV diastolic dysfunction (1).

Statistical Analysis

Results of previous studies have shown that an allometric height- and weight-based index of LV mass has a better predictive value for events associated with LV hypertrophy than LV mass alone or indexing by body surface area or height (28). As described previously, LV mass was normalized for body size on the basis of a MESA subset of normotensive study participants with a body mass index of less than 25 kg/m^2 with no diabetes or impaired fasting glucose (1). In this approach, the LV mass percentage of predicted is the LV mass of a study participant divided by the predicted LV mass based on height, weight, and sex, as follows: $100\% \cdot \text{LV mass} / (a \cdot \text{height}^{0.54} \cdot \text{weight}^{0.61})$, where a = 6.82 for women and 8.25 for men, with mass in grams, height in meters, and weight in kilograms (28). A calculator for LV mass percentage of predicted is available at *https://www.mesa-nhlbi.org/MESALVmass/MesaLVMPercentPredicted.aspx*.

We explored regression models with LV mass percentage of predicted as a continuous variable and with LV mass percentage of predicted greater than the 95th percentile. For all end points in our study, most excess risk occurred in participants with LV mass percentage of predicted greater than the 95th percentile; LV mass above this level was defined as LV hypertrophy, and was used as a cutpoint in corresponding regression models.

Descriptive statistics (Table 1) are presented as means and standard deviations for the continuous covariates and as percentages and numbers of participants for the discrete covariates. Kaplan-Meier curves were used to display cumulative event rate curves for each of the end points. Cox regression models were used to model the association of LV hypertrophy to hard CHD, MI, coronary artery disease–related death, other cardiovascular deaths, and HF. To adjust for possible confounders, backward elimination was used with $P < .05$ to select variables to include in the model from among the following covariates: age, sex, race/ethnicity, log of CAC score (CAC + 1), body mass index, hypertension, use of antihypertensive medication, diastolic and systolic blood pressure, diabetes (coded as normal, impaired fasting glucose, untreated diabetes, or diabetic), cigarette use (coded as never, former, or current smoker), total and high-density lipoprotein cholesterol, and statin use. The CAC score was log transformed to ln(CAC + 1) to maintain the normality of CAC measures.

Because of the strong relationship of CAC for cardiovascular events, we sought to understand the relative contribution of LV hypertrophy and CAC to cardiovascular events. For this purpose, hazard ratios (HRs) are insufficient because of different scales. Instead, to describe the strength of association of LV hypertrophy compared with CAC for prediction of the risk of cardiovascular events, the z statistic, which is the regression coefficient for the HR for each variable divided by its standard deviation, is used. This is the statistic used to test the hypothesis that the HR is statistically significant in the Cox model.

In sensitivity analysis, analyses of LV size were repeated, including body size–adjusted LV volume and LV remodeling pattern (29), but these variables were not statistically significant after accounting for body size–adjusted LV mass (results not shown). Interactions of sex and ethnicity with LV mass percentage of predicted were not statistically significant (results not shown), indicating that the risk associated with LV mass percentage of predicted was not significantly different when comparing men versus women or participants according to ethnicity.

To account for the statistical tests for each of the five end points, a P value of .01 was used to determine statistical significance. Schoenfeld residuals used to test for proportional hazards were nonsignificant for all the end points. All analyses were performed by using STATA (version 15.0; Stata, College Station, Tex) statistical software.

Results

Study Population

Of 6814 MESA participants, 4988 underwent an MRI examination and had available follow-up events data (Fig 1). The mean baseline age of study participants in this analysis was 62 years; 52% of participants were women, 39% were white, 13% were Chinese, 26% were black/African

