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# Left ventricular hypertrophy and risk reclassification for coronary events in multi-ethnic adults

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## Abstract

**Background:** Left ventricular hypertrophy (LVH) has not been evaluated for reclassification improvement in the intermediate Framingham risk category for incident hard coronary events in a large multi ethnic population free of cardiovascular disease at baseline.

**Design:** A post-hoc analysis on the Multi Ethnic Study of Atherosclerosis (MESA) dataset ($n = 4921$) was performed.

**Methods:** LVH was defined as the upper 95 th percentile of cardiac magnetic resonance imaging derived left ventricular mass (LVM) indexed based on body surface area (BSA) and height. Multivariate Cox proportional hazards models were used to assess the independent association between LVH and composite outcomes like all cardiovascular disease (CVDa) and hard coronary heart disease (CHDh) events over a mean follow-up period of 4.5 years. To assess the incremental value of LVH over traditional CV risk factors for CHDh prediction, we compared the discrimination, calibration and net reclassification index (NRI) of models comprising of traditional CV risk factors with and without LVH.

**Results:** LVH derived from LVM indexed by BSA (LVH-BSA) and height$^{1.7}$(LVH-height) showed an independent association with CVDa (LVH-BSA: hazard ratio (HR) 1.52, 95% confidence interval (CI) 1.05–2.20, $p = 0.03$; LVH-height$^{1.7}$: HR 1.58, 95% CI 1.14–2.18, $p = 0.012$) and CHDh (LVH-BSA: HR 2.36, 95% CI 1.37–4.04, $p = 0.002$; LVH-height$^{1.7}$: HR: 1.95, 95% CI: 1.17–3.26, $p = 0.01$). Addition of LVH to the model based on traditional CV risk factors demonstrated no significant improvement in NRI for CHDh in either the entire cohort (LVH-BSA: NRI 1.7%, 95% CI: –8.3% to 11.7%, $p = 0.74$; LVH-height$^{1.7}$: NRI 2.7%, 95% CI: –5.8% to 11.3%, $p = 0.62$) or the intermediate risk group (LVH-BSA: NRI 12.0%, 95% CI: –5.7% to 29.8%, $p = 0.19$; LVH-height$^{1.7}$: NRI 14.5%, 0.1% to 28.8%, $p = 0.05$).

**Conclusions:** Although an independent predictor of cardiovascular events, LVH does not lead to clinically meaningful reclassification of the overall and intermediate risk population for CHDh.

## Keywords

Left ventricular hypertrophy, hard coronary events, risk marker, net reclassification index

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## Introduction

Despite a decline in cardiovascular disease (CVD) associated mortality and morbidity over the last decade, the burden of residual coronary heart disease (CHD) events still remains significant.[1] Traditional CVD risk factors (such as age, blood pressure, smoking, cholesterol levels and diabetes mellitus) based models have been of proven clinical value for the prediction of CHD risk in large prospective epidemiologic studies.[2] However, it is widely recognized that the composite of individuals classified as having low or intermediate risk

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for CHD by these models, nonetheless, still experience a high number of CHD events. While this observation in part is related to the large sample size of this population, it also underscores the inadequacy of traditional risk factors based models such as the Framingham Risk Score (FRS) to appropriately classify risk in these subsets of individuals.[3–5]

The deficiencies of current risk prediction models comprising of traditional risk factors to completely identify the residual cardiovascular risk,[6] has prompted a search for novel risk makers with a demonstrated ability to add incremental value to existing risk prediction models. In addition to adjudication of such a marker with conventional calibration and discrimination statistics, it is also imperative that a candidate marker, cost effectively leads to a reclassification or refinement of cardiovascular risk prediction.

