The Relationship of Left Ventricular Trabeculation to Ventricular Function and Structure Over 9.5 Years Follow-Up: the Multi-Ethnic Study of Atherosclerosis

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Running title: LV trabeculation and function in MESA

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ABSTRACT
Background: Left ventricular (LV) trabeculation is highly variable between individuals, is increased in some diseases (e.g., congenital heart disease or cardiomyopathies), but its significance in population-representative individuals is unknown.
Objectives: The goal of this study was to determine if excessive LV trabeculation in population-representative subjects is associated with preceding changes in cardiac volumes and function.
Methods: For technical reasons, the extent of trabeculation, expressed as the ratio of noncompacted to compacted (NC/C) myocardium was measured on cardiac magnetic resonance (CMR) long-axis cine images in 2,742 subjects in the Multi-Ethnic Study of Atherosclerosis (mean age 68.7 years, 52.3% women, 56.4% with hypertension, 16.8% with diabetes) at the exam 5. These were considered in quintiles of trabeculation extent, with quintile 5's NC/C 2.46 to 5.41. We determined the relationship between maximal NC/C ratio and preceding change (9.5 years between exam 1 and 5) in end-systolic volume indexed to body surface area (ESVi). Secondary analyses assessed the associations between maximal NC/C and preceding changes in end-diastolic volume indexed to body surface area (EDVi) and ejection fraction (EF).
Results: Over 9.5 years, ESVi decreased by 1.3 ml/m^2, EDVi decreased by 5.1 ml/m^2 and EF decreased by 0.6% ($p < 0.0001$). , Even in subjects with excessive trabeculation, there were no clinically relevant differences in LV volumes and systolic function change between the quintiles of trabeculation extent.
Conclusions: Greater extent of, and even excessive, LV trabeculations, measured in end-diastole in asymptomatic population-representative individuals, appears benign and is not associated with deterioration in LV volumes or function over an almost 10-year period.

Keywords: cardiac magnetic resonance; left ventricular trabeculation; left ventricular function;

Abbreviations
CMR = cardiovascular magnetic resonance
EDVi = end-diastolic volume index
EF = ejection fraction
ESVi = end-systolic volume index
LV = left ventricle/ventricular
LVEF = left ventricular ejection fraction
LVNC = left ventricular noncompaction
MESA = Multi-Ethnic Study of Atherosclerosis
NC/C = noncompaction to compaction
SSFP = steady-state free precession

Human left ventricular (LV) cardiac trabeculation is highly variable between individuals. Although some differences may be related to ethnicity (1), there have been concerns that extreme trabeculation may be either pathologic or a marker of underlying heart muscle disease. LV non-compaction (LVNC) is considered a distinct form of cardiomyopathy (2, 3), where the hallmark phenotypic feature is extensive LV trabeculation. The disease may lead to cardiac failure, thromboembolism, and malignant arrhythmias. To date, only small studies using cardiovascular magnetic resonance (CMR) have described patterns and extent of LV trabeculations in cohorts with a probable LVNC diagnosis on the basis of symptoms, family history, or impaired cardiac function (4, 5). However, although increased LV trabeculation is associated with other cardiac conditions such as cardiomyopathies (6) and congenital heart diseases (7), it has also been frequently observed in healthy individuals (8). Extensive LV trabeculation is commonly detected following CMR imaging. When LVNC imaging diagnostic criteria are met as an incidental finding, a diagnosis of LVNC remains controversial. The natural history and outcomes in people with pronounced LV trabeculation in the absence of any other structural heart abnormalities is unknown.

This background, combined with difficulties in measuring trabeculae, raised concerns that extensive trabeculation in apparently normal individuals may be either a pre-phenotypic marker of underlying disease, a marker of adverse outcome, or just a normal phenotypic variant. Accordingly, individuals with extensive trabeculation may be offered costly long-term follow-up and are subject to the emotional and financial implications of a cardiomyopathy diagnosis.

The purpose of this study was to determine the relationship between the extent of LV trabeculation (using CMR) and myocardial structure and function in a large population-based cohort study. Specifically, our primary aim was to evaluate whether excessive LV trabeculation,

measured as the maximal ratio of noncompaction to compaction (NC/C), was associated with preceding changes in end-systolic volume indexed to the body surface area. In secondary analyses, we evaluated associations between maximal NC/C and preceding changes in end-diastolic volume indexed to the body surface area and development of LV dysfunction, expressed by deterioration in LV ejection fraction (EF).

Methods

***Study population*.** The Multi-Ethnic Study of Atherosclerosis (MESA) is a population-based prospective cohort study. See (9) for a full list of participating MESA investigators. Between 2000 and 2002, 5,004 of the 6,814 study participants, who were free of clinically recognized cardiovascular disease and from 4 different ethnicities, underwent CMR imaging at enrollment (exam 1) (10). Of these, 3,016 participants underwent CMR imaging between 2010 and 2011 (exam 5). Study subjects were excluded due to insufficient image quality (n = 241) and incomplete CMR data sets (n = 33), leaving 2,742 participants (**Figure 1**). Clinical data, including the incidence of heart failure, atrial fibrillation, myocardial infarction, stroke, and transient ischemic attacks were available for all participants. MESA criteria for clinical events and follow-up procedures were previously described (11). Institutional Review Boards of each of the 6 participating field sites in the United States approved the study, and all participants provided written informed consent at the time of enrollment into MESA.