Table 1: Baseline Characteristics of the MESA Study Cohort

Characteristic	No Events (n = 4534)	Hard CHD Events (n = 290)*	MI (n = 207)	CHD Death (n = 95)	Other CV Death (n = 57)	Heart Failure (n = 215)
Age (y)†	61.0 ± 10.0	66.3 ± 10.1	65.1 ± 10.0	69.4 ± 9.2	70.0 ± 8.3	68.3 ± 8.7
Sex						
Female	2451 (54.1)	95 (32.8)	66 (31.9)	27 (28.4)	23 (40.4)	81 (37.7)
Male	2083 (45.9)	195 (67.2)	141 (68.1)	68 (71.6)	34 (59.7)	134 (62.3)
Race/ethnicity						
White	1765 (38.9)	118 (40.7)	91 (44.0)	33 (34.7)	19 (33.3)	95 (44.2)
Chinese	610 (13.5)	27 (9.3)	16 (7.7)	13 (13.7)	8 (14.0)	14 (6.5)
Black/African American	1154 (25.5)	76 (26.2)	45 (21.7)	30 (31.6)	19 (33.3)	67 (31.1)
Hispanic	1005 (22.2)	69 (23.8)	55 (26.6)	19 (20.0)	11 (19.3)	39 (18.1)
Height (m)†	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1
Weight (kg)†	76.7 ± 16.1	79.3 ± 15.6	79.5 ± 14.8	78.4 ± 17.2	78.5 ± 15.0	82.1 ± 16.3
Body mass index (kg/m^2)†	27.7 ± 5.0	28.1 ± 4.7	28.0 ± 4.3	27.9 ± 5.1	28.4 ± 5.4	28.9 ± 4.9
BSA (m^2)†	1.8 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2
Cholesterol (mg/dL)†						
Total	194.6 ± 35.3	193.8 ± 36.5	195.8 ± 36.2	189.5 ± 39.6	189.8 ± 43.8	190.5 ± 35.4
HDL	51.5 ± 15.0	47.5 ± 14.2	47.6 ± 14.4	46.5 ± 13.3	48.8 ± 11.9	48.9 ± 13.9
Lipid-lowering medication use						
No	3890 (85.9)	231 (79.7)	165 (79.7)	77 (81.1)	48 (84.2)	178 (82.8)
Yes	641 (14.2)	59 (20.3)	42 (20.3)	18 (19.0)	9 (15.8)	37 (17.2)
Glycemic status						
Normal glucose	2781 (61.5)	149 (51.4)	108 (52.2)	43 (45.3)	23 (40.4)	97 (45.1)
Impaired fasting glucose	1208 (26.7)	69 (23.8)	47 (22.7)	29 (30.5)	14 (24.6)	56 (26.1)
Untreated diabetes	161 (3.6)	19 (6.6)	12 (5.8)	5 (5.3)	5 (8.8)	13 (6.1)
Treated diabetes	371 (8.2)	53 (18.3)	40 (19.3)	18 (19.0)	15 (26.3)	49 (22.8)
Blood pressure (mm Hg)†						
Systolic	124.5 ± 20.9	134.4 ± 22.7	132.6 ± 22.9	136.8 ± 21.9	136.0 ± 23.8	136.8 ± 23.2
Diastolic	71.6 ± 10.2	74.0 ± 11.1	74.1 ± 11.3	73.0 ± 9.8	73.2 ± 12.5	73.6 ± 11.7
Hypertension medication use						
No	2996 (66.1)	157 (54.1)	117 (56.5)	46 (48.4)	22 (38.6)	91 (42.3)
Yes	1535 (33.9)	133 (45.9)	90 (43.5)	49 (51.6)	35 (61.4)	124 (57.7)
Smoking status						
Never	2366 (52.3)	129 (44.5)	91 (44.0)	43 (45.3)	29 (50.9)	87 (40.7)
Former smoker	1599 (35.4)	110 (37.9)	81 (39.1)	30 (31.6)	21 (36.8)	94 (44.0)
Current smoker	556 (12.3)	51 (17.6)	35 (16.9)	22 (23.2)	7 (12.3)	33 (15.4)
Ln(CAC + 1) (ln[Agatston units + 1])†	1.9 ± 2.4	4.1 ± 2.5	4.1 ± 2.5	4.2 ± 2.4	4.0 ± 2.9	3.8 ± 2.8
LV mass percentage of predicted†‡	103.3 ± 17.7	110.3 ± 22.7	110.2 ± 21.4	111.3 ± 26.6	121.2 ± 31.2	118.7 ± 27.2
LV mass/BSA (g/m^2)†	77.0 ± 15.3	85.9 ± 19.4	86.0 ± 18.5	87.1 ± 22.2	93.4 ± 27.4	92.2 ± 23.0
LV hypertrophy§						
No	4364 (96.1)	248 (85.5)	180 (87.0)	75 (79.0)	41 (71.9)	166 (77.2)
Yes	175 (3.9)	42 (14.5)	27 (13.0)	20 (21.1)	16 (28.1)	49 (22.8)