A large body of evidence suggests that left ventricular hypertrophy (LVH) is independently associated with adverse cardiovascular outcomes.[7–11] Along these lines, pharmacological regression of LVH has been shown to improve the aforementioned outcomes irrespective of blood pressure control.[12–16] Various hypotheses including a diminished ventricular performance and coronary vasodilator reserve, increased arrhythmogenicity and subendocardial ischemia have been proposed as plausible mechanistic links.[17] The United States Preventive Services Task Force (USPSTF) suggests that for any new risk factor to be clinically useful, it should be able to reclassify and add to a risk scoring system over and above its ability to predict major CHD events.[4] Despite its independent predictive association, the utility of LVH in reclassifying the risk for coronary events beyond traditional risk prediction algorithms has not been clearly defined.[18,19] Accordingly, we sought to evaluate: (a) the predictive value of LVH for prognosticating CVD outcomes in a multi-ethnic cohort and (b) To further determine whether LVH adds any incremental value to the traditional risk prediction model in terms of reclassification properties.

## Methods

### Study population

MESA (Multi Ethnic Study of Atherosclerosis) is a population-based study initiated in July 2000 with a sample size of 6814 adults comprising of diverse ethnicities including White (38%), Black (28%), Chinese (22%) and Hispanic (12%) subjects, aged 45–84 years, without clinical CVD at baseline. The design model and methods used in the MESA database compilation has been published earlier.[20] After obtaining the approval by the Institutional Review Board, a post-hoc analysis of the limited access dataset was performed to investigate the association of LVH with composite endpoints such as all CVD (CVDa) and hard CHD (CHDh) events over a mean follow-up period of 4.5 years.

### Study outcomes

CVDa and CHDh events were considered primary outcomes in separate survival analyses. CVDa events were a composite outcome consisting of myocardial infarction, resuscitated cardiac arrest, definite angina, probable angina (if followed by revascularization), stroke, stroke death, CHD death, other atherosclerotic death, and other CVD death. CHDh events were defined as myocardial infarction, resuscitated cardiac arrest, or CHD death.

### Reference population

To define reference standards for normal body size and left ventricular mass (LVM) in healthy individuals, we selected the reference subsample comprising of normal weight adults (body mass index: 18–25 $kg/m^2$) free of clinical CVD at baseline who did not meet any of the following criteria:[21] (a) hypertension (systolic blood pressure $\geq$140 mm Hg, diastolic blood pressure $\geq$90 mm Hg, or antihypertensive drug treatment); (b) current smoking; (c) diabetes mellitus (fasting blood glucose $\geq$7 mmol/l or anti-diabetic medication use); (d) low-density lipoprotein cholesterol $\geq$4.14 mmol/l; (e) triglycerides $\geq$1.69 mmol/l; (f) high density lipoprotein cholesterol $\leq$1.03 mmol/l (men) or $\leq$1.29 mmol/l (women); and (g) use of lipid-lowering medication(s). The reference sample consisted of 500 MESA individuals that included 249 Caucasians, 60 African-Americans, 136 American-Chinese and 55 Hispanics.

### Derivation of LVH

In MESA, LVM was measured from end-diastolic short-axis gradient-echo cardiac magnetic resonance imaging (MRI) as follows: (epicardial-endocardial contour) (slice thickness+image gap)$\times$ 1.05 g/ml.[22] The papillary muscle mass was excluded from LVM. Since LVM is highly influenced by body size, LVM must be appropriately normalized with body-size to define LVM index (LVMI).[23] Based on the study by Chirinos et al.,[21] we used two validated criteria – body surface area (BSA) and $height^{1.7}$to normalize LVM for body size. Since BSA tends to underestimate the prevalence of LVH in obese and hypertensive individuals, we used an allometric exponent, $height^{1.7}$, that had been shown to be more sensitive to identify obesity-related LVH and was more consistently associated with adverse cardiovascular events and all-cause mortality.[21]

BSA was calculated based on the Gehan method ($BSA = 0.0235 \times height\ in\ cm^{0.42246} \times weight\ in\ kg^{0.51456}$).[21,24] Accordingly, LVMI was defined as LVM/BSA and LVM/height$^{1.7}$. LVH was defined as the upper 95 th percentile of LVMI calculated based on BSA (LVH-BSA) and height$^{1.7}$(LVH-height$^{1.7}$) in the reference population. Of the 6814 MESA study participants, 5004 (73%) had technically adequate MRI data. Thirty-six participants had no follow-up information, 47 individuals had missing information on study variables leaving 4921 participants in the final analysis. LVH defined by LVMI based on BSA identified 445 individuals with LVH while LVMI based on height$^{1.7}$ identified 966 individuals with LVH.