***Magnetic resonance imaging*.** CMR examinations were performed at 6 centers (in Baltimore, Winston-Salem, New York, Minneapolis, Los Angeles, and Chicago) using either a Signa Excite (General Electric Medical Systems, Waukesha, WI) or Avanto/Espree (Siemens, Erlangen, Germany) 1.5-Tesla MR scanners for exams 1 and 5. Planning of the cardiac cine images for both exams was standardized to minimize variation between centers. Cine images were obtained

with a temporal resolution of approximately 50 ms or less using segmented k-space, electrocardiogram-gated fast spoiled gradient-recalled echo (GRE) pulse sequence during MESA exam 1 (12) and, retrospectively, electrocardiogram-gated long-axis and short-axis cine images were acquired using a steady-state free precession (SSFP) sequence at MESA exam 5. (13)

Image Evaluation

LV volumes and function: All MESA exam 1 and exam 5 CMR images (**Figure 2**) were analyzed for LV volumes and function in a core laboratory and analyzed at a single image analysis center by readers blinded to clinical outcomes, as previously described (13, 14). Calibration between the 2 CMR examinations was performed in 498 participants who had both image sequences acquired at MESA exam 5. The calibration group was selected to be representative of all body sizes. Calibration was performed for both technologist readers (by rereading 498 MESA exam 1 images) and pulse sequences (same technologist reader, analyzing both pulse sequences using identical software). All calibration curves were found to be linear and were fitted with ordinary regression methods.

For quality control purposes, all readers independently analyzed every 10^{th} consecutive CMR exam. The overall interobserver intraclass correlation coefficients for LV mass and LV end-diastolic volume were 0.95 and 0.96, respectively, and technical errors of measurement were 6.1% and 5.4%, respectively. The interobserver agreements were similar to those of the baseline study (12).

LV trabeculation: CMR examinations were evaluated for NC/C ratio using the post-processing software tool, CVI42 (Circle Cardiovascular Imaging Inc., Calgary, Canada). NC/C ratio could only be determined for the MESA exam 5 CMR data, as the CMR sequence used at MESA exam 1 does not provide the level of detail and contrast required. While there are different approaches

to assessing the extent of LV trabeculation in both echocardiography and CMR, we restricted our analysis to the NC/C ratio proposed by Petersen et al. (4).

Horizontal and vertical long axis cine SSFP images were used for measuring the thickness of the compacted myocardium and of the trabeculations at the center of 8 LV regions: anterior; inferior; septal; and lateral at midventricular and apical levels at end-diastole, as previously described by Kawel (8) (**Figure 2**). The NC/C ratio was calculated for each segment. Measurements were not performed at the LV base, as trabeculations are not typically observed in this region. In normal subjects, the true apex is usually very thin, with prominent trabeculations; therefore, it was also excluded (4, 14). Compacted myocardium was defined as a myocardial layer of homogeneous moderate signal intensity on SSFP images without inclusion of blood of higher signal intensity. Trabeculations were defined as a meshwork of the trabeculae carneae of moderate signal intensity adjacent to compacted myocardium interspersed with blood of higher signal intensity. Measurements of the thickness of the compacted myocardium and of adjacent trabeculations were obtained perpendicular to the compacted myocardium. Fifty percent of the thickness of chemical shift artifact (appearing as a black line) on the epicardial surface was included in the compact myocardium. Papillary muscles that were clearly observed as compact tubular structures were not included in the measurements. Short-axis views and cine mode were used additionally to separate papillary muscles from trabeculation. The orientation of long-axis images was cross-referenced with short-axis views, allowing exclusion of off-axis images. Measurements of 60 randomly selected studies were repeated by the first reader and by a second reader to quantify intraobserver and interobserver variability. The NC/C ratio > 2.3 was considered a current diagnostic criterion for LVNC (Petersen's criterion)(4).

Statistical Analysis. Unless otherwise stated, descriptive statistics for continuous variables are presented as mean and the standard deviation (SD), if normally distributed. Categorical variables are presented as a percentage. Differences between quintiles were evaluated by the analysis of variance (ANOVA) with post-hoc Tukey tests for continuous variables and with chi-square tests for categorical variables.

Simple and multivariate linear regression models were developed to examine the relationship of the independent variables (maximal NC/C ratio, NC/C ratio >2.3 in 1 segment and NC/C ratio >2.3 in more than 1 segment) to functional continuous dependent variables related to heart failure, which included changes in LV volumes and EF between exam 1 and exam 5. Covariates used for multivariable regression models are listed in **Table 2**.

All statistical analyses were performed using R software version 3.0.1 (R Foundation for Statistical Computing, Vienna, Austria) (15).

Intraclass correlation coefficients were used to evaluate intraobserver and interobserver agreement. In all cases statistical significance was set for a $p < 0.05$ (2-tailed).

Results

Demographics. Detailed demographic and CMR data are presented in **Table 1**. The mean age of study subjects at exam 5 was 68.7 years (52.3% women). Ethnicity was self-reported as Caucasian/white in 42.1%, Chinese American in 12.5%, African American/black in 24.9%, and Hispanic in 20.5%. Hypertension was present in 56.4% of participants. At exam 5,536 (19.5%) of the study subjects were treated with angiotensin converting enzyme inhibitors, 248 (9.0%) with angiotensin II antagonists, 475 (17.3%) with beta-blockers and 1,035 (37.7%) subjects were treated with one or more of the above agents. Four hundred and twenty three participants (15.5%) had treated diabetes and 1,456 (53.3%) were current or former smokers. Impaired

systolic function at baseline exam 1 (EF <50%) was present in 111 (4.0%) subjects, but they were symptom-free and there were no differences between quintiles of maximal NC/C ratio (p = 0.62).

