New statin use and left ventricular structure: estimating long-term associations in the Multi-Ethnic Study of Atherosclerosis (MESA)

Lauren N. Strand

A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Science

University of Washington

2016

Committee:

Joseph A. “Chris” Delaney

Susan R. Heckbert

Rebekah L. Young

Program Authorized to Offer Degree:

Epidemiology

University of Washington

Abstract

New statin use and left ventricular structure: estimating long-term associations in the Multi-Ethnic Study of Atherosclerosis (MESA)

Lauren N. Strand

Chair of the Supervisory Committee:
Joseph A. "Chris" Delaney, Research Assistant Professor
Epidemiology

Recent treatment guidelines in the United States have increased the number of statin-eligible individuals. While statin use is associated with a modest reduction in heart failure hospitalizations in meta-analyses of statin trials, the mechanism is unclear. Only small and short-term studies have evaluated statins in relation to changes in heart structure. We estimated the association of new statin use with 10-year remodeling of the left ventricle. The Multi-Ethnic Study of Atherosclerosis (MESA) collected data on statin use at five clinic exams over about 10 years, and conducted cardiac magnetic resonance (CMR) imaging at both baseline and the 10-year exam. Participants were free of known cardiovascular disease (CVD) and we excluded statin users at baseline. Cumulative statin use and statin dose were estimated between exam

intervals for each positive report of current use. Primary outcomes were the change in left ventricular mass index (LVMI; % predicted by height, weight and sex relative to a healthy population) and mass-to-volume ratio (MVR). Associations were estimated in multivariable linear regression analyses, adjusting for baseline age, race, sex, traditional CVD risk factors, anti-hypertensive medication, exercise, health insurance, and coronary artery calcium. A total of 3113 participants (53% female; 40% white, 25% African-American, 22% Hispanic, 13% Chinese-American) had a valid CMR scan and no statin use at baseline; 2431 returned for a follow-up CMR after a median of 9.4 years. Statin therapy (moderate dose in 76%) was started by 36% of participants (N=872) and the duration of use ranged from 1.5-8 years among new users (median: 3.25 years). We excluded 42 participants with an incident myocardial infarction during follow-up. Each additional year of statin use was had a marginal association with 10-year progression in LVMI (-0.30, 95%CI: -0.59, -0.02, p=0.04) but not MVR (-0.002, 95%CI: -0.006, 0.002, p=0.42). A modest dose response was observed where higher statin doses were associated with less progression of LVMI (p=0.004, test for trend); association with LVMI was statistically significant only for moderate dose vs. never use (-1.64, 95%CI: -2.95, -0.33, p=0.01). Techniques to account for missing data did not appreciably alter estimates. We found no robust or substantive associations between statin use and indices of left ventricular remodeling over 10 years in a diverse population without clinical CVD at baseline.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGEMENTS

I would like to extend my sincere thanks to my Committee Members for their tremendous support on this work, in particular, Susan for the attention to detail, Rebekah for encouraging clarity, and Chris for much the needed optimism.

I would also like to thank Mary Lou Biggs, Traci Bartz, Robin Nance, and Bridget Kruszka for listening as I wrapped my head around this project, as well as Richard Kronmal and Robyn McClelland for the opportunity to work with the beautiful MESA data.

DEDICATION

This thesis is dedicated to my teammate, Chris Hughes. I am unspeakably grateful for your patience and support while on this adventure.

Chapter 1. INTRODUCTION

1.1 HEART FAILURE

Heart failure (HF) is a common[1] clinical syndrome consisting of abnormal hemodynamics, changes in metabolic and neurohormonal activity, and structural and functional impairment of the left ventricle.[2] With high treatment costs due to repeat hospitalization, HF is associated with an increasingly high level of patient morbidity over time including progressive decline in physical functioning. Drug therapies exist, though they are not curative. One potential focus of health systems may be on the prevention of HF rather than management once the condition has been clinically recognized. Among many treatments explored for HF, statins, or HMG-CoA reductase inhibitors, have been evaluated in both primary and secondary prevention. While an approximate 10% reduction in the risk of HF hospitalization has been shown in meta-analyses of statin primary and secondary prevention trials,[3,4] the mechanism of action is unclear. The beneficial effects of statins may occur via cholesterol-lowering and reduction in the risk of ischemic heart disease and clinical events including myocardial infarction (MI). However, early statin trials reported that the magnitude of risk reduction for clinical cardiovascular events was greater than expected given the observed lipid-lowering effects.[5] This suggests that statins may be active in non-cholesterol mediated pathways.[6] These agents may slow or reduce the cardiac remodeling[7] that occurs on the pathway from left ventricular hypertrophy (LVH) to HF.

1.2 REMODELING

Ventricular remodeling is the process of structural and compositional changes of the myocardium (i.e. increased mass) and/or ventricular cavity (i.e. increased volume) over time. Changes in the myocardium may be characterized by increases in myocyte size, vascular

changes, and accumulation of collagen tissues in the extracellular matrix (i.e. fibrosis).[8] Increased left ventricular mass can be adaptive in response to exercise and strength training or an age-related process, though there may be sex-specific differences.[9] Changes may also be a pathological compensatory response to hemodynamic overload. LVH, typically defined by myocardial wall thickness at the end of diastole, is an adaptational state before HF and an independent risk factor for ischemia, arrhythmia, and sudden death.[10] Statin therapies have been investigated in remodeling and LVH, and some evidence has suggested a beneficial effect on structure and function.[11,12]

1.3 Clinical Relevance

Clinical guidelines from the American Heart Association (AHA) and the American College of Cardiology (ACC) have increased the number of statin-eligible individuals.[13] Those recommended statins may be young and expected to take these drugs for extended periods.[14,15] Understanding the potential benefits and harms of long-term treatment with statins is essential for clinical decision making. Among other side effects, there is some evidence that statins may produce memory impairment, myopathy, and diabetes, which prompted the US Food and Drug Administration to expand advising on the risk of statins in 2014.[16] The short-term efficacy of statins is well studied, but few investigations have evaluated statins and long-term changes in cardiac structure, especially among healthy individuals. The purpose of this study was to estimate the association of new statin use with ten-year longitudinal changes in structure and function of the left ventricle in a diverse population free of clinical CVD at baseline. The primary outcomes were left ventricular mass (LVM), an important measure of LVH and predictor of cardiovascular events,[17] and mass-to-volume ratio (MVR), a measure of concentric remodeling of the left ventricle.[18]

Chapter 2. METHODS

2.1 PARTICIPANTS

The Multi-Ethnic Study of Atherosclerosis (MESA) has been described previously.[19] Briefly, MESA is an ongoing prospective observational cohort study designed to investigate the pathogenesis of cardiovascular disease in four racial/ethnic groups. At enrollment, participants were free of known CVD (Supplemental material). Between 2000 and 2002, MESA enrolled 6814 participants ages 45 to 84 years from six locations in the U.S.: Baltimore City and County, Maryland; Manhattan and the Bronx, New York; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; and St. Paul, Minnesota. All MESA protocols were approved by the Institutional Review Board at participating study institutions.

MESA participants attended a baseline examination (exam 1) between 2000 and 2002, and four subsequent exams. Exams 1 through 4 occurred at average intervals of 9-21 months, and exam 5 occurred between 2010 and 2012, approximately 10 years after the baseline exam. Demographic information, medical history, anthropometric measurements, and medication inventories were collected at each exam. Current medications were evaluated at all five MESA exams using a validated medication inventory[20] in which interviewers transcribed names, strengths, and dosage from medication bottles brought to the exam by participants. Participants were also asked about actual medication use in the previous two weeks, which allowed for calculation of an average medication intake. Clinical cardiovascular events including stroke, transient ischemic attack (TIA), MI, and HF were ascertained and adjudicated throughout the study period by a committee of MESA investigators that included experts in neurology, cardiology, and epidemiology.[19] Cardiac magnetic resonance (CMR) imaging protocols have been described previously.[21] Technical errors of measurement quantified at exam 1 were small

(approximately 6% for LVM and 4% for end-diastolic volume).[21] Changes in CMR pulse sequence technology and software between exams required that exam 1 parameters be adjusted to be comparable to those at exam 5. Calibration was performed with a subset of participants at exam 5 who were imaged using both the original gradient echo and the newer steady state free precession (SSFP) techniques as well as the different software packages for reading images.[21] Recent analyses have been published using longitudinal CMR measures in MESA.[9,18] For this analysis, we included all MESA participants free of statin use and with a valid CMR at baseline.