Note.—Unless otherwise specified, data are numbers of patients, with percentages in parentheses. BSA = body surface area, CAC = coronary artery calcium, CHD = coronary heart disease, CV = cardiovascular, HDL = high-density lipoprotein, LV = left ventricle, MI = myocardial infarction.

* Hard CHD events include MI and CHD death. The sum of MI and CHD deaths does not equal the number of hard CHD events because some participants had MI followed by CHD death.

† Data are means ± standard deviations.

‡ LV mass percentage predicted is LV mass divided by the predicted LV mass for sex, height, and weight expressed as a percentage.

§ LV hypertrophy was defined as when LV mass percentage predicted was greater than the 95th percentile (>136%).

American, and 22% were Hispanic. Table 1 shows baseline characteristics for participants with and participants without events. Participants with events tended to be older and were more likely to be men compared with participants without events. Participants with events also had a higher body weight and body mass index, were more likely to have diabetes, had a higher blood pressure, were more likely to be smokers, and had a higher CAC score.

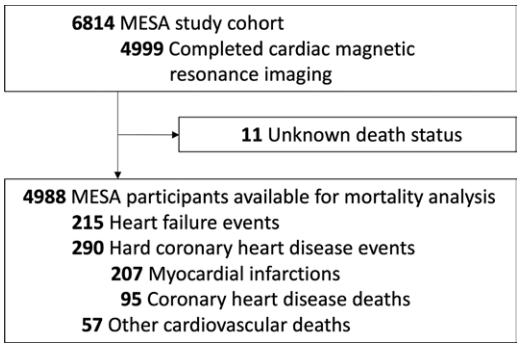

Figure 1: Flow diagram of events. Hard coronary heart disease events were a composite end point and included myocardial infarction and coronary artery disease–related death. The sum of myocardial infarction and coronary artery disease–related deaths does not equal the number of hard coronary heart disease events because some participants had myocardial infarction followed by coronary artery disease–related death. Other cardiovascular death excluded stroke and was adjudicated not to be atherosclerotic in origin (eg, pulmonary embolism, arrhythmia, and cardiomyopathy). MESA = Multi-Ethnic Study of Atherosclerosis.

Over a follow-up time of 15 years (median, 13.5 years), 290 participants had hard CHD events, including 207 MIs and 95 coronary artery disease–related deaths (83 had coronary artery disease–related death after an MI), and 57 had other cardiovascular deaths. A total of 215 participants developed HF. Some study participants had more than one event (eg, MI followed by HF). If a participant had more than one event, the events were considered individually depending on the end point of the analysis. By 15 years of follow-up, about 22% of the MESA participants with LV hypertrophy had a hard CHD event, compared with only about 6% of participants without LV hypertrophy. The cumulative death rates were about 10% for coronary artery disease–related deaths and other cardiovascular deaths in participants with LV hypertrophy, compared with less than 2% in those without LV hypertrophy.

Relationship of LV Hypertrophy to Hard CHD Events

Participants with LV hypertrophy had a higher cumulative rate of hard CHD events throughout follow-up compared with participants without LV hypertrophy (Fig 2, *A*). LV hypertrophy was a predictor of hard CHD events (coronary artery disease–related death plus MI) in all regression models (Table 2). After adjustment for demographics, traditional cardiovascular risk factors, medication use, and CAC score, LV hypertrophy remained a predictor of hard CHD events (HR: 2.7; 95% confidence interval [CI]: 1.9, 3.8; $z = 5.8$; $P < .001$). CAC score was also associated with hard CHD events ($z = 8.3$; $P < .001$).