### Statistical analysis

*Independent association of LVH with composite outcomes.* The baseline characteristics of the study population by LVH categories were compared using chi-square test for categorical variables and the *t*-test for continuous variables. Log transformation was performed to normalize skewed continuous variables. After identification of the univariate predictors of both composite outcomes, the association of LVH with CVDa and CVDh was assessed using adjusted Cox proportional-hazards regression with the construction of two distinct models with CVDa and CVDh as the endpoints and LVH as the exposure variable. LVMI analysis was performed per unit increase in standard deviation change.

*Reclassification properties of LVH.* Using the logistic regression technique, the FRS was calculated for the study subjects with individual risk factor components. The FRS which provides a 10-year risk of incident CHD for the study cohort was subsequently recalculated to obtain the CHD risk estimates corresponding to the MESA follow-up period. Subsequently, low, intermediate and high risk groups were defined by CHD risk estimates of <5%, 5% to <10% and 10% or more, respectively.

To test the potential incremental value of LVH over traditional CVD risk markers for risk stratification of CHDh we calculated the discrimination, calibration, and reclassification statistics. To assess discrimination, we calculated and compared area under the receiver operating characteristic (AU-ROC) curves and Harrell's C-statistic for models with and without LVH. For reclassification analysis, based on the method described by Pencina et al.,[25] we derived the net reclassification index (NRI) improvement in the overall and intermediate risk categories and integrated discrimination improvement (IDI). NRI is a measure of the change in risk prediction obtained when the risk marker under evaluation is added to an existing risk prediction model.[25] Subsequently, LVH was incorporated into the traditional risk factors based model with CHDh as the endpoint to assess risk reclassification. NRI was calculated for the models comprising of traditional risk factors with and without LVH using methodology described elsewhere in both the intermediate risk cohort and the whole cohort. Finally, we assessed the calibration statistics of the models with and without LVH using the Hosmer-Lemeshow chi-square test, likelihood ratio test and Bayesian information criteria (BIC). A detailed description of methodology has been described elsewhere.[25,26] We performed all the analyses for both LVH-BSA and LVH-height$^{1.7}$. Statistical significance was defined as a $p$-value <0.05 for entire analysis. All the analyses were performed using statistical software STATA, version 10 (STATACorp LP, College Station, Texas, USA).

## Results

Baseline characteristics of the study population by LVH categories are depicted in Table 1. As compared to non-LVH individuals, individuals in LVH-BSA and LVH-height$^{1.7}$ groups were more likely to be of African-American ethnicity, male gender, smokers, hypertensive, diabetics, lower total and high density lipoprotein cholesterol, higher BSA, and with higher high sensitivity C-reactive protein (hsCRP) and waist circumference. Both LVMI and LVH based on BSA and height$^{1.7}$were independently associated with CVDa and CHDh events. As shown in Table 2, LVH-BSA and LVH-height$^{1.7}$showed a statistically significant and independent association with CVDa events (LVH-BSA: hazard ratio (HR) 1.52 (95% confidence interval (CI) 1.05–2.20); $p = 0.03$; LVH-height$^{1.7}$: HR 1.58 (95% CI 1.14–2.18); $p = 0.012$) and CHDh events (LVH-BSA: HR 2.36 (95% CI 1.37–4.04); $p = 0.002$; LVH-height$^{1.7}$: HR: 1.95 (95% CI: 1.17–3.26), $p = 0.01$). We found no significant interaction between race and LVH (both LVH-BSA and LVH-height$^{1.7}$) for CVDa events and CHDh events.