2.2 STATIN USE

In order to summarize statin dose, we estimated the mean daily dose inventoried during the study period (approximately 10 years) among the subset of individuals who began using statins. For example, if a participant reported a low dose at exam 2, a moderate dose at exam 3 and 4, and a high dose at exam 5, the mean dose would be moderate. National drug codes (NDC) recorded in the medication inventory at each clinical exam were used to group statins into low, moderate, and high dose according to the ACC/AHA Guideline on the Treatment of Blood Cholesterol.[13] A new user study design was selected to increase the likelihood that baseline characteristics were not impacted by current statin use.[22] We also estimated maximum and minimum statin dose inventoried during the study in order to assess the effect of misclassification of dose.

Cumulative years of new statin use over the study period was the main exposure of interest. Duration of statin use was estimated from medication inventory data from five clinical exams that occurred at unequal intervals over a ten year period. Among participants with at least one follow-up exam, the average time between exams was approximately 1.8 years. From each positive report of statin use, we defined the years of use as the sum of half of the preceding and subsequent exam intervals. When participants did not attend the 3rd or 4th exam, we logically

edited statin use or non-use at the missed exam based on concordant statin use statuses at the prior and the subsequent exams. Those with at least one missing report of statin use at a clinical exam and no reported statin use at other exams were classified as having unclear or missing statin use.

2.3 Cardiac Magnetic Resonance Imaging

The primary cardiac measures of interest were the absolute change in left ventricular end-diastolic mass (LVM) and mass-to-volume ratio (MVR) over the study period, derived from the MESA CMR SSFP readings. Prior to calculating absolute change, baseline and follow-up LVM were indexed using the allometric height-weight-gender methods described in Brumback *et al*.[23] Briefly, Brumback developed an index of predicted LVM based on height, weight, and gender in the subgroup of normal weight, normotensive, non-diabetic MESA participants. Then, the measured LVM value for each MESA participant was divided by their predicted LVM based on height, weight, and gender to generate an "indexed" LVM (LVMI). The LVMI derived by Brumback *et al*. was more strongly associated with a CVD event (defined as a composite of nonfatal and fatal CHD and stroke) during follow-up than alternative indexing schemes, including indexing by body-surface area (BSA).[23] The following formulae were used:

$$LVMI_{women} = \frac{LVM}{6.82 \times height(m)^{0.561} \times weight(kg)^{0.608}}$$

$$LVMI_{men} = \frac{LVM}{8.17 \times height(m)^{0.561} \times weight(kg)^{0.608}}$$

Because height and weight changed between baseline and follow-up exams, we indexed baseline LVM by gender and baseline height and weight and follow-up LVM by gender and follow-up height and weight. We studied BSA-indexed LVM and unindexed LVM as secondary outcomes.

MVR is the most commonly used measure of concentric remodeling, and was calculated as the ratio of unadjusted end-diastolic mass to left ventricular end-diastolic volume (LVEDV). Additional secondary outcomes included the absolute change in LVEDV and LVEF, where LVEF was defined as the stroke volume divided by the end diastolic volume and multiplied by 100.[17] A subset of 1814 MESA participants underwent late gadolinium enhanced CMR at follow-up exam, which allowed for the detection of myocardial scar.[24]

2.4 Statistical Analysis

We estimated descriptive statistics for baseline characteristics among non-statin users, those who began and used statins for less than four years, and those who began and used statins for four or more years. Four years was selected as the threshold in consideration of the length of previous randomized and observational studies. We included descriptive measures for the subset of individuals with unclear or missing statin use and prevalent statin users at baseline in order to evaluate differences across groups. Baseline values of cardiac measures were also calculated, as well as the unadjusted absolute change among those participants with complete covariates. Statin doses were analyzed for association with change in CMR indices using multivariable linear regression with robust standard errors in order to account for heteroscedasticity in the outcome. We fit both indicator variable and linear dose models and used a likelihood ratio (LR) test when there was evidence for a linear trend in the analysis with the indicator variables. For duration of statin use, the departure from linearity in the relationship between continuous years of statin use and change in primary outcomes was explored using locally weighted scatterplot smoothing (LOWESS). All regressions were adjusted for baseline covariates defined a priori to include age, gender, race and other traditional cardiovascular risk factors[9,25–27] (smoking status, systolic blood pressure, diastolic blood pressure, treated diabetes, body mass index (BMI), waist circumference,

HDL cholesterol, triglycerides, and total cholesterol), antihypertensive medication use (indicator variables for angiotensin-converting-enzyme inhibitors, angiotensin type 2 agonists, beta blockers, calcium channel blockers, and diuretics), potential predictors of statin use (intentional exercise and health insurance status), and the Agatston coronary artery calcium (CAC) score (range: 0-5148) derived from the baseline computed tomography (CT) scan. We present the following nested models, adjusted for: 1) age, sex, race; 2) model 1 plus cardiovascular risk factors; 3) model 2 plus predictors of statin use; and 4) model 3 plus CAC score. All CAC scores + 1 were transformed by the natural-log to approximate a normal distribution among those with positive CAC. We restricted the analysis to the subset of individuals without an incident MI during the study period, because the presence of an MI may predict both statin treatment and alterations in left ventricular structure and function; however, we also evaluated the subset of participants with incident MI in an exploratory analysis. The primary analysis was based on individuals with complete data on covariates of interest. Because only a subset of participants returned for a follow-up CMR scan approximately 10 years after baseline, we accounted for loss to follow-up in sensitivity analyses for duration of statin use. Models were weighted by the inverse probability of any censoring (i.e. death, loss-to-follow-up, missing second CMR scan), with weights generated in logistic regression with all the candidate risk factors for changes in primary outcomes. In addition, sensitivity analyses tested whether results were robust to the use of multiple imputation for missing data. Potential effect modification by dose was assessed by inclusion of an interaction term between dose and continuous duration of use. All analyses were completed using either Stata version 14.0 or SAS version 9.4. A two-tailed p-value less than 0.05 was considered statistically significant.

Chapter 3. RESULTS

3.1 Baseline Characteristics

Of 6814 MESA participants, 4265 MESA participants were not statin users and had valid CMR measures at baseline (Figure 1). Among 4265 participants, 4234 had complete covariates at baseline. A total of 1844 (43%) participants had no statin use over the study period, 712 (17%) had statin use <4 years, 577 (13%) had statin use ≥4 years, and 1132 (27%) had unclear or missing statin use based on the study definitions. Baseline clinical and demographic characteristics are shown in Table 1 along with baseline CMR measures of left ventricular structure and function for the subset of individuals with complete follow-up data. In general, never users of statins were more likely to be younger, female, of Chinese ethnicity, and have lower blood pressure and total cholesterol compared with new statin users. Rates of diabetes and hypertension, and CMR indices of LVM, were higher among new users of statins. New users of statins were also more likely to be using antihypertensive agents and were more physically active. A smoothed distribution of estimated years of statin use is shown in Suppl. Figure 1. Most new statin users (76%) started a moderate dose statin (Table 2). Statin formulation and dose used during the study are described in Suppl. Table 2.

3.2 Unadjusted Ten-year Change in Cardiac Indices

Follow-up data were available for 2431 participants (57% of the original sample). The unadjusted mean changes in measures of left ventricular structure and function between baseline and follow-up are shown in Table 3. The average time between CMR scans was similar in new users and never users of statins. Over this time, average mass and volume increased for all groups, while average LVEF declined. In general, indices of mass change were higher among

never users. There were 114 participants with incident MI over the study period, of which 42 (37%) had a follow-up CMR scan (and complete covariates). The proportion with an incident MI was higher in new users than in never users of statins.

3.3 Association Between Statin Dose and Change in Cardiac Indices

In multivariable adjusted linear statin dose models of the 10-year change in cardiac indices, excluding those with an incident MI, results for LVMI were numerically consistent with a dose response (Table 4). Moderate and high dose statin use was associated with less progression of LVMI relative to never statin use, but the differences were small. Moderate dose statins were associated with a statistically significantly lower LVMI change relative to never use (-1.64, 95%CI: -2.95, -0.33, p=0.01). There was an overall linear trend for the association between statin dose and LVMI change (LR chi2(1)=8.12, p=0.004 for linear dose model vs. reduced model; LR chi2(2)=0.07, p=0.97 for linear dose model vs. indicator variable dose model).

The change in LVEF was different across statin dose groups ((LR chi2(3)=9.32, p=0.03 for indicator variable dose model vs. reduced model); Table 4). High dose statin users trended towards a greater decline in LVEF relative to never users (-1.98, 95%CI: -3.98, 0.01); but there were relatively few participants in the high dose group and the estimate was not statistically significant (p=0.05). A statistically significant association was observed between LVEF change and statin dose (LR chi2(3)=9.32, p=0.03 for indicator variable dose model vs. reduced model). No other indices demonstrated significant associations with dose.