For the two individual components of hard CHD events, both MI and coronary artery disease–related deaths also showed higher cumulative rates of events for participants with LV hypertrophy than for those without LV hypertrophy (Fig 2, *B* and *C*). In fully adjusted models, participants with LV hypertrophy had 2.8 times the risk of MI compared with participants without LV hypertrophy (HR: 2.8; 95% CI: 1.8, 4.0; $z = 4.7$; $P < .001$) (Table 2). Participants with LV hypertrophy had 4.3 times the risk of coronary artery disease–related death compared with participants without LV hypertrophy (HR: 4.3; 95% CI: 2.5, 7.3; $z = 5.4$; $P < .001$). CAC was positively related to MI ($z = 9.8$; $P < .001$) and coronary artery disease–related death ($z = 3.4$; $P < .001$) in the fully adjusted models; however, LV hypertrophy was a stronger predictor of coronary artery disease–related death than CAC score ($z = 5.4$ vs $z = 3.4$).

Relationship of LV Hypertrophy to Other Cardiovascular Death

The cumulative event rate for other (nonatherosclerotic) cardiovascular death events was greater in participants with LV hypertrophy than in those without LV hypertrophy (Fig 2, *D*). In the fully adjusted model, participants with LV hypertrophy had 7.5 times the risk of other cardiovascular death compared with participants without LV hypertrophy (HR: 7.5; 95% CI: 4.2, 13.5; $z = 6.8$; $P < .001$) (Table 2). CAC was also associated with other cardiovascular death ($z = 2.4$; $P = .02$). As was the case for coronary artery disease–related death (described above), LV hypertrophy was a stronger predictor of other cardiovascular death than CAC score ($z = 6.8$ vs $z = 2.4$).

Relationship of LV Hypertrophy to HF

The cumulative event rate for HF was greater in participants with LV hypertrophy than in those without LV hypertrophy (Fig 2, *E*). In the fully adjusted model, participants with LV hypertrophy had 5.4 times the risk to develop HF compared with participants without LV hypertrophy (HR: 5.4; 95% CI: 3.8, 7.5; $z = 9.7$; $P < .001$) (Table 2). CAC was also associated with HF ($z = 3.2$; $P = .001$); however, LV hypertrophy was a stronger predictor of HF than CAC score ($z = 9.7$ vs $z = 3.2$).

Discussion

In our study, a component of the ongoing long-term Multi-Ethnic Study of Atherosclerosis (MESA) study, we assessed the relationship of left ventricular (LV) mass quantified with MRI to cardiovascular events and coronary artery calcium (CAC) score in a contemporary, ethnically diverse multicenter cohort with long-term follow-up of 15 years. LV hypertrophy was an independent predictor of hard CHD events (HR: 2.7), including MI (HR: 2.8) and coronary artery disease–related death (HR: 4.3), other cardiovascular disease–related death (HR: 7.5), and HF (HR: 5.4) ($P < .001$ for all end points). LV hypertrophy was a stronger predictor of long-term risk of cardiovascular events than CAC score for coronary artery disease–related death, other cardiovascular disease–related death, and HF (z scores: 5.4 vs 3.4, 6.8 vs 2.4, and 9.7 vs 3.2 for LV hypertrophy vs CAC score, respectively). Kaplan-Meier analysis demonstrated an increased risk of cardiovascular events in participants with LV hypertrophy, particularly after 5 years.