Adding LVH to a model comprising of traditional CHD risk factors (age, sex, systolic blood pressure, anti-hypertensive medications, high density lipoprotein cholesterol, total cholesterol, smoking, and diabetes) resulted in non-significant improvement in discrimination and calibration statistics (Table 3(a) and (b)). Furthermore, addition of either LVH-BSA or LVH-height$^{1.7}$ to the traditional CVD risk factors model did not enhance risk reclassification for CHDh. For LVH-BSA, the net reclassification improvement in the entire cohort was 1.7%, 95% CI: –8.3% to 11.7%, $p = 0.74$; while NRI in the intermediate risk group was 12.0%, 95% CI: –5.7% to 29.8%, $p = 0.19$ Table 3(a).

**Table 1.** Baseline characteristics distribution for study participants based on left ventricular hypertrophy (LVH)

| | LVH defined by LVM indexed by BSA | | | LVH defined by LVM indexed by height | | |
|---|---|---|---|---|---|---|
| | LVH ($n=445$) | No LVH ($n=4476$) | $p$-value | LVH ($n=966$) | No LVH ($n=3955$) | $p$-value |
| Age (years) | 62.3 ± 10.2 | 61.4 ± 10.1 | 0.083 | 61.3 ± 9.8 | 61.6 ± 10.2 | 0.433 |
| Male (%) | 88.3 | 43.6 | <0.001 | 75 | 41 | <0.001 |
| Race (%) | | | | | | |
| Caucasian Americans | 26.5 | 40.5 | | 30.2 | 41.4 | |
| African Americans | 39.1 | 24 | <0.001 | 36.8 | 22.6 | <0.001 |
| Hispanic Americans | 27.2 | 21.7 | | 29 | 20.5 | |
| Chinese Americans | 7.2 | 13.8 | | 4 | 15.4 | |
| History of smoking (%) | 62.3 | 47.2 | <0.001 | 57.6 | 46.4 | <0.001 |
| Systolic blood pressure (mm Hg) | 137 ± 24 | 125 ± 20 | <0.001 | 135 ± 23 | 124 ± 20 | <0.001 |
| Anti-hypertensive medications, (%) | 47 | 34.1 | <0.001 | 47 | 32.4 | <0.001 |
| Total cholesterol (mmol/l) | 4.86 ± 0.91 | 5.04 ± 0.91 | <0.001 | 4.89 ± 0.89 | 5.06 ± 0.92 | <0.001 |
| High density lipoprotein (mmol/l) | 1.29 ± 0.37 | 1.33 ± 0.39 | <0.001 | 1.22 ± 0.34 | 1.35 ± 0.39 | <0.001 |
| Lipid lowering therapy (%) | 13.9 | 16.2 | 0.21 | 15.1 | 16.2 | 0.39 |
| History of diabetes (%) | 18.4 | 12.1 | <0.001 | 19.1 | 11.1 | <0.001 |
| High sensitivity C-reactive protein (μmol/l) | 3.55 ± 6.60 | 3.53 ± 5.50 | 0.935 | 4.02 ± 6.28 | 3.41 ± 5.42 | 0.003 |
| Waist circumference (cm) | 98.9 ± 11.9 | 96.3 ± 13.4 | <0.001 | 104.1 ± 12.3 | 94.7 ± 12.9 | <0.001 |
| Body mass index (kg/m$^2$) | 28.1 ± 4.4 | 27.7 ± 5.0 | 0.114 | 30.6 ± 4.9 | 27.0 ± 4.7 | <0.001 |

BSA: body surface area; LVM: left ventricular mass; Continuous variables are represented by mean ± standard deviation.