The minimum and maximum statin doses reported during follow-up are shown in Suppl. Table 1. Sensitivity analyses with the minimum and maximum statin dosage showed similar results (Suppl. Table 3). No statistically significant interactions were observed between

cumulative years of statin use and statin dose (Suppl. Table 4). Nested models for all outcomes are shown in Suppl. Table 5.

3.4 Association Between Duration of Statin Use and Change in Cardiac Indices

Results from LOWESS models provided evidence for a linear relationship between years of statin use and primary outcomes, LVM and MVR (data not shown). In statin years of use models of the 10-year change in primary outcomes (Table 5), excluding those with an incident MI, there was no statistically significant association between years of new statin use and change in LVMI or MVR. Each additional year of statin use was associated with less progression in LVMI (-0.30, 95%CI: -0.59, -0.02, p=0.04), but not MVR (-0.002, 95%CI: -0.006, 0.002, p=0.42). Results for the 10-year change in secondary outcomes are shown in Suppl. Table 6. No changes in these indices were associated with years of statin use. Across primary and secondary outcomes, the results did not differ materially when the model was weighted by the inverse probability of any censoring between exams (Suppl. Table 6). Results were also robust to multiple imputation for missing covariate and outcome data.

Chapter 4. DISCUSSION

This investigation did not consistently show an association between new statin use and long-term changes in cardiac structure and function in a diverse population with no clinical CVD at baseline. While there was some evidence for a linear association between statin dose and change in left ventricular mass, as well as a marginally statistically significant association between statin duration of use and left ventricular mass, all effect sizes were small. Additionally, there was no evidence that statin duration was associated with progression of other cardiac indices in this

primary prevention cohort. This contrasts with previous studies of statins and cardiac structure, and a growing body of literature that is concerned with statin pleiotropic effects. Our result may be consistent with short-term or modest dose-related effects of statins on cardiac structure; however, these findings suggest that there is minimal long-term effect of statins on indices of cardiac structure in the primary prevention clinical setting.

4.1 Clinical Evidence for Heart Failure

Statins are well-documented to reduce the risk of cardiovascular events.[28] A recent meta-analysis of statin primary and secondary prevention trials found a 10% decrease in the risk of first non-fatal HF hospitalization among statin users relative to non-users (relative risk [RR]: 0.90, 95%CI: 0.84, 0.97).[4] This result did not differ whether the non-fatal HF hospitalization was preceded by MI. The estimate was no longer statistically significant in the subgroup analysis of the primary prevention trials (RR: 0.89, 95%CI: 0.67, 1.17), likely due to low event rates in these studies.

4.2 Mechanism

The cholesterol-independent effect of statins on left ventricular mass is postulated to occur through activity on both cardiomyocytes and fibroblasts, which account for 30% and 70% of the myocardium, respectively.[29] Among cardiomyocytes, statins may prevent or reduce hypertrophy via the inhibition of small GTPase signaling pathways (i.e. Rho, Rac, and especially, Ras).[30] In addition, statins may protect against other cardiac injury, including necrosis through activation of the reperfusion injury salvage kinase (RISK) pathway, and contractile dysfunction through several pathways including up-regulated expression of the proteins involved in calcium handling in the sarcoplasmic reticulum.[31] Unfortunately, statins can also induce myopathy in skeletal

muscle.[32] With seemingly paradoxical effects on skeletal and cardiac muscle, it is uncertain what net effect statins may have on cardiomyocytes. Several in vitro studies even suggest an association with cardiomyocyte cell death and other cardiotoxicity.[33–35] Among fibroblasts, which provide structure and connectivity across the myocardium, statins may reduce the remodeling that occurs after infarction and on the pathway to HF. Remodeling processes include fibroblast proliferation and migration, myofibroblast differentiation, and synthesis of extra-cellular matrix.[31] For example, statins reduce DNA synthesis in animal fibroblasts, where synthesis was used as a marker of fibroblast proliferation.[35,36] Biochemical pathways through which statins may act on fibroblast function include inhibition of small GTPases as well as ERK, AKT, and p38 MAP kinase signaling. The activity of statins on fibroblasts is less studied, especially in vivo, due to the complexity of the involved biochemical pathways. Current investigations in vivo are hindered by the lack of a biomarker for statin pleiotrophy.[37]

4.3 Animal Studies

In animal models of CVD, statins have been shown both to prevent development of cardiac hypertrophy and to induce regression of established hypertrophy.[38–44] Animal studies of early stage hypertension[45] and hypercholesterolemia[46] have also noted benefits of statins on LVM. Among rabbits fed a 1% cholesterol diet for 8 weeks, treatment with simvastatin was associated with 14% less progression of index left ventricular mass relative to placebo.[46] This study also demonstrated less increase in cardiomyocyte area in isolated samples from statin-treated animals. Similarly, normocholesterolemic spontaneously hypertensive rats treated at the early stages of cardiac hypertrophy for 8 weeks with pravastatin had attenuated hypertrophy relative to a controls who received a vehicle only.[47] The result from this study was shown to be independent of blood pressure- and lipid-lowering changes, and cardiomyocyte area was also reduced relative

to control. However, animal studies have not uniformly shown an effect of statins on established hypertrophy.[48]

4.4 Clinical Studies

Early observational studies in humans have mostly evaluated current or short-term duration of statin use.[49,50] Randomized studies of statin use and cardiac structure and/or function have often focused on small populations with moderate to severe cardiovascular diseases including cardiomyopathy,[51–56] congenital aortic stenosis,[57] and heart failure.[58–60] These investigations have not consistently demonstrated statin effects on LVM and other indices in addition to having short time frames and limited power. One study each in hypertrophic cardiomyopathy and aortic stenosis did not show effects of statins relative to placebo in up to 2.4 years of treatment.[52,57] Another small clinical trial in hypertrophic cardiomyopathy did not find regression of LVM over 12 months among those treated with atorvastatin.[56] Similarly, in a study of non-ischemic heart failure, there were no significant changes in BSA-indexed LVM among those treated with low dose atorvastatin relative to placebo over one year;[58] however, this study did demonstrate increased LVEF among statin-treated relative to placebo.

Observational studies and trials in populations similar to MESA (Suppl. Table 7), including those evaluating hypertensive and hypercholesteremic patients, have shown associations between statin use and LVM regression[47,50] or reduced progression of LVM.[61] In the longest and largest of these studies, the Hypertension High Risk Management Trial (HYRIM), drug-treated hypertensive patients randomized to fluvastatin had significantly reduced two-year progression of LVM compared with placebo-treated patients.[61] However, this study represents a markedly less healthy population than MESA, as evidenced by the magnitude of increase in LVM over two years among placebo-treated participants (approximately 30 grams vs. 3 grams

among non-statin users in MESA). In contrast, a different randomized investigation of fluvastatin versus placebo in hypertensive patients, demonstrated similar magnitude of LVMI change between fluvastatin (-17 g) and placebo (-16 g) randomized groups over 1 year, though this study was not powered to detect difference between groups.[62] A randomized study of rosuvastatin did not find a significant effect of six months of treatment on LVMI relative to placebo among patients with hypertension and left-ventricular hypertrophy.[63] Collectively, these conclusions are supported by the null results in our investigation.

4.5 Strengths of This Study

MESA is a unique setting for investigating statin exposure and long-term changes in cardiac structure and function because the cohort is a population of relatively healthy individuals followed for medication use and subclinical measures, as well as clinical events. In addition, while a majority of previous investigations have relied upon two-dimensional echocardiographic measures of ventricular structure and function, MESA used CMR, which has higher resolution for structure, requiring fewer geometric and modeling assumptions. MESA provides the largest and longest investigation of statin exposure and heart structure to date. This investigation evaluated change over approximately 10 years, while few previous studies have evaluated statin use and cardiac structure/function for periods longer than one year.[54,57,61] Short-term studies are useful because cardiac remodeling may be a relatively fast process. For instance, preclinical studies have demonstrated regression of cardiac mass within a few weeks of statin administration.[63] The long-term benefits and harms of statin use are also important. Statins have been associated with adverse side effects, including liver injury, memory loss, diabetes, and muscle damage, in as many as 20% of statin users.[64] While we did not detect associations between statin duration and measures of structure and function of the left ventricle, the

relationship between statin dose and change in most cardiac indices was consistent with a small dose response. Relatively few participants began low or high dose statins, so our dose-related findings must be interpreted with caution. An overall null result adds support to studies suggesting that attenuation of structural remodeling is not the main mechanism through which statin therapy could produce a benefit on HF clinical outcomes. Alternative mechanisms may involve improved cardiovascular function (possibly occurring via reduced inflammation),[65] though we did not observe any statistically significant associations between statin use and the one evaluated functional measure, change in LVEF.