Extent of LV trabeculation. The NC/C ratio was calculated in 19,320 (88.1%) segments; 2,616 (11.9%) segments were excluded because of insufficient contrast between blood pool and myocardium to confidently measure the NC/C ratios. The intraclass correlation coefficient was 0.83 (p <0.0001) for intraobserver NC/C ratio measurements and 0.82 (p <0.0001) for interobserver measurements. Petersen's LVNC criterion (NC/C >2.3) was fulfilled in 706 (25.7%) of participants for at least 1 cardiac segment and in 218 (8.0%) for at least 2 segments. The mean of the maximal NC/C ratio of each subject's analyzed segments was 1.96 ± 0.66. This was higher in women: 2.0 ± 0.68 versus 1.92 ± 0.64 (p <0.001), but independent of age (p = 0.051). There were no differences in the maximal NC/C ratio between the four ethnicities studied in MESA: 1.98 ± 0.69 in Caucasians, 1.91 ± 0.56 in Chinese Americans, 1.93 ± 0.66 in African-Americans and 2.00 ± 0.65 in Hispanics (p = 0.08).

The maximal NC/C ratio correlated with the number of segments fulfilling LVNC criteria (r = 0.76, p <0.0001) and was greater in larger LV cavities: the ratio increased by 0.2 ± 2.1 for each 100 ml larger end-diastolic volume (p <0.0001) and by 0.3 ± 3.6 for each 100 ml larger end-systolic volume (p <0.0001). There was no association of maximal NC/C ratio with LV EF (p = 0.16).

Relationship between extent of trabeculation and precedent changes in LV volumes and EF

We divided the cohort into quintiles by the extent of maximal NC/C ratio. Detailed demographic data and CMR parameters are presented in **Table 1**.

In the 9.5-year interval between exam 1 and 5, end-systolic volume index decreased on average by 1.3 ± 7.3 ml/m^2 ($p < 0.0001$), and there were no differences between quintiles of maximal NC/C ratio (**Figure 3**).

Similarly, end-diastolic volume index decreased on average by 5.1 ± 12.3 ml/m^2 ($p < 0.0001$). The decrease was smaller with increasing extent of trabeculation; significant differences were seen between quintiles 1 and 4 (-6.5 ± 13.1 ml/m^2 vs. -4.4 ± 12.3 ml/m^2, $p < 0.05$), between quintiles 1 and 5 (-6.5 ± 13.1 ml/m^2 vs. -3.6 ± 11.3 ml/m^2, $p < 0.001$) and also between quintiles 2 and 5 (-6.0 ± 12.4 ml/m^2 vs. -4.4 ± 12.3 ml/m^2, $p < 0.01$) (**Figure 3**).

The EF decreased by 0.6 ± 7.8% ($p < 0.0001$) over 9.5 years, however there were no differences between the quintiles of maximal NC/C ratio (**Figure 3**). Several demographic parameters and clinical characteristics differed by small amounts, but reached statistical significance in univariate analyses with regards to the extent or distribution between quintiles of maximal NC/C ratio (**Table 1**).

After adjustment for age, sex, ethnicity, and baseline CMR parameters from exam 1 (Model 2), 1 unit greater maximal NC/C ratio (e.g., from 1 to 2, from 2 to 3, and so forth) was associated with 2.7 ± 16.1 ml/m^2 ($p < 0.0001$) decrease in end-diastolic volume index and 1.0 ± 10.2 ml/m^2 ($p < 0.0001$) decrease in end-systolic volume index. These models accounted for 26.1% and 19.5% of the variances in the volume changes, respectively (**Table 2**). Multivariate regression models with conventional risk factors (body mass index, systolic blood pressure, diabetes, smoking, total cholesterol to high density lipoprotein ratio) (**Table 2**) as well as exercise, education and family history of heart attack showed similar findings to Model 2 (data not presented). Overall, despite statistical significance, the observed changes in end-diastolic volume index and end-systolic

volume index in relationship to NC/C were not clinically relevant. The maximal NC/C ratio was not associated with a change in LVEF.

Sensitivity analysis. The relationships described earlier for maximal NC/C ratio as a continuous variable were repeated using NC/C ratio >2.3 and number of segments with NC/C ratio >2.3. All results showed the same trends as for the continuous NC/C ratio variable.

***Extent of LV trabeculation and adverse clinical events*.** The incidence of atrial fibrillation, congestive cardiac failure, stroke, transient ischemic attack, history of myocardial infarction, composite cardiovascular endpoints, and all cardiovascular endpoints in quintiles of maximal NC/C ratio are presented in **Table 3**. In view of low event incidence, no formal statistical analysis was performed.

Discussion

The long-term relationship between excess LV trabeculation and change in myocardial function and structure was not previously known. This is the first study to show that greater extent of LV trabeculation is not associated with an absolute increase in end-systolic and end-diastolic volumes over the almost 10 years of the MESA study. Greater NC/C ratio was not associated with a decline in systolic function.

These results advance our understanding of ventricular morphology in regards to asymptomatic trabeculation in relatively healthy individuals in the community. In particular, MESA subjects with greater trabeculation had only minor relative changes in LV end-diastolic volume index, in comparison to subjects with lesser, although statistically significant, trabeculation, which were unlikely to have clinical implications.

Prevalence of imaging diagnosis LVNC. The estimated prevalence of LVNC is between 0.014% and 1.3% in the general population (2, 16, 17). However, all echocardiographic or CMR-based

imaging criteria for LVNC were established on pre-selected, symptomatic individuals with heart failure or cardiovascular complications. It is important to emphasize that currently there are no diagnostic tools, neither genetic nor imaging, to identify patients affected by LVNC with absolute certainty. This is the main reason why cardiac imaging studies have limitations when attempting to determine diagnostic accuracies on the basis of a likely LVNC diagnosis, rather than a definitive diagnosis.