**Table 2.** Association of left ventricular mass and left ventricular hypertrophy with adverse cardiovascular events

| | Left ventricular mass index | | Left ventricular hypertrophy | |
|---|---|---|---|---|
| | HR (95% CI)[a] | $p$-value | HR (95% CI) | $p$-value |
| Indexed for body surface area | | | | |
| All cardiovascular events | | | | |
| Model 1 | 1.23 (1.08–1.40) | 0.002 | 1.51 (1.05–2.18) | 0.03 |
| Model 2 | 1.23 (1.08–1.40) | 0.002 | 1.52 (1.05–2.20) | 0.03 |
| Hard coronary heart disease events | | | | |
| Model 1 | 1.36 (1.13–1.65) | 0.001 | 2.32 (1.36–3.98) | 0.002 |
| Model 2 | 1.37 (1.14–1.66) | 0.001 | 2.36 (1.37–4.04) | 0.002 |
| Indexed for height | | | | |
| All cardiovascular events | | | | |
| Model 1 | 1.22 (1.07–1.40) | 0.004 | 1.54 (1.12–2.12) | 0.007 |
| Model 2 | 1.23 (1.08–1.41) | 0.003 | 1.58 (1.14–2.18) | 0.006 |
| Hard coronary heart disease events | | | | |
| Model 1 | 1.36 (1.11–1.67) | 0.003 | 1.83 (1.10–3.02) | 0.02 |
| Model 2 | 1.40 (1.15–1.71) | 0.001 | 1.95 (1.17–3.26) | 0.01 |

CI: confidence interval; HR: hazard ratio; [a]Data show hazard ratio per standard deviation increase in the left ventricular mass index. Model 1: adjusted for age, sex, race, systolic blood pressure, smoking, high density lipoprotein, total cholesterol, lipid lowering therapy, diabetes, use of antihypertensive therapy, waist circumference. Model 2: Model 1 + adjusted for log (C-reactive protein), body mass index.

**Table 3.** Reclassification properties of left ventricular hypertrophy (LVH) for prediction of hard coronary heart disease events

| (a) LVH indexed by body surface area | Traditional risk factors | Traditional risk factors + LVH-BSA |
|---|---|---|
| Discrimination | | |
| ROC-AUC | 0.7585 | 0.7658 |
| Difference in ROC-AUC, *p*-value | 0.323 | |
| C-statistic | 0.767 | 0.772 |
| Absolute net reclassification index (95% CI), *p*-value | 1.7% (−8.3% to 11.7%), $p = 0.738$ | |
| Intermediate net Reclassification Index (95% CI), *p*-value | 12.0% (−5.7% to 29.8%), $p = 0.189$ | |
| Absolute integrated discrimination index, *p*-value | 0.004, $p = 0.06$ | |
| Calibration | | |
| Hosmer-Lemeshow $\chi 2$ value, *p*-value | 11.8, $p = 0.161$ | 9.8, $p = 0.277$ |
| Likelihood ratio test, *p*-value | 0.006 | |
| BIC | −40963 | −40962 |
| Evidence of support for new model based on BIC | Negative | |

| (b) LVH indexed by height$^{1.7}$ | Traditional risk factors | Traditional risk factors + LVH-height |
|---|---|---|
| Discrimination | | |
| ROC-AUC | 0.7585 | 0.7639 |
| Difference in ROC-AUC, *p*-value | $p = 0.412$ | |
| C-statistic | 0.767 | 0.771 |
| Absolute net reclassification index (95% CI), *p*-value | 2.7% (−5.8% to 11.3%), $p = 0.623$ | |
| Intermediate net reclassification index (95% CI), *p*-value | 14.5% (0.1% to 28.8%), $p = 0.05$ | |
| Absolute integrated discrimination index, *p*-value | 0.001, $p = 0.328$ | |
| Calibration | | |
| Hosmer-Lemeshow $\chi^2$ value, *p*-value | 11.8, $p = 0.161$ | 6.5, $p = 0.589$ |
| Likelihood ratio test, *p*-value | 0.055 | |
| BIC | −40963 | −40959 |
| Evidence of support for new model based on BIC | Positive | |

BIC: Bayesian information criterion; CI: confidence interval; LVH-BSA: Left ventricular hypertrophy based on left ventricular mass indexed by body surface area; LVH-height: Left ventricular hypertrophy based on left ventricular mass indexed by height; ROC-AUC: Area under curve - receiver operating characteristic.