4.6 Myocardial Infarction

Because statins may play an important role in the secondary prevention setting, the effect of statins on the risk of potential clinical cardiovascular events is an important consideration in this study. Only a small group of individuals with MI had sufficient data and returned for a second CMR scan (42/114, 37%; Suppl. Figure 2; Suppl. Table 8; Suppl. Table 9). This group may represent the healthiest subset of MI survivors; however, it is difficult to know how this group might differ from those who did not return for a second scan. Thus, they were excluded from all analyses. The degree of myocardial scarring may play a role in the observed results, as fibrosis may contribute to the measure of ventricular mass.[24] A descriptive account of fibrosis at follow-up scan is shown by incident MI status in Suppl. Table 10.

4.7 Limitations

This study has several limitations. Firstly, there is measurement error in the estimation of statin use duration. Because we relied upon recent use data from the medication inventory to model years of use continuously, we may have over- or underestimated the duration of statin use. In

clinical care settings, a large number of new statin users discontinue use within the first year.[66] This is also true in MESA, where approximately half of individuals prescribed statins discontinued use during follow-up (and may have restarted); however, we note that the results did not differ in an analysis using three duration of use categorizations (i.e. no use, <4 years of use, and ≥4 years of use; data not shown).Though it is difficult to classify duration of use, the medication inventory has been shown to be valid and reliable for current use (in comparison to directed recall)[20] and we used multiple sequential inventories to define duration. We were also able to categorize statin dose based on the recorded National Drug Codes (NDC), which included some doses and formulations of statins that are no longer used. We tested the sensitivity of this analysis to dose changes by considering the minimum and maximum statin dose observed, with no differences in results from the main analysis.

Loss to follow-up is a challenge to all longitudinal research. As shown in previous MESA analyses,[67] complete-case analyses using only participants who returned for follow-up exams may yield biased estimates if loss to follow-up was informative. Individuals who have the greatest cardiac changes may be more likely to have events and less likely to return for a second scan. Indeed, individuals with an incident infarction during the study who had follow-up demonstrated the greatest changes in cardiac indices. Loss to follow-up bias may mask an association between statins and cardiac structure. Re-weighting data by the inverse probability of censoring (IPCW)[68] and using multiple imputation for missing data on covariates did not produce a material difference in the results. This suggests that either the effect of loss to follow-up bias may be minimal or that the mechanism is dependent on unmeasured covariates. No observational study can confirm that participants missing data are similar to those with complete data without ascertainment of participants who are lost to follow-up. An additional limitation of

this study may be the incomplete consideration of time-varying factors. Statin use was quantified based on all clinical exams, though other covariates were considered only at baseline. Several important variables that changed during the study follow-up may have impacted results. These include weight changes,[18] use of antihypertensive agents,[69] and the occurrence of clinical events.

Lastly, findings are susceptible to indication[70] and healthy user biases.[71] Indication bias is not a major concern because we relied upon a new-user design and statins were not indicated for the primary prevention of heart failure during most of the observation period. Moreover, cardiac structure is not directly observable in routine clinical practice. Healthy user bias may have been mitigated in accounting for characteristics that could differ between statin users and non-users (i.e. exercise, health insurance, and other medication use); however, after accounting for predictors of cardiac structure and function, adjustment for these characteristics did not substantially impact the results. A set of analyses restricted to individuals who only reported positive evidence of statin use is provided in Suppl. Table 11.

Chapter 5. CONCLUSIONS

We found no strong associations between statin duration of use and long-term changes in indices of cardiac remodeling, regardless of age, sex, race, and other cardiovascular risk factors. These results contribute to the growing literature investigating statin pleiotropism. Importantly, results are consistent with previous literature suggesting that an effect on cardiac remodeling is not the main mechanism of statin benefit in primary prevention of HF. Future investigations may further investigate long-term statin associations, especially in young and healthy individuals who are at inherently lower CVD risk and may now be eligible for statin treatments.

BIBLIOGRAPHY

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation*. 2013;127(1):e6-e245. doi:10.1161/CIR.0b013e31828124ad.

2. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;128(16):e240-e327. doi:10.1161/CIR.0b013e31829e8776.

3. Wang J-Q, Wu G-R, Wang Z, Dai X-P, Li X-R. Long-term clinical outcomes of statin use for chronic heart failure: a meta-analysis of 15 prospective studies. *Heart Lung Circ*. 2014;23(2):105-113. doi:10.1016/j.hlc.2013.07.012.

4. Preiss D, Campbell RT, Murray HM, et al. The effect of statin therapy on heart failure events: a collaborative meta-analysis of unpublished data from major randomized trials. *Eur Heart J*. March 2015:ehv072. doi:10.1093/eurheartj/ehv072.

5. Davidson MH. Clinical Significance of Statin Pleiotropic Effects. *Circulation*. 2005;111(18):2280-2281. doi:10.1161/01.CIR.0000167560.93138.E7.

6. Michele Correale SA. Pleiotropic Effects of Statin in Therapy in Heart Failure: A Review. *Curr Vasc Pharmacol*. 2014;12(6). doi:10.2174/15701611129991411271615O8.

7. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. *J Am Coll Cardiol*. 2000;35(3):569-582. doi:10.1016/S0735-1097(99)00630-0.

8. Drazner MH. The Progression of Hypertensive Heart Disease. *Circulation*. 2011;123(3):327-334. doi:10.1161/CIRCULATIONAHA.108.845792.

9. Eng J, McClelland RL, Gomes AS, et al. Adverse Left Ventricular Remodeling and Age Assessed with Cardiac MR Imaging: The Multi-Ethnic Study of Atherosclerosis. *Radiology*. October 2015:150982. doi:10.1148/radiol.2015150982.

10. Vakili BA, Okin PM, Devereux RB. Prognostic implications of left ventricular hypertrophy. *Am Heart J*. 2001;141(3):334-341. doi:10.1067/mhj.2001.113218.

11. Warita S, Kawasaki M, Tanaka R, et al. Effects of pitavastatin on cardiac structure and function and on prevention of atrial fibrillation in elderly hypertensive patients: a prospective study of 2-years' follow-up. *Circ J Off J Jpn Circ Soc*. 2012;76(12):2755-2762.

12. Pan X-D, Zeng Z-H, Liang L-Y, et al. The Effects of Simvastatin on Left Ventricular Hypertrophy and Left Ventricular Function in Patients with Essential Hypertension. *Clin Exp Hypertens*. 2011;33(8):558-564. doi:10.3109/10641963.2011.577486.

13. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults A Report of the

American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 suppl 2):S1-S45. doi:10.1161/01.cir.0000437738.63853.7a.

14. Steinberg D. Earlier intervention in the management of hypercholesterolemia: what are we waiting for? *J Am Coll Cardiol*. 2010;56(8):627-629. doi:10.1016/j.jacc.2009.12.057.

15. Draft Recommendation Statement: Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: Preventive Medication - US Preventive Services Task Force. http://www.uspreventiveservicestaskforce.org/Page/Document/draft-recommendation-statement175/statin-use-in-adults-preventive-medication1. Accessed May 13, 2016.

16. Commissioner O of the. Consumer Updates - FDA Expands Advice on Statin Risks. http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm293330.htm. Accessed July 3, 2016.

17. Bluemke DA, Kronmal RA, Lima JAC, et al. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) study. *J Am Coll Cardiol*. 2008;52(25):2148-2155. doi:10.1016/j.jacc.2008.09.014.

18. Shah RV, Murthy VL, Abbasi SA, et al. Weight loss and progressive left ventricular remodelling: The Multi-Ethnic Study of Atherosclerosis (MESA). *Eur J Prev Cardiol*. July 2014:2047487314541731. doi:10.1177/2047487314541731.

19. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: Objectives and Design. *Am J Epidemiol*. 2002;156(9):871-881. doi:10.1093/aje/kwf113.

20. Psaty BM, Lee M, Savage PJ, Rutan GH, German PS, Lyles M. Assessing the use of medications in the elderly: methods and initial experience in the Cardiovascular Health Study. The Cardiovascular Health Study Collaborative Research Group. *J Clin Epidemiol*. 1992;45(6):683-692.

21. Natori S, Lai S, Finn JP, et al. Cardiovascular Function in Multi-Ethnic Study of Atherosclerosis: Normal Values by Age, Sex, and Ethnicity. *Am J Roentgenol*. 2006;186(6_supplement_2):S357-S365. doi:10.2214/AJR.04.1868.

22. Ray WA. Evaluating Medication Effects Outside of Clinical Trials: New-User Designs. *Am J Epidemiol*. 2003;158(9):915-920. doi:10.1093/aje/kwg231.

23. Brumback LC, Kronmal R, Heckbert SR, et al. Body size adjustments for left ventricular mass by cardiovascular magnetic resonance and their impact on left ventricular hypertrophy classification. *Int J Cardiovasc Imaging*. 2010;26(4):459-468. doi:10.1007/s10554-010-9584-5.