Prior studies have shown the short term (4–7 years) adverse effect of LV hypertrophy; specifically, the strong relationship of LV hypertrophy to HF, with variable or no relationship to coronary artery disease–related events (1,2,8,22). However, our

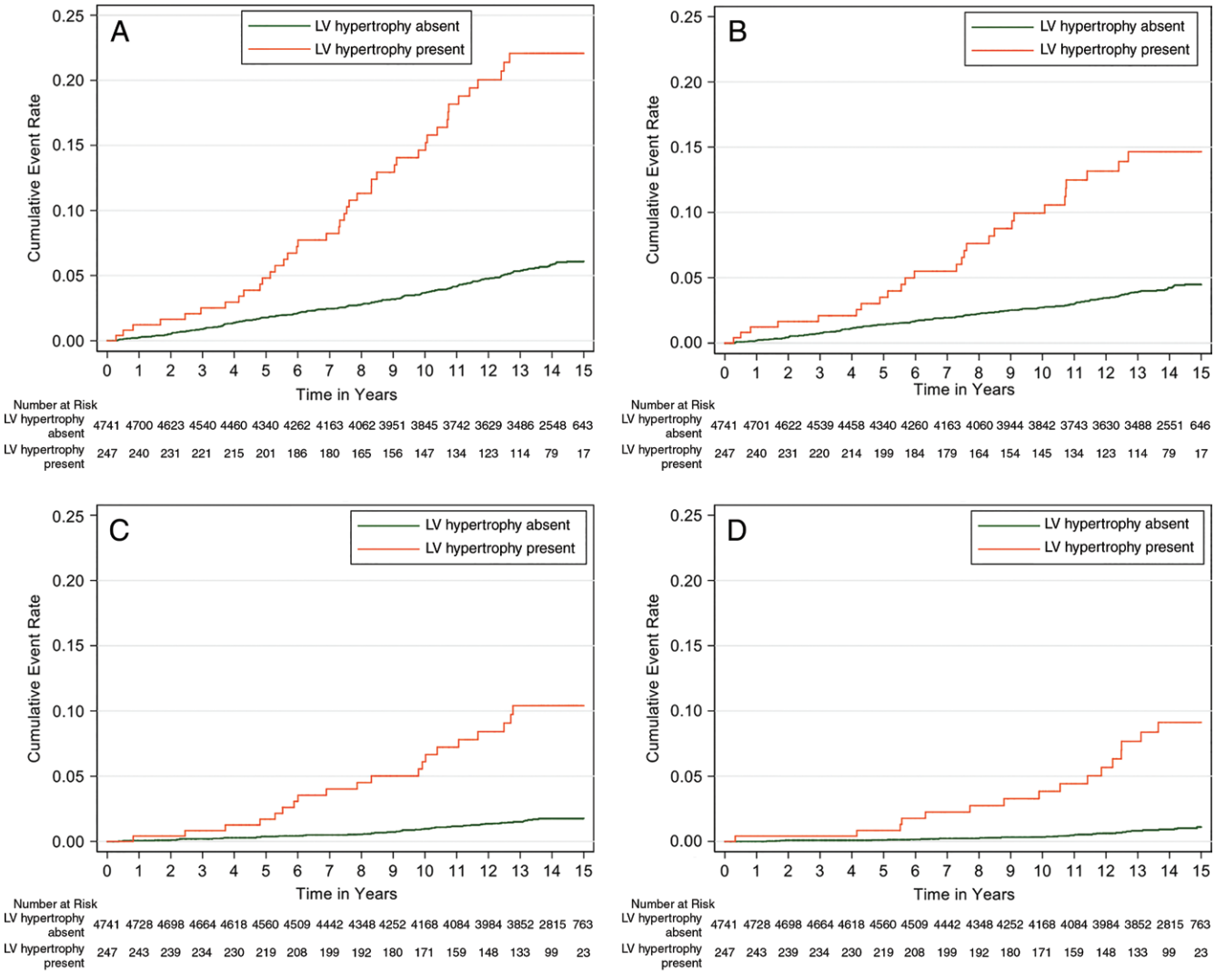

Figure 2: Kaplan-Meier analysis of the cumulative incidence of, *A,* hard coronary heart disease events, *B,* myocardial infarction, *C,* coronary artery disease–related death, *D,* other cardiovascular death events, and, *E,* heart failure for participants with left ventricular (LV) hypertrophy versus those without LV hypertrophy.