For LVH-height$^{1.7}$, the overall NRI was observed to be 2.7%, 95% CI: –5.8% to 11.3%, $p = 0.62$ and the intermediate risk NRI was 14.5%, 95% CI: 0.1% to 28.8%, $p = 0.05$ Table 3(b).

## Discussion

Our study results show an independent association between LVH and CVD outcomes in a multi ethnic cohort free of clinical CVD. However, a non-significant improvement in the net cardiovascular risk stratification was observed when LVH was added to a traditional risk factors based model. From a clinical perspective, these observations are highly relevant as the reclassification properties of LVH using NRI criteria have not been previously described.

### *LVH and risk assessment*

LVH has been shown to be a significant independent predictor of CHD.[7,10,11,15] Higher LVM portends significantly worse CVD outcomes in asymptomatic hypertensive patients[11] with an increased propensity to develop a depressed left ventricular ejection fraction.[8] Furthermore, LVH is a potentially reversible entity especially with the optimal control of hypertension, indeed LVH regression has demonstrated mortality benefit in prior studies.[12,13] However, the literature

on this issue is controversial and in sharp contrast to the aforementioned studies, a meta-regression analysis of 12,800 hypertensive patients from 14 trials with 2259 events performed by Costanzo et al. failed to reveal an association between LVH and major adverse CVD events.[27] Unlike our analyses that exclusively used cardiac MRI data, this meta-analysis included studies that adjudicated the presence of LVH using electrocardiographic or echocardiographic criteria. Furthermore, data were analyzed with LVH as a continuous variable in contrast to the aforementioned studies where it was studied as a categorical variable. The existence of conflicting evidence has created ambiguity among clinicians regarding the clinical implications of LVH. Data on the incremental predictive value provided by LVH beyond the traditional risk factor models are sparse and inadequate. As emphasized by the USPSTF,[4] the clinical utility of a non-traditional risk marker is best assessed by its effectiveness in reclassifying a significant proportion of individuals in the intermediate FRS risk category into a higher risk stratum.

To date, several risk markers have demonstrated reclassification properties and include family history of CHD,[28] carotid intima–media thickness,[29] homocysteine,[26] coronary artery calcium scores,[30] brachial flow–mediated dilation,[31] ankle-brachial index,[32] and hsCRP.[33,34] For every proposed cardiac risk marker, an independent association with adverse CVD outcomes is a prerequisite but reclassification properties offer definitive evidence of risk prediction.[25] We used LVH based on cardiac MRI derived LVM normalized by BSA and height$^{1.7}$to analyze the prognostic and risk stratification utility of LVH. In the present study, even though LVH was independently associated with adverse CVD outcomes, the addition of LVH to traditional CVD risk factors model provided no significant improvement in NRI for future CHDh events.

### *Study limitations*

Change in the risk factors and improved risk factor management with therapy during the follow up period can substantially alter the size of the intermediate risk population and these have not been accounted for. However, a large sample size with a multi-ethnic cohort, comprehensive adjustment for confounding factors, the use of MRI (gold standard) for quantifying LVH and a detailed analysis using risk classification techniques add to the strengths of our study. Our observations were derived from a multi-ethnic cohort of relatively healthy individuals and should not be extrapolated to higher risk populations such as those with established coronary artery disease, isolated hypertensive heart disease or heart failure.

Although, cardiac MRI has been shown to be more accurate, precise and reproducible in assessing LVM and LVH than echocardiography, echocardiography is very widely used in routine clinical practice. These data should be viewed as cautionary, although our study results may be replicated in future studies, particularly when adjudicating the predictive value of LVH as a clinical risk marker in asymptomatic individuals free of overt CVD. Further risk reclassification data using echocardiography derived LVH data are awaited.

## Conclusion

Despite an independent association with adverse cardiovascular outcomes, LVH provided no significant improvement in the reclassification of overall and intermediate risk population for future coronary events thereby, limiting its utility as a cardiac risk marker.

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### Conflict of interest

None declared.

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