24. Venkatesh BA, Volpe GJ, Donekal S, et al. Association of Longitudinal Changes in Left Ventricular Structure and Function With Myocardial Fibrosis The Multi-Ethnic Study of Atherosclerosis Study. *Hypertension*. 2014;64(3):508-515. doi:10.1161/HYPERTENSIONAHA.114.03697.

25. Psaty BM, Delaney JA, Arnold AM, et al. The Study of Cardiovascular Health Outcomes in the Era of Claims Data: The Cardiovascular Health Study. *Circulation*. November 2015:CIRCULATIONAHA.115.018610. doi:10.1161/CIRCULATIONAHA.115.018610.

26. Heckbert SR, Post W, Pearson GDN, et al. Traditional cardiovascular risk factors in relation to left ventricular mass, volume, and systolic function by cardiac magnetic resonance imaging: The Multi-

Ethnic Study of Atherosclerosis. *J Am Coll Cardiol*. 2006;48(11):2285-2292. doi:10.1016/j.jacc.2006.03.072.

27. Gidding SS, Liu K, Colangelo LA, et al. Longitudinal Determinants of Left Ventricular Mass and Geometry The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Circ Cardiovasc Imaging*. 2013;6(5):769-775. doi:10.1161/CIRCIMAGING.112.000450.

28. Taylor F, Huffman MD, Macedo AF, et al. Statins for the primary prevention of cardiovascular disease. In: *Cochrane Database of Systematic Reviews*. John Wiley & Sons, Ltd; 2013. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD004816.pub5/abstract. Accessed February 20, 2016.

29. Jugdutt BI. Ventricular Remodeling After Infarction and the Extracellular Collagen Matrix When Is Enough Enough? *Circulation*. 2003;108(11):1395-1403. doi:10.1161/01.CIR.0000085658.98621.49.

30. Zhou Q, Liao JK. Pleiotropic effects of statins. - Basic research and clinical perspectives -. *Circ J Off J Jpn Circ Soc*. 2010;74(5):818-826.

31. Porter KE, Turner NA. Statins and myocardial remodelling: cell and molecular pathways. *Expert Rev Mol Med*. 2011;13. doi:10.1017/S1462399411001931.

32. Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. *Eur Heart J*. 2015;36(17):1012-1022. doi:10.1093/eurheartj/ehv043.

33. Rabkin SW. Lovastatin Induces Cell Death in Cardiomyocytes that Is Not Reversible by Coenzyme Q 10. *Pharmacol Toxicol*. 2002;90(6):343-345. doi:10.1034/j.1600-0773.2002.900609.x.

34. Demyanets S, Kaun C, Pfaffenberger S, et al. Hydroxymethylglutaryl-coenzyme A reductase inhibitors induce apoptosis in human cardiac myocytes in vitro. *Biochem Pharmacol*. 2006;71(9):1324-1330. doi:10.1016/j.bcp.2006.01.016.

35. Martin J, Denver R, Bailey M, Krum H. In Vitro Inhibitory Effects of Atorvastatin on Cardiac Fibroblasts: Implications for Ventricular Remodelling. *Clin Exp Pharmacol Physiol*. 2005;32(9):697-701. doi:10.1111/j.1440-1681.2005.04256.x.

36. Chen J, Mehta JL. Angiotensin II-mediated oxidative stress and procollagen-1 expression in cardiac fibroblasts: blockade by pravastatin and pioglitazone. *Am J Physiol - Heart Circ Physiol*. 2006;291(4):H1738-H1745. doi:10.1152/ajpheart.00341.2006.

37. Fertin M, Dubois E, Belliard A, Amouyel P, Pinet F, Bauters C. Usefulness of circulating biomarkers for the prediction of left ventricular remodeling after myocardial infarction. *Am J Cardiol*. 2012;110(2):277-283. doi:10.1016/j.amjcard.2012.02.069.

38. Luo JD, Zhang WW, Zhang GP, Guan JX, Chen X. Simvastatin inhibits cardiac hypertrophy and angiotensin-converting enzyme activity in rats with aortic stenosis. *Clin Exp Pharmacol Physiol*. 1999;26(11):903-908.

39. Patel R, Nagueh SF, Tsybouleva N, et al. Simvastatin induces regression of cardiac hypertrophy and fibrosis and improves cardiac function in a transgenic rabbit model of human hypertrophic cardiomyopathy. *Circulation*. 2001;104(3):317-324.

40. Bauersachs J, Galuppo P, Fraccarollo D, Christ M, Ertl G. Improvement of left ventricular remodeling and function by hydroxymethylglutaryl coenzyme a reductase inhibition with cerivastatin in rats with heart failure after myocardial infarction. *Circulation*. 2001;104(9):982-985.

41. Nahrendorf M, Hu K, Hiller K-H, et al. Impact of hydroxymethylglutaryl coenzyme a reductase inhibition on left ventricular remodeling after myocardial infarction: an experimental serial cardiac magnetic resonance imaging study. *J Am Coll Cardiol*. 2002;40(9):1695-1700.

42. Hayashidani S, Tsutsui H, Shiomi T, et al. Fluvastatin, a 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitor, attenuates left ventricular remodeling and failure after experimental myocardial infarction. *Circulation*. 2002;105(7):868-873.

43. Senthil V, Chen SN, Tsybouleva N, et al. Prevention of cardiac hypertrophy by atorvastatin in a transgenic rabbit model of human hypertrophic cardiomyopathy. *Circ Res*. 2005;97(3):285-292. doi:10.1161/01.RES.0000177090.07296.ac.

44. Takemoto M, Node K, Nakagami H, et al. Statins as antioxidant therapy for preventing cardiac myocyte hypertrophy. *J Clin Invest*. 2001;108(10):1429-1437.

45. Lee T-M, Lin M-S, Chou T-F, Tsai C-H, Chang N-C. Effect of pravastatin on development of left ventricular hypertrophy in spontaneously hypertensive rats. *Am J Physiol Heart Circ Physiol*. 2005;289(1):H220-H227. doi:10.1152/ajpheart.00417.2004.

46. Lee T-M, Lin M-S, Chou T-F, Chang N-C. Effect of simvastatin on left ventricular mass in hypercholesterolemic rabbits. *Am J Physiol - Heart Circ Physiol*. 2005;288(3):H1352-H1358. doi:10.1152/ajpheart.00527.2003.

47. Lee T-M, Chou T-F, Tsai C-H. Association of pravastatin and left ventricular mass in hypercholesterolemic patients: role of 8-iso-prostaglandin f2alpha formation. *J Cardiovasc Pharmacol*. 2002;40(6):868-874.

48. Chang S-A, Kim Y-J, Lee H-W, et al. Effect of rosuvastatin on cardiac remodeling, function, and progression to heart failure in hypertensive heart with established left ventricular hypertrophy. *Hypertension*. 2009;54(3):591-597. doi:10.1161/HYPERTENSIONAHA.109.131243.

49. Hiroaki Nishikawa SM. Statins induce the regression of left ventricular mass in patients with angina. *Circ J Off J Jpn Circ Soc*. 2004;68(2):121-125. doi:10.1253/circj.68.121.

50. Su S-F, Hsiao C-L, Chu C-W, Lee B-C, Lee T-M. Effects of pravastatin on left ventricular mass in patients with hyperlipidemia and essential hypertension. *Am J Cardiol*. 2000;86(5):514-518. doi:10.1016/S0002-9149(00)01004-3.

51. Node K, Fujita M, Kitakaze M, Hori M, Liao JK. Short-term statin therapy improves cardiac function and symptoms in patients with idiopathic dilated cardiomyopathy. *Circulation*. 2003;108(7):839-843. doi:10.1161/01.CIR.0000084539.58092.DE.

52. Bauersachs J, Störk S, Kung M, et al. HMG CoA reductase inhibition and left ventricular mass in hypertrophic cardiomyopathy: a randomized placebo-controlled pilot study. *Eur J Clin Invest*. 2007;37(11):852-859. doi:10.1111/j.1365-2362.2007.01877.x.

53. Bielecka-Dabrowa A, Goch JH, Mikhailidis DP, Rysz J, Maciejewski M, Banach M. The influence of atorvastatin on parameters of inflammation and function of the left ventricle in patients with dilated cardiomyopathy. *Med Sci Monit Int Med J Exp Clin Res*. 2009;15(12):MS12-MS23.

54. Bielecka-Dabrowa A, Mikhailidis DP, Rizzo M, von Haehling S, Rysz J, Banach M. The influence of atorvastatin on parameters of inflammation left ventricular function, hospitalizations and mortality in patients with dilated cardiomyopathy – 5-year follow-up. *Lipids Health Dis*. 2013;12:47. doi:10.1186/1476-511X-12-47.