Recent studies using high-resolution imaging techniques, such as multidetector computed tomography and CMR, revealed the frequent presence of pronounced trabeculation reaching diagnostic thresholds for LVNC in healthy volunteers (8, 18).

This study, which extended Kawel et al.'s analysis of 323 MESA participants free from cardiovascular disease to the whole MESA cohort, showed that only 25.7% fulfilled current diagnostic criteria for LVNC, compared to the 43% described by Kawel. This discrepancy is likely to be partly related to software differences. The CVI42 software used in this analysis allowed identification of "off-axis acquisitions," while the software used by Kawel did not provide a cross-reference tool.

Association of extent of LV trabeculation on adverse cardiac remodeling and clinical outcomes. Baseline LV dimensions and EF are among the most powerful predictors of survival in heart failure and in people without cardiovascular disease, and are now well-established surrogate markers in heart failure trials (19-22). In this study, we evaluated the change in end-systolic volume index, end-diastolic volume index, and EF. Our main findings were that maximal NC/C ratio and other measures of the extent of LV trabeculation were associated with small, but clinically negligible, changes in LV parameters over an almost 10 year of MESA study period. The multivariate regression model incorporating maximal NC/C ratio, demographic

data and the baseline CMR data (Model 2, **Table 2**) increased the explained variance almost 10-fold compared with the model incorporating only the extent of trabeculations and demographic factors (Model 1, **Table 2**), suggesting that the maximal NC/C ratio plays a very small clinical role in cardiac remodeling. End-diastolic and end-systolic volume indices decreased over the 9.5 years of MESA study period, even in participants with the most pronounced trabeculation (by 3.6 ml/m^2 and 1.0 ml/m^2 in the highest quintile of maximal NC/C ratio).

In comparison, a previous study by Doughty and colleagues in subjects with congestive heart failure due to ischemic heart disease described an increase in end-diastolic volume index by 10.5 ml/m^2 over only 12 months in the placebo group (23).

Similarly, measures of the degree of LV trabeculation were not associated with the adverse clinical outcomes known to be associated with a clinical diagnosis of LVNC. These data may seem contrary to the many reports of embolic events in patients with LVNC, however the studied population was considered healthy and the probability of LVNC (or other cardiac diseases) was extremely low in this group.

Importance of clinical information when interpreting imaging LVNC criteria. Our study again demonstrates that Petersen's criteria (NC/C >2.3) are frequent findings in a "healthy" population-representative cohort. Importantly, our study underlines the importance of interpreting such an imaging diagnosis in the context of the available clinical information (24). Our findings suggest that in subjects or patients with a low pre-test probability for cardiomyopathy or LVNC and marked trabeculation, regular and frequent imaging and clinical follow-up may be unnecessary.

Petersen's criteria were derived from a group of patients with high pre-test probability imaged at a tertiary cardiomyopathy center and showed high sensitivity and specificity for diagnosing

LVNC (4). Current diagnostic criteria are applicable as a rule-in test if the suspicion (pre-test probability) of LVNC is over 10%, and could theoretically be used as a rule-out test if applied in patients with low pre-test probability for LVNC (24).

Study limitations. The data of the current study must be interpreted in the context of the study design. As described in the methods section, we were only able to analyze trabeculation on the most recent SSFP cine images from the MESA exam 5 data, but not on the gradient-recalled echocardiogram cine images acquired during the MESA exam 1. Although, this makes the data more applicable to current clinical practice, we imply that trabeculation has not changed over the approximately 10 years beforehand. The rationale for this implication is the evidence that the development and extent of trabeculations are determined during cardiac development in utero (25). Some case reports describe an undulating phenotype of LV trabeculations, but this is unlikely to be common enough to influence this study's results. Despite this, survivor bias may be present and firm conclusions on causality cannot be drawn. This question cannot be addressed without this limitation for another 15 years, until MESA or other large-scale population based cohort studies, such as UK Biobank, have sufficient serial CMR studies using SSFP cines. Adverse clinical events were rare and were therefore not treated as primary outcomes in this paper. Measurement of NC/C ratio is operator dependent; however, there was a good intraobserver and interobserver agreement. We used only 1 approach to measure the extent of LV trabeculations. Other reported strategies differ with respect to measuring in short-axis or long-axis views, measuring at end-diastole or end-systole, calculating ratios based on the thicknesses of trabeculated and compacted myocardial layers or trabecular mass as a percentage of total LV mass. There is currently no consensus as to the best approach, as each has advantages

and disadvantages with respect to their reported diagnostic accuracy, reproducibility, observer variability, and ability to avoid inadvertent inclusion of papillary muscle in the measurements.

Conclusions

Although there is the potential for confounding and survivor bias, this study does not find a clinically relevant impact of trabeculae on LV function measured in end-diastole over an almost 10-year period in a population of representative adult individuals.

This information should guide clinical decision-making in the common scenario of identifying patients with marked LV trabeculation and low pre-test probability of LV noncompaction that there is no clear need for follow-up imaging or pharmacotherapy.

Perspectives

Competency in medical knowledge: More extensive left ventricular trabeculation (the ratio of noncompacted to compacted myocardium) did not predict the development of clinically significant left ventricular enlargement or systolic dysfunction over a decade of follow-up.

Translational Outlook: Since adverse changes in myocardial structure and function are an uncommon sequela of left ventricular noncompaction, further studies in which large numbers of individuals are followed for longer periods are needed to identify predictors of phenotypic cardiomyopathy.