results, with longer-term follow-up, reveal the broad, adverse impact of LV hypertrophy, in models fully adjusted for traditional cardiovascular risk factors and CAC score. LV hypertrophy was independently associated with both coronary- (MI, coronary artery disease–related death) and non–coronary-related cardiovascular events, as well as HF. These relationships remained even after adjustment for CAC score. Deaths from coronary- and non–coronary-related cardiovascular causes were more strongly related to LV hypertrophy than to CAC score.

In the Framingham Heart Study, the relative risk (RR) for the incidence of death from cardiovascular disease increased for each increment of 50 g/m (LV mass/height) in men (RR: 1.7; 95% CI: 1.2, 2.5) and women (RR: 2.1; 95% CI: 1.3, 3.5) over a follow-up period of 4 years (8). Similar results were reported in single-center settings with smaller numbers of participants and events (30,31). Interestingly, in MESA, the relationship of LV hypertrophy to CHD events was not evident at shorter-term (approximately 4 years) follow-up (1). In our study, we saw the risk of CHD events start to increase, particularly after 5 years and beyond.

We had expected that regression models adjusted for CAC score would negate the effects of LV hypertrophy in relationship

Table 2: Relationship of LV Hypertrophy to Cardiovascular End Points Assessed by the Cox Proportional Hazard Model in Unadjusted, Minimally Adjusted (Model 1), and Fully Adjusted (Model 2) Models

	Unadjusted Model		Model 1*		Model 2†	
LV Hypertrophy in Relationship to End Point	HR	*P* Value	HR	*P* Value	HR	*P* Value
Hard CHD events (*n* = 290)		<.001		<.001		<.001
No LV hypertrophy	1 [Reference]		1 [Reference]		1 [Reference]	
LV hypertrophy	4.1 (2.9, 5.7)		3.5 (2.5, 4.9)		2.7 (1.9, 3.8)	
Myocardial infarction (*n* = 207)		<.001		<.001		<.001
No LV hypertrophy	1 [Reference]		1 [Reference]		1 [Reference]	
LV hypertrophy	3.6 (2.4, 5.4)		3.3 (2.2, 4.9)		2.8 (1.8, 4.0)	
CHD death (*n* = 95)		<.001		<.001		<.001
No LV hypertrophy	1 [Reference]		1 [Reference]		1 [Reference]	
LV hypertrophy	6.3 (3.8, 10.3)		5.2 (3.1, 8.6)		4.3 (2.5, 7.3)	
Other cardiovascular death (*n* = 57)		<.001		<.001		<.001
No LV hypertrophy	1 [Reference]		1 [Reference]		1 [Reference]	
LV hypertrophy	9.7 (5.4, 17.2)		8.1 (4.5, 14.8)		7.5 (4.2, 13.5)	
Heart failure (*n* = 215)		<.001		<.001		<.001
No LV hypertrophy	1 [Reference]		1 [Reference]		1 [Reference]	
LV hypertrophy	7.3 (5.4, 10.1)		6.3 (4.5, 8.7)		5.4 (3.8, 7.5)	

Note.—Data in parentheses are 95% confidence intervals. Left ventricular (LV) hypertrophy was defined as when LV mass percentage predicted (LV mass percentage predicted = LV mass divided by the predicted LV mass for sex, height, and weight expressed as a percentage) was greater than the 95th percentile (>136%). CHD = coronary heart disease, HR = hazard ratio.

* Model 1 (the minimally adjusted model) was adjusted for age, sex, and race/ethnicity. The total number of participants was 4988.