55. Broch K, Askevold ET, Gjertsen E, et al. The effect of rosuvastatin on inflammation, matrix turnover and left ventricular remodeling in dilated cardiomyopathy: a randomized, controlled trial. *PloS One*. 2014;9(2):e89732. doi:10.1371/journal.pone.0089732.

56. Hersi AS, Giannoccaro P, Exner D, et al. 697 Statin induced regression of cardiomyopathy trial (SIRCAT): A randomized, placebo-controlled double-blind trial. *Can J Cardiol*. 2011;27(5):S318. doi:10.1016/j.cjca.2011.07.581.

57. van der Linde D, Yap SC, van Dijk APJ, et al. Effects of Rosuvastatin on Progression of Stenosis in Adult Patients With Congenital Aortic Stenosis (PROCAS Trial). *Am J Cardiol*. 2011;108(2):265-271. doi:10.1016/j.amjcard.2011.03.032.

58. Sola S, Mir MQS, Lerakis S, Tandon N, Khan BV. Atorvastatin improves left ventricular systolic function and serum markers of inflammation in nonischemic heart failure. *J Am Coll Cardiol*. 2006;47(2):332-337. doi:10.1016/j.jacc.2005.06.088.

59. Krum H, Ashton E, Reid C, et al. Double-blind, randomized, placebo-controlled study of high-dose HMG CoA reductase inhibitor therapy on ventricular remodeling, pro-inflammatory cytokines and neurohormonal parameters in patients with chronic systolic heart failure. *J Card Fail*. 2007;13(1):1-7. doi:10.1016/j.cardfail.2006.09.008.

60. Erbs S, Beck EB, Linke A, et al. High-dose rosuvastatin in chronic heart failure promotes vasculogenesis, corrects endothelial function, and improves cardiac remodeling--results from a randomized, double-blind, and placebo-controlled study. *Int J Cardiol*. 2011;146(1):56-63. doi:10.1016/j.ijcard.2010.02.019.

61. Anderssen SA, Hjelstuen AK, Hjermann I, Bjerkan K, Holme I. Fluvastatin and lifestyle modification for reduction of carotid intima-media thickness and left ventricular mass progression in drug-treated hypertensives. *Atherosclerosis*. 2005;178(2):387-397. doi:10.1016/j.atherosclerosis.2004.08.033.

62. Teixeira AA, Buffani A, Tavares A, et al. Effects of fluvastatin on insulin resistance and cardiac morphology in hypertensive patients. *J Hum Hypertens*. 2011;25(8):492-499. doi:10.1038/jhh.2010.87.

63. Folkeringa RJ, de Vos C, Pinto YM, et al. No effect of rosuvastatin on left ventricular hypertrophy in patients with hypertension: a prospective randomised open-label study with blinded endpoint assessment. *Int J Cardiol*. 2010;145(1):156-158. doi:10.1016/j.ijcard.2009.07.023.

64. Godlee F. Adverse effects of statins. *BMJ*. 2014;348:g3306. doi:10.1136/bmj.g3306.

65. Tousoulis D, Psarros C, Demosthenous M, Patel R, Antoniades C, Stefanadis C. Innate and adaptive inflammation as a therapeutic target in vascular disease: the emerging role of statins. *J Am Coll Cardiol*. 2014;63(23):2491-2502. doi:10.1016/j.jacc.2014.01.054.

66. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of Statins in Routine Care SettingsA Cohort Study. *Ann Intern Med*. 2013;158(7):526-534. doi:10.7326/0003-4819-158-7-201304020-00004.

67. Delaney JAC, Oddson BE, McClelland RL, Psaty BM. Estimating ethnic differences in self-reported new use of antidepressant medications: results from the Multi-Ethnic Study of Atherosclerosis. *Pharmacoepidemiol Drug Saf*. 2009;18(7):545-553. doi:10.1002/pds.1751.

68. Robins JM, Finkelstein DM. Correcting for noncompliance and dependent censoring in an AIDS Clinical Trial with inverse probability of censoring weighted (IPCW) log-rank tests. *Biometrics*. 2000;56(3):779-788.

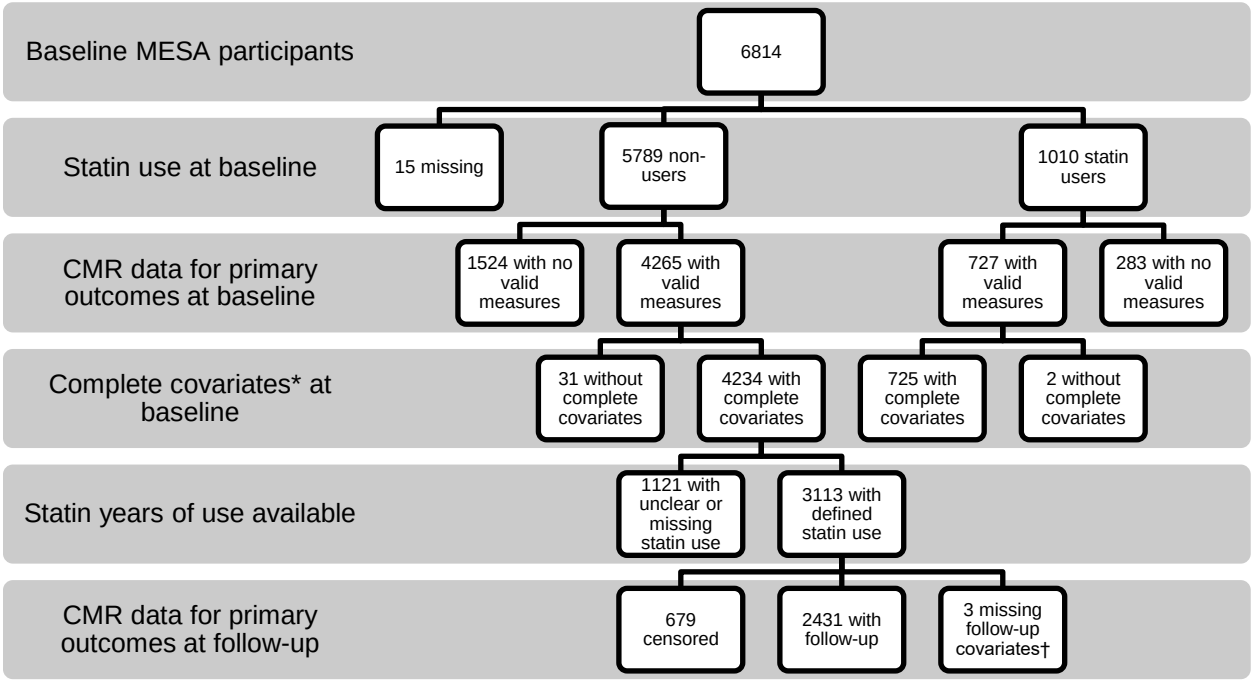
69. Fagard RH, Celis H, Thijs L, Wouters S. Regression of Left Ventricular Mass by Antihypertensive Treatment A Meta-Analysis of Randomized Comparative Studies. *Hypertension*. 2009;54(5):1084-1091. doi:10.1161/HYPERTENSIONAHA.109.136655.

70. Psaty BM, Siscovick DS. Minimizing bias due to confounding by indication in comparative effectiveness research: the importance of restriction. *JAMA*. 2010;304(8):897-898. doi:10.1001/jama.2010.1205.

71. Brookhart MA, Patrick AR, Dormuth C, et al. Adherence to lipid-lowering therapy and the use of preventive health services: an investigation of the healthy user effect. *Am J Epidemiol*. 2007;166(3):348-354. doi:10.1093/aje/kwm070.