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Figure Legends

Central Illustration. Changes over 9.5 year period in end-systolic volume index and ejection fraction.
The changes over this time period in end-systolic volume index and ejection fraction were not different between quintiles of maximal non-compaction to compaction ratio, even in subjects exceeding the current "normal value" (<2.3). The decrease in end-diastolic volume index was smaller with increasing extent of trabeculation; significant differences were seen between quintiles 1 and 4 ($p<0.05$), between quintiles 1 and 5 ($p <0.001$) and also between quintiles 2 and 5 ($p <0.01$), but these changes are clinically insignificant.
EDVi – end-diastolic volume index, EF – ejection fraction, ESVi – end-systolic volume index, NC/C – non-compaction to compaction ratio

Figure 1. Flow Diagram of Exclusion Process
Exclusion criteria of subjects from the Multi-Ethnic Study of Atherosclerosis (MESA) for this study. CMR = cardiovascular magnetic resonance.

Figure 2. Measurement of NC/C Ratios
Example of an end-diastolic 4-chamber steady-state free precession image of a participant with very high maximal NC/C ratio (= 4.2) in the Multi-Ethnic Study of Atherosclerosis exam 5. Red arrows show measurements of compacted myocardium, yellow arrows represent measurements of the noncompacted (trabeculated) layer. NC/C = noncompaction to compaction.

Figure 3. Changes in Cardiac Volumes and Function
Changes in left ventricular (LV) volumes and function between MESA exam 1 and exam 5 and the relationship to the extent of LV trabeculation (in quintiles) at exam 5 presented in 2 ways: the bottom panel shows box and whisker plots and the lack of clinically relevant change in volume or function; the top panel shows similar slopes for the quintiles of trabeculation extent with regard to volumes and function between both exams. Boxes represent the interquartile range (IQR) and whiskers are within 1.5 *IQR. Outliers are plotted as points. The line within the box represents the median. NC/C = noncompaction to compaction. * $p <0.05$; ** $p <0.01$; *** $p <0.001$

Table 1. Demographic and Cardiovascular Magnetic Resonance data at MESA exam 5

Subjects with the highest trabeculation (Quintile 5) had larger left ventricular volumes, end-diastolic mass index, and blood pressure values and lower incidence of treated diabetes, weight, and body mass index.

	All	Quintile 1 NC/C: 0 - 1.41	Quintile 2 NC/C: 1.42 - 1.71	Quintile 3 NC/C: 1.72 - 2.00	Quintile 4 2.01 - 2.45	Quintile 5 2.46 - 5.41
n =	2,742	549	548	548	548	549
Age	68.7 ± 9.1	69.1 ± 9.2	69.1 ± 9.3	68.6 ± 8.9	68.6 ± 9.0	68.0 ± 9.2
Females	1,435 (52.3%)	**266 (48.5%)**	**286 (52.2%)**	**261 (47.6%)**	**304 (55.5%)**	**318 (57.9%)**
Race						
Caucasian	1,154 (42.1%)	230 (41.9%)	242 (44.2%)	207 37.8%)	238 (43.4%)	237 (43.2%)
Chinese American	343 (12.5%)	60 (10.9%)	75 (13.7%)	82 (15.0%)	69 (12.6%)	57 (10.4%)
Black, African American	682 (24.9%)	148 (27.0%)	141 (25.7%)	139 (25.4%)	131 (23.9%)	123 (22.4%)
Hispanic	563 (20.5%)	111 (20.2%)	90 (16.4%)	120 (21.9%)	110 (20.1%)	132 (24.0%)
Body mass index	27.9 ± 5.1	**28.3 ± 5.2**	**28.1 ± 5.2**	**28.1 ± 5.3**	**28.0 ± 5.2**	**27.2 ± 4.7**
Height (cm)	165.7 ± 9.8	166.0 ± 9.8	165.5 ± 9.5	165.7 ± 10.1	165.7 ± 10.0	165.5 ± 9.7

Weight (kg)	76.9 ± 16.5	**78.0 ± 16.0**	**77.3 ± 17.1**	**77.5 ± 17.5**	**77.0 ± 16.5**	**74.8 ± 15.4**
Hypertension	1546 (56.4%)	323 (58.8%)	326 (59.5%)	314 (57.3%)	305 (55.8%)	278 (50.6%)
Systolic blood pressure (mm Hg)	122.6 ± 20.0	**123.7 ± 21.1**	**125.7 ± 20.8**	**122.9 ± 20.3**	**121.4 ± 19.0**	**119.4 ± 18.1**
Diastolic blood pressure (mm Hg)	68.3 ± 9.9	**69.0 ± 9.8**	**69.0 ± 10.4**	**68.8 ± 9.8**	**67.6 ± 9.7**	**67.0 ± 9.7**
Diabetes by 2003 ADA (n =2,613)						
Normal	1,702 (62.5%)	337 (61.7%)	319 (58.5%)	329 (60.5%)	341 (62.5%)	376 (69.2%)
Impaired Fasting Glucose	564 (20.7%)	104 (19.0%)	122 (22.4%)	118 (21.7%)	118 (21.6%)	102 (18.8%)
Untreated Diabetes	35 (1.3%)	8 (1.5%)	7 (1.3%)	8 (1.5%)	5 (0.9%)	7 (1.3%)
Treated Diabetes	423 (15.5%)	**97 (17.8%)**	**97 (17.8%)**	**89 (16.4%)**	**82 (15.0%)**	**58 (10.7%)**
Family history of a heart attack	1127 (43.5%)	240 (46.2%)	226 (44.1%)	206 (39.9%)	243 (46.6%)	212 (40.8%)
Coronary disease	96 (3.5%)	27 (4.9%)	14 (2.6%)	15 (2.7%)	19 (3.5%)	21 (3.8%)
Smoking						