† Model 2 (the fully adjusted model) included only the risk factors that were statistically significantly associated with the end point in the backward selection Cox model from among the following covariates: age, sex, race/ethnicity, body mass index, total and high-density lipoprotein (HDL) cholesterol, lipid-lowering medication use, systolic and diastolic blood pressure, diabetes, hypertension (defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure of ≥ 90 mm Hg), hypertension medication use, smoking status, and ln(coronary artery calcium [CAC] score + 1). The Cox model with the end point CHD (total number of participants, 4953) included the variables LV hypertrophy, age, sex, hypertension, hypertension medication use, diabetes, smoking status, and ln(CAC + 1). The Cox model with the end point myocardial infarction (total number of participants = 4952) included the variables LV hypertrophy, age, sex, hypertension, hypertension medication use, diabetes, smoking status, and ln(CAC + 1). The Cox model with the end point CHD death (total number of participants = 4961) included the variables LV hypertrophy, age, sex, smoking status, systolic blood pressure, diastolic blood pressure, HDL cholesterol, and ln(CAC + 1). The Cox model with the end point other cardiovascular death (total number of participants = 4975) included the variables LV hypertrophy, sex, diabetes, and ln(CAC + 1). The Cox model with the end point heart failure (total number of participants = 4955) included the variables LV hypertrophy, age, sex, smoking status, hypertension medication use, diabetes, body mass index, and ln(CAC + 1).

to MI and coronary artery disease–related death, but our results showed that this was not the case (Table 2). CAC score is known to have a high predictive value for CHD events, effectively acting as an integrated index of multiple cardiovascular risk factors related to atherosclerosis (6,14,15). Our study results showed that while LV hypertrophy and CAC score were both independent predictors of hard CHD events, LV hypertrophy was an even stronger predictor of coronary artery disease–related death, other cardiovascular death, and HF. In this context, elevated LV mass reflects diminished myocardial functional reserve due to relatively impaired microvascular circulation/coronary flow reserve (32,33). In particular, LV hypertrophy was a strong predictor of other cardiovascular death adjudicated to be not directly attributable to atherosclerosis (eg, pulmonary embolism, arrhythmia, and cardiomyopathy) (HR: 7.5; 95% CI: 4.2, 13.5; $P < .001$ [Table 2]). Our results further suggest marked diminution of myocardial functional reserve leading to death in the presence of LV hypertrophy.

Regarding HF, different mechanisms for LV hypertrophy leading to HF have been proposed, including alterations in myocardial perfusion (33) and subclinical myocardial fibrosis/scarring as a result of myocardial injury and aging (34,35). Over a mean of 3.5 years, Aronow and Ahn (36) found a higher incidence of HF in participants with ECG-diagnosed LV hypertrophy than in participants without LV hypertrophy in a single-center study with 2638 participants. In the Cardiovascular Health Study, LV mass quantified with echocardiography was predictive of HF over a follow-up period of 6–7 years (4). The results of our study agree with the shorter-term impact of elevated LV mass and further show a sustained relationship of LV hypertrophy to HF events (Fig 2) over 15 years of follow-up.

A limitation of our study was survival bias. At study entry, MESA study participants may be relatively healthier than the general population of the United States. Instead of more widely available ECG and echocardiography, we used MRI as a more accurate method for quantifying LV hypertrophy. ECG is relatively insensitive for LV hypertrophy assessment compared with MRI (17). Another limitation was the fact that we assessed the relationship between cardiovascular events and LV hypertrophy in general but did not distinguish between different subtypes of hypertrophy (eg, hypertrophic cardiomyopathy and hypertrophy related to hypertension). However, the etiology is frequently not known or might be multifactorial.

In conclusion, our results underscore the importance of left ventricular (LV) hypertrophy as an enduring risk factor for cardiovascular events (including myocardial infarction, coronary artery disease–related death, other forms of cardiovascular death, and heart failure), as we observed in a contemporary, ethnically diverse cohort. In contrast to the widely used CAC score, which is not known to regress with medical therapy, elevated LV mass is potentially reversible with treatment (10–12,37,38), and individuals with the most elevated risk are in the upper 5% of the population, allowing physicians to target therapy to this group. Our results provide further evidence and motivation for aggressive treatment of individuals with LV hypertrophy.

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