TABLES & FIGURES

Figure 1. Study flow for MESA participants



*Covariates include age, gender, race, smoking status, BMI, diabetes status, hypertension status, waist circumference, blood pressure, HDL cholesterol, triglycerides, and total cholesterol, intentional exercise, and health insurance at baseline and MI during the study period.
† 3 participants were missing follow-up data on height and weight and so it was not possible to index the follow-up left ventricular mass.
Abbreviations: CMR = Cardiac magnetic resonance (imaging); MESA = Multi-Ethnic Study of Atherosclerosis

Table 1. Baseline characteristics of participants who were never users of statins and who had new statin use

	Never users of statin	**New statin users**		
Characteristic		**<4 years**	**≥4 years**	**Unclear or missing**
	N=1559	N=475	N=397	N=1121
Age (years)	58.2 (9.5)	60.0 (8.7)	61.6 (8.9)	63.6 (11.1)
Race, n (%)				
White	620 (39.8)	193 (40.6)	184 (46.4)	376 (33.5)
Chinese	223 (14.3)	55 (11.6)	43 (10.8)	165 (14.7)
Black	392 (25.1)	124 (26.1)	87 (21.9)	303 (27.9)
Hispanic	324 (20.8)	103 (21.7)	83 (20.9)	277 (24.7)
Gender, n (%)				
Female	827 (53.1)	246 (51.8)	206 (51.9)	552 (49.2)
Male	732 (46.9)	229 (48.2)	191 (48.11)	569 (50.8)
Smoking status, n (%)				
Never	840 (53.9)	270 (56.8)	183 (46.1)	560 (50.0)
Former	529 (33.9)	154 (32.4)	171 (43.1)	390 (34.8)
Current	190 (12.2)	51 (10.7)	43 (10.8)	171 (15.3)
BMI (kg/m^2)	27.3 (5.0)	28.5 (4.8)	27.9 (4.8)	27.4 (4.9)
Waist circumference (cm)	94.6 (13.6)	98.1 (12.2)	97.3 (13.2)	96.3 (13.2)
Diabetes (2003 ADA Fasting Criteria), n (%)				
Normal	1330 (85.3)	358 (75.3)	280 (70.5)	832 (74.2)
IFG	168 (10.8)	66 (13.9)	47 (11.8)	153 (13.7)
Untreated diabetes	17 (1.1)	15 (3.2)	16 (4.0)	38 (3.4)
Treated diabetes	44 (2.8)	36 (7.6)	54 (13.6)	98 (8.7)
Hypertension (JNC VI Criteria), n (%)				
Normal	1074 (68.9)	244 (51.4)	175 (44.1)	611 (54.5)
Untreated	142 (9.1)	42 (8.8)	60 (15.1)	143 (12.8)
Treated	343 (22.0)	189 (39.8)	162 (40.8)	367 (32.7)

Antihypertensive use				
Diuretic	112 (7.2)	69 (14.5)	55 (13.8)	129 (11.5)
Calcium channel blocker	118 (7.6)	68 (14.3)	46 (11.6)	117 (10.4)
Beta-blockers (no diuretic)	90 (5.8)	40 (8.4)	36 (9.1)	78 (7.0)
ACE inhibitors (no diuretic)	85 (5.5)	52 (11.0)	88 (15.3)	113 (10.1)
Angiotensin type 2 antagonists	26 (1.7)	11 (2.3)	21 (5.3)	26 (2.3)
SBP (mmHg)	120.6 (20.3)	125.4 (18.2)	127.9 (19.6)	127.4 (22.8)
DBP (mmHg)	71.3 (10.4)	72.7 (9.9)	73.1 (10.3)	72.0 (10.5)
Cholesterol Level				
HDL (mg/dl)	52.5 (16.0)	48.8 (13.3)	50.3 (14.3)	51.2 (15.4)
Triglycerides (mg/dl)	116.1 (64.2)	145.2 (89.5)	148.0 (80.2)	125.9 (79.7)
Total (mg/dl)	188.2 (31.2)	207.3 (37.4)	216.1 (33.2)	192.1 (35.1)
Moderate and vigorous physical activity total in met-min/wk)	6126 (5820)	6313 (6654)	6496 (7575)	5501 (5787)
Health Insurance, n (%)				
Insurance	1428 (91.6)	437 (92.0)	366 (92.2)	953 (85.0)
None	131 (8.4)	38 (8.0)	31 (7.8)	168 (15.0)
Agatston Calcium Score	55.6 (201.6)	110.7 (323.3)	154.1 (359.7)	162.9 (436.5)
CMR Indices				
LVM (g)	118.9 (28.1)	122.7 (28.6)	122.0 (29.4)	121.0 (30.8)
LVMI*	85.62 (12.98)	86.10 (13.41)	87.04 (14.65)	87.90 (15.74)
LVM-BSA indexed (g/m^2)	63.80 (10.86)	64.83 (11.60)	65.17 (12.18)	65.84 (12.96)
LVEDV (mL)	131.39 (28.84)	129.51 (28.88)	129.63 (27.65)	127.26 (32.64)
MVR (g/mL)	0.92 (0.16)	0.96 (0.18)	0.95 (0.17)	0.97 (0.20)
LVEF (%)	62.45 (5.62)	62.73 (5.79)	62.86 (6.10)	61.89 (6.65)

All values are mean (SD) unless otherwise indicated. Among new statin users and never users, the number of participants evaluated for baseline covariates were based on those with complete covariates and follow-up CMR scan. Unclear or missing statin users were characterized by at least one missing report of statin use at a clinical exam and no other reported statin use at other exams.

* LVM is indexed by height, weight, and gender and multiplied by 100 using methods defined in the MESA cohort; an individual's LVMI of 125 suggests that LVM is 25% greater than height, weight, and gender would predict.

Abbreviations: ADA = American Diabetes Association; BMI = Body mass index; BSA = Body surface area; CMR = Cardiac magnetic resonance; HDL = High-density lipoprotein; IFG = Impaired fasting glucose; JNC = Joint National Committee; LDL = Low-density lipoprotein; LVEDV = Left ventricular end diastolic volume; LVEF = Left ventricular ejection fraction; LVM = Left ventricular mass; LVMI = Left ventricular mass index (defined as the percentage predicted by height, weight, and gender); MVR = Mass to volume ratio; SD = Standard deviation

Table 2. Distribution of statin doses among 872 new users of statins

	New statin users		
	<4 years	**≥4 years**	**Overall**
Dose	N=475	N=397	N=872
Low dose statin	84 (17.68)	36 (9.07)	120 (13.76)
Moderate dose statin	349 (73.47)	317 (79.85)	666 (76.38)
High dose statin	42 (8.84)	44 (11.08)	86 (9.86)

All values are n (%). Statin dose was defined according to the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.

Table 3. Unadjusted change over 10 years in cardiac magnetic resonance indices of left ventricular structure and function and incident MI, among participants who were never users of statins and who were new statin users

	Never users of statin	**New statin users**	
		<4 years	**≥4 years**
	N = 1559	N=475	N=397
Time between CMR (years)	9.48 (0.53)	9.50 (0.50)	9.46 (0.48)
Height (cm)	-1.47 (1.39)	-1.52 (1.27)	-1.60 (1.47)
Weight (lbs)	-1.73 (14.76)	-1.16 (15.73)	-0.86 (14.58)
Δ LVMI, %	2.57 (12.74)	2.43 (12.96)	2.04 (15.83)
Δ LVM-BSA indexed	2.12 (9.43)	2.04 (9.86)	1.75 (11.69)
Δ LVM (unindexed)	2.99 (17.87)	3.03 (19.54)	2.39 (21.68)
Δ LVEDV, ml	11.13 (21.52)	9.34 (24.02)	12.17 (23.86)
Δ MVR (unindexed)	0.11 (0.20)	0.11 (0.22)	0.13 (0.23)
Δ LVEF, %	-0.74 (7.18)	-0.82 (8.18)	-0.60 (7.85)
Incident MI, N (%)	5 (0.32)	15 (3.16)	22 (5.54)

All values are mean (SD) unless otherwise indicated. All CMR indices are unadjusted.
Abbreviations: BSA = Body surface area; CMR = Cardiac magnetic resonance; LVEDV = Left ventricular end diastolic volume; LVEF = Left ventricular ejection fraction; LVM = Left ventricular mass; LVMI = Left ventricular mass index (defined as the percentage predicted by height, weight, and gender); MI = Myocardial infarction; MVR = Mass to volume ratio; SD = Standard deviation

Table 4. Adjusted mean 10-year change in cardiac magnetic resonance indices of left ventricular structure and function for never users and new statin users by dose of statins, among 2389 participants without an incident MI

Dose	N	Estimate	95%CI	p-value
Δ LVMI¥ (percent predicted by height, weight, and gender)				
Never users	1554	-11.56	(-19.23, -3.89)	0.003
Low dose	118	-12.36	(-20.50, -4.21	0.003
Moderate dose	640	-13.20*	(-21.11, -5.29)	0.001
High dose	77	-14.44	(-22.72, -6.16)	0.001
Δ MVR (no units)				
Never users	1554	-0.154	(-0.278, -0.029)	0.016
Low dose	118	-0.185	(-0.318, -0.053)	0.006
Moderate dose	640	-0.166	(-0.295, -0.037)	0.011
High dose	77	-0.196	(-0.331,-0.062)	0.004
Δ LVM Unindexed¥ (grams)				
Never users	1554	1.39	(-9.40,12.19)	0.800
Low dose	118	1.57	(-9.90, 13.04)	0.788
Moderate dose	640	0.14	(-11.00, 11.28)	0.980
High dose	77	0.64	(-11.01, 12.30)	0.914
Δ LVM-BSA Adjusted (grams/BSA)				
Never users	1554	-5.99	(-11.67, -0.31)	0.039
Low dose	118	-6.35	(-12.39, -0.32)	0.039
Moderate dose	640	-7.11*	(-12.97, -1.25)	0.017
High dose	77	-7.64	(-13.78, -1.51)	0.015
Δ EDV (mL)				
Never users	1554	-11.98	(-25.05, 1.10)	0.073
Low dose	118	-14.97	(-28.86, -1.08)	0.035
Moderate dose	640	-12.58	(-26.07, 0.91)	0.068
High dose	77	-14.31	(-28.42, -0.19)	0.047
Δ LVEF† (percent)				
Never users	1553	1.17	(-3.22, 5.57)	0.60
Low dose	118	2.28	(-2.39, 6.94)	0.34
Moderate dose	640	1.50	(-3.03, 6.03)	0.52
High dose	77	-0.81*	(-5.55, 3.93)	0.74