Never	1275 (46.7%)	242 (44.2%)	260 (47.7%)	262 (48.1%)	247 (45.2%)	264 (48.4%)
Former	1249 (45.7%)	260 (47.4%)	240 (44.0%)	245 (45.0%)	262 (47.9%)	242 (44.3%)
Current	207 (7.6%)	46 (8.4%)	45 (8.3%)	38 (7.0%)	38 (6.9%)	40 (7.3%)
Education						
No school	9 (0.3%)	3 (0.5%)	0	0	3 (0.5%)	3 (0.5%)
Grades 1-8	196 (7.2%)	39 (7.1%)	45 (8.2%)	38 (7.0%)	32 (5.9%)	42 (7.7%)
Grades 9-11	119 (4.3%)	26 (4.7%)	22 (4.0%)	31 (5.7%)	17 (3.1%)	23 (4.2%)
Completed High School	445 (16.3%)	87 (15.8%)	73 (13.4%)	98 (17.9%)	101 (18.5%)	86 (15.7%)
Some College but no degree	435 (15.9%)	84 (15.3%)	90 (16.5%)	92 (16.8%)	98 (17.9%)	71 (12.9%)
Technical School Certificate	203 (7.4%)	39 (7.1%)	44 (8.1%)	44 (8.1%)	40 (7.3%)	36 (6.6%)
Associate Degree	145 (5.3%)	26 (4.7%)	36 (6.6%)	26 (4.8%)	25 (4.6%)	32 (5.8%)
Bachelor's Degree	555 (20.3%)	116 (21.1%)	110 (21.1%)	95 (17.4%)	109 (19.9%)	125 (22.8%)
Graduate or Professional School	630 (23.0%)	129 (23.5%)	126 (23.1%)	122 (22.3%)	122 (22.3%)	131 (23.9%)

LV end-diastolic volume index (ml/m^2)	65.2 ± 13.6	**62.4 ± 14.3**	**63.5 ± 13.4**	**65.7 ± 13.1**	**66.0 ± 13.3**	**68.3 ± 13.2**
LV end-systolic volume index (ml/m^2)	25.0 ± 8.5	**24.1 ± 9.3**	**23.9 ± 8.0**	**25.4 ± 8.6**	**25.5 ± 8.4**	**26.3 ± 8.0**
LVEF (%)	62.0 ± 7.3	62 ± 7.4	62.8 ± 7.3	61.7 ± 7.8	61.7 ± 6.8	61.9 ± 7.0
LV mass index (g/m^2)	66.4 ± 13.8	**68.1 ± 14.3**	**68.2 ± 14.9**	**67.3 ± 14.0**	**65.1 ± 12.8**	**63.1 ± 12.4**

ADA = American Diabetes Association, LV = left ventricle, LVEF = left ventricular ejection fraction; NC/C = noncompaction to compaction ratio.

Table 2. Regression Models With Maximal NC/C Ratio, Demographic Data, CMR Data and Classic Risk Factors

Exposure variable	Outcome variables (change between exam 1 and exam 5)	Univariable regression		Multivariable regression					
				Model 1		Model 2		Model 3	
		Beta (95%CI)	R^2	Beta (95%CI)	R^2	Beta (95%CI)	R^2	Beta (95%CI)	R^2
Maximal NC/C ratio	End-diastolic volume index (ml/m^2)	1.6*** (0.9 to 2.3)	0.008	1.9*** (1.2 to 2.6)	0.034	2.7*** (2.1 to 3.3)	0.261	2.6*** (2.0 to 3.3)	0.269
	End-systolic volume index (ml/m^2)	0.3 (-0.1 to 0.8)	0.0009	0.5* (0.1 to 0.9)	0.026	1.0*** (0.6 to 1.4)	0.195	1.0*** (0.6 to 1.4)	0.200
	EF (%)	0.4 (-0.1 to 0.8)	0.0009	0.3 (-0.1 to 0.7)	0.013	-0.2 (-0.6 to 0.2)	0.324	-0.2 (-0.6 to 0.1)	0.320

Univariate and multivariate linear regression analysis models for the changes in the end-diastolic volume, end-diastolic volume index and ejection fraction (EF) between MESA exam 1 and 5 as dependent variables in models incorporating maximal NC/C ratio, demographic data, baseline CMR parameters at MESA exam 1 and traditional risk factors as predictor variables.

Model 1: adjusted for age, sex, and ethnicity. Model 2: adjusted for Model 1 parameters plus baseline EDVi (for change in EDVi), ESVi (for change in ESVi), and EF (for change in EF) Model 3: adjusted for Model 2 parameters plus diabetes, smoking history, total cholesterol, systolic blood pressure, and BMI. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, 95%CI = 95% confidence intervals, EDVi = end-diastolic volume index, EF = ejection fraction, ESVi = end-systolic volume index, NC/C = noncompaction to compaction

Table 3. Cardiovascular adverse outcomes in relation to the extent LV trabeculations