Estimates are from the main (complete case) that exclude 42 individuals with an incident MI. Models used indicator variables for dose and were adjusted for the following at baseline: age, gender, race, smoking status (former, never, current), BMI, diabetes status (normal, impaired fasting glucose, untreated diabetes, treated diabetes), waist circumference, antihypertensive agent use (yes/no for diuretics, calcium channel blockers, beta-blockers, ace-inhibitors, and angiotensin type 2 antagonists), systolic and diastolic blood pressure, HDL cholesterol, triglycerides, total

cholesterol, intentional exercise defined as moderate and vigorous physical activity total (met-min per week), health insurance status (yes/no), and the Agatston CAC Score as the ln(score + 1).

* $p<0.05$ for the change relative to never users of statins.

† One participant was missing LVEF change, thus the analysis consisted of 2388 participants.

¥ LVM and LVMI are in opposite directions due to changes in height/weight among participants between exams 1 and 5. We used current height and weight to index LVM, and not baseline.

Abbreviations: CI = Confidence interval; LVEF = Left ventricular ejection fraction; LVEDV = Left ventricular end diastolic volume; LVM-BSA = Left ventricular mass that is indexed by body surface area; LVMI = Left ventricular mass index; MVR = Mass-to-volume ratio

Table 5. Adjusted difference in 10-year change in primary outcomes for each additional year of new statin use, among those without an incident MI, among 2389 participants without an incident MI

	Estimate	**95%CI**	**p-value**
Δ LVMI (percent predicted by height, weight, and gender)			
Model I	-0.10	(-0.37,0.17)	0.46
Model II	-0.13	(-0.40,0.14)	0.35
Model III	-0.21	(-0.48,0.06)	0.13
Model IV	-0.30	(-0.59,-0.02)	0.04
Model V	-0.30	(-0.59,-0.02)	0.04
Model VI	-0.30	(-0.59,-0.02)	0.04
Δ MVR (no units)			
Model I	0.00	(-0.00,0.01)	0.33
Model II	0.00	(-0.00,0.01)	0.48
Model III	0.00	(-0.00,0.00)	0.92
Model IV	0.00	(-0.01,0.00)	0.42
Model V	0.00	(-0.01,0.00)	0.42
Model VI	0.00	(-0.01,0.00)	0.42

Estimates are from the main (complete case) analysis that excluded 42 individuals with incident MI. Model I is unadjusted. Model II-VI are adjusted for age, gender, and race. Models III-VI additionally included adjustment for traditional cardiovascular risk factors (smoking status [former, never, current], BMI, diabetes status [normal, impaired fasting glucose, untreated diabetes, treated diabetes], waist circumference, antihypertensive agent use [yes/no for diuretics, calcium channel blockers, beta-blockers, ace-inhibitors, and angiotensin type 2 antagonists], and systolic and diastolic blood pressure, and HDL cholesterol). Models IV-VI additionally included adjustment for triglycerides, total cholesterol, Models V and VI additionally included adjustment for intentional exercise defined as moderate and vigorous physical activity total (met-min per week) and health insurance status (yes/no). The final model VI additionally included adjustment for the Agatston CAC Score as the ln(score + 1).

Abbreviations: CAC = Coronary artery calcium; CI = Confidence interval; IPCW = Inverse probability of censoring weighted

SUPPLEMENTARY MATERIALS

Methods
At baseline, potential participants were excluded from the MESA cohort if they had a history of prior MI, stroke, or transient ischemic attack (TIA), angina, HF, current atrial fibrillation, and/or a history of any cardiovascular procedure.

Results
Statin formulations used during the study are shown by dose in Suppl. Table 2.

Suppl. Table 7 provides a summary of the previous literature informing the assessment of left ventricular mass in hypertensive and hypercholesterolemic populations similar to that in this study.

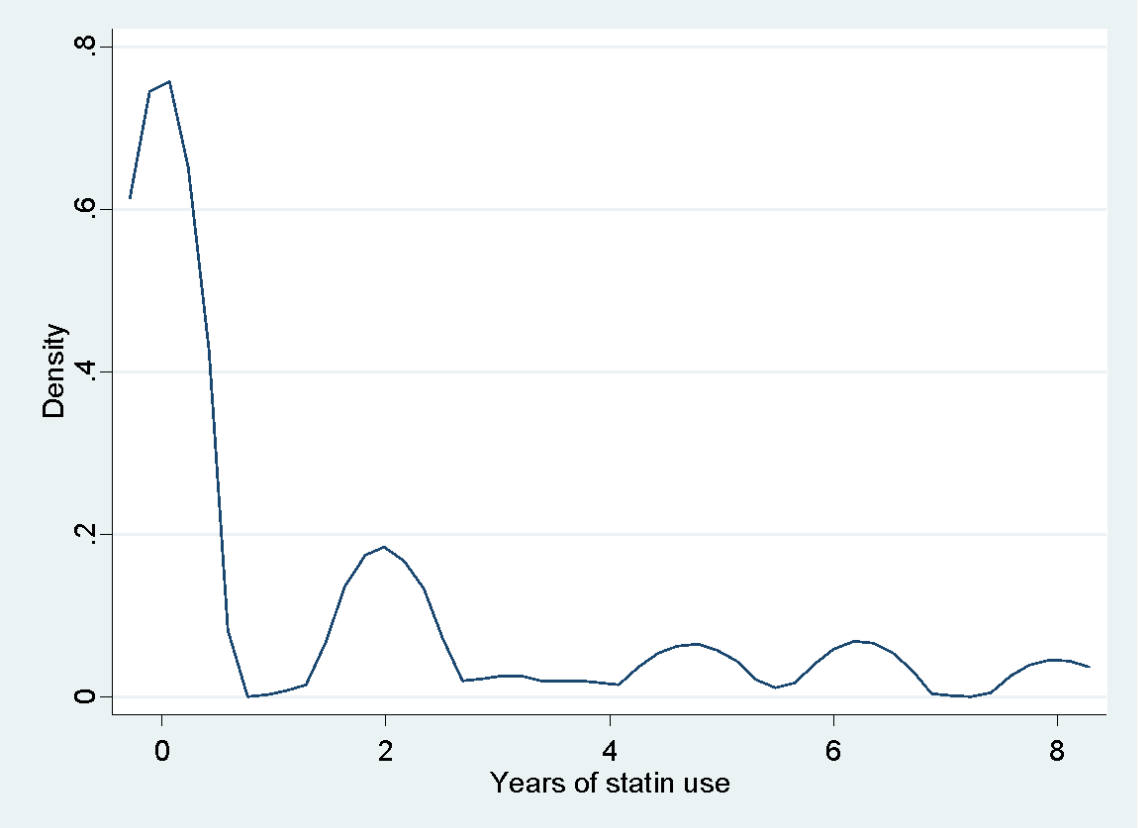
Suppl. Figure 2 depicts the 10-year change in left ventricular mass index, among the 42 individuals with an incident myocardial infarction who also had a follow-up CMR. The subset of participants with incident MI during the study who returned for a second CMR had an average 10-year increase in LVM of 7.8 g (SD 23.6). Among the 42 participants with MIs, 11 (26%) were taking statins at exams prior to MI, 5 (12%) did not report statin use at exams either before or after MI, and 26 (62%) had unclear timing of statin use in relation to the MI. Among the 42 participants with an MI, each additional year of statin use was associated with approximately two fewer units of progression in LVMI (-1.97, 95%CI: -3.44, -0.49, p=0.01; model adjusted for age, sex, race only; Suppl. Table 9); however, results from this highly selected sample must be interpreted with caution.

A descriptive account of fibrosis at follow-up scan is shown by incident infarction status in Suppl. Table 10.

An assessment of the effect of cumulative years of statin use on cardiac structure and function may be most relevant among those who use statins due to the potential for healthy user and other biases. Thus, a set of analyses restricted to individuals who only reported positive evidence of statin use is provided in Suppl. Table 11. This analysis may better account for residual confounding by fundamental differences in statin users and non-users, though these results were not meaningfully different from the main analysis.