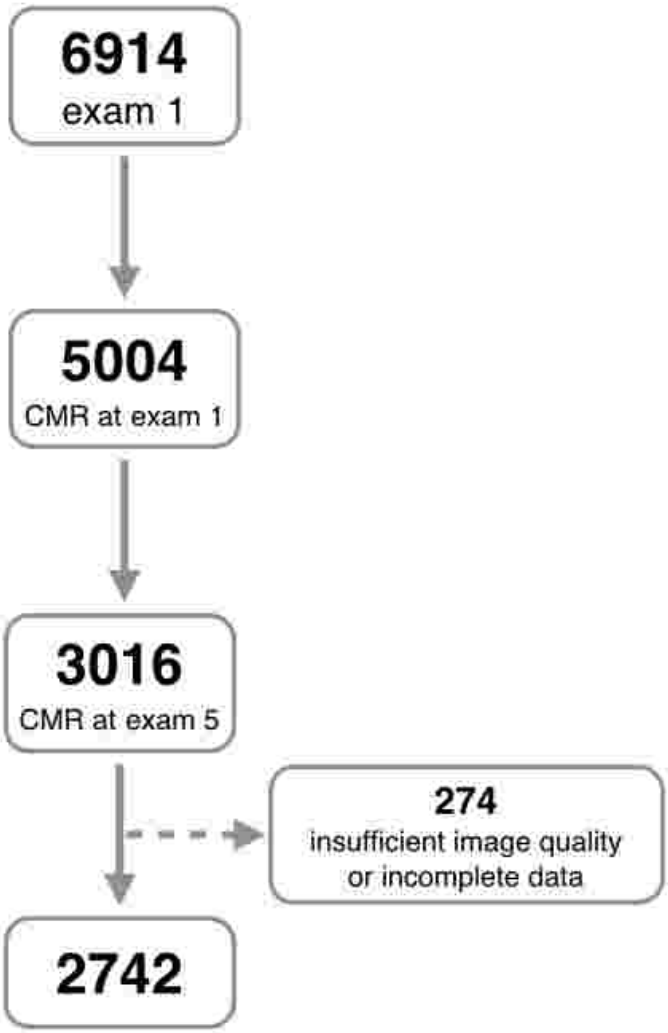
	All	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Atrial fibrillation	24	10 (1.9%)	7 (1.3%)	1 (0.2%)	3 (0.6%)	3 (0.6%)
Congestive heart failure	22	4 (0.7%)	5 (0.9%)	5 (0.9%)	4 (0.7%)	4 (0.7%)
Stroke	28	4 (0.7%)	8 (1.5%)	10 (1.9%)	2 (0.4%)	4 (0.7%)
Transient ischemic attack	17	4 (0.7%)	3 (0.6%)	4 (0.7%)	4 (0.7%)	2 (0.4%)
Myocardial infarction	41	15 (2.8%)	2 (0.4%)	8 (1.5%)	9 (1.7%)	7 (1.3%)
Hard cardiovascular endpoints	68	19 (3.6%)	10 (1.9%)	18 (3.4%)	11 (2.0%)	10 (1.9%)
All cardiovascular endpoints	121	31 (6.0%)	21 (4.0%)	25 (4.8%)	20 (3.8%)	24 (4.6%)

The incidence of cardiovascular adverse outcomes in the whole studied cohort and quintiles of maximal NC/C ratio are shown.

Hard cardiovascular endpoints include: myocardial infarction, resuscitated cardiac arrest, stroke

All cardiovascular endpoints include hard cardiovascular endpoints plus: definite angina, probable angina followed by coronary revascularization

EXTENT OF NC/C RATIO IN QUINTILES	Quintile 1 (0 to 1.41)	Quintile 2 (1.42 to 1.72)	Quintile 3 (1.73 to 2.01)	Quintile 4 (2.02 to 2.45)	Quintile 5 (2.46 to 5.41)	P
CHANGE IN ESVI (ML/M^2)	-1.3 ± 8.0	-2.1 ± 7.1	-1.4 ± 7.5	-0.9 ± 7.4	-1.0 ± 7.2	0.08
CHANGE IN EDVI (ML/M^2)	-6.5 ± 13.1	-6.0 ± 12.4	-5.1 ± 12.1	-4.4 ± 12.3	-3.6 ± 11.3	<0.001
CHANGE IN EF (%)	-1.4 ± 8.2	-0.1 ± 7.6	-0.4 ± 8.0	-0.8 ± 7.5	-0.3 ± 7.9	0.053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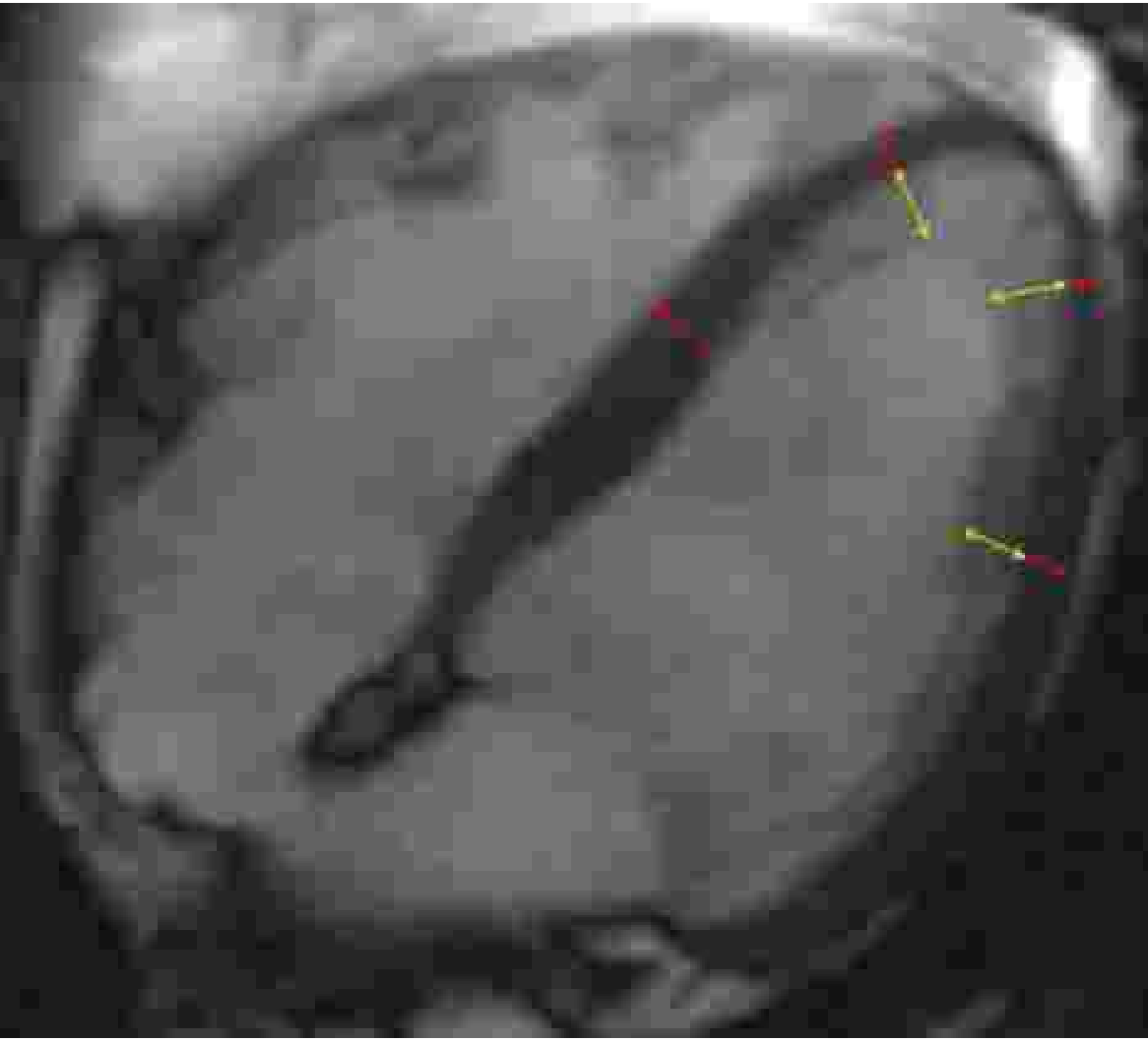

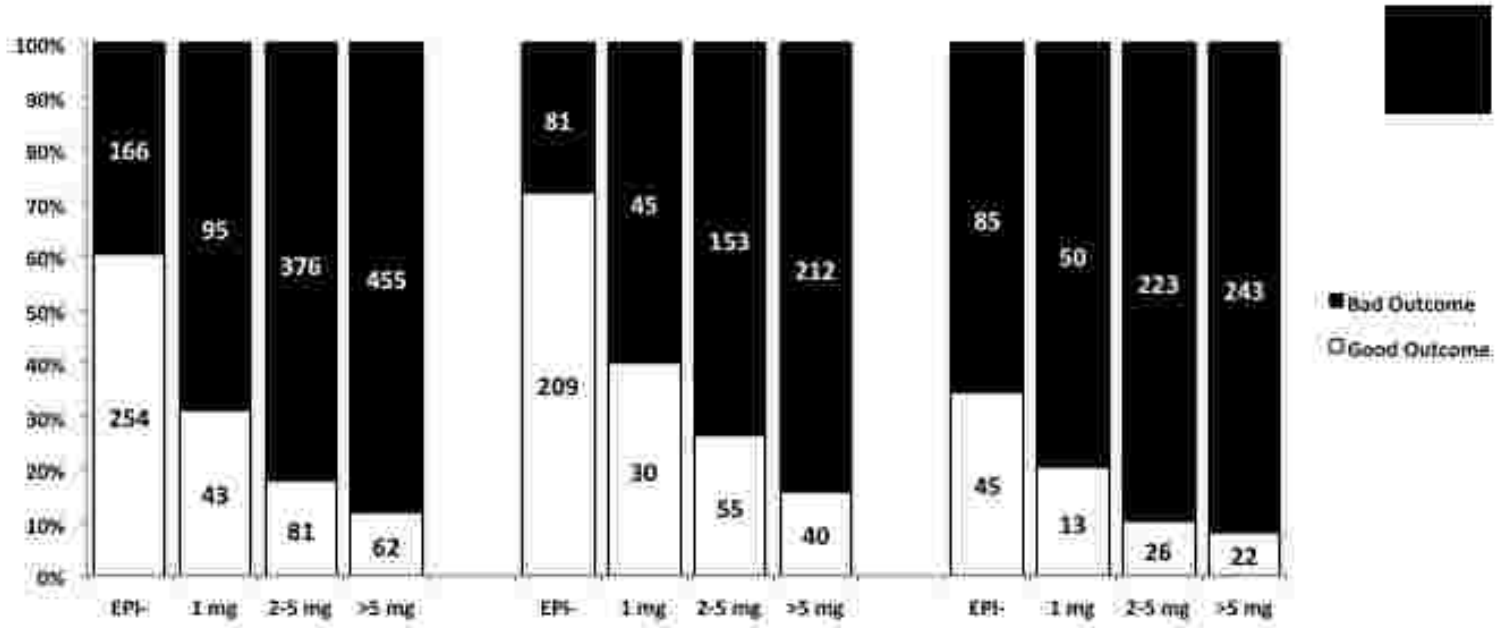

	Overall			Shockable			Non-Shockable		
	Odds Ratio	[95%CI]	p-value	Odds Ratio	[95%CI]	p-value	Odds Ratio	[95%CI]	p-value
EPI-	1			1			1		
1 mg	0.48	[0.27-0.84]	0.01	0.38	[0.18-0.78]	0.008	0.60	[0.23-1.60]	0.31
2-5mg	0.30	[0.20-0.47]	<0.001	0.25	[0.14-0.44]	<0.001	0.40	[0.19-0.84]	0.02
>5 mg	0.23	[0.14-0.37]	<0.001	0.16	[0.08-0.30]	<0.001	0.36	[0.16-0.82]	0.01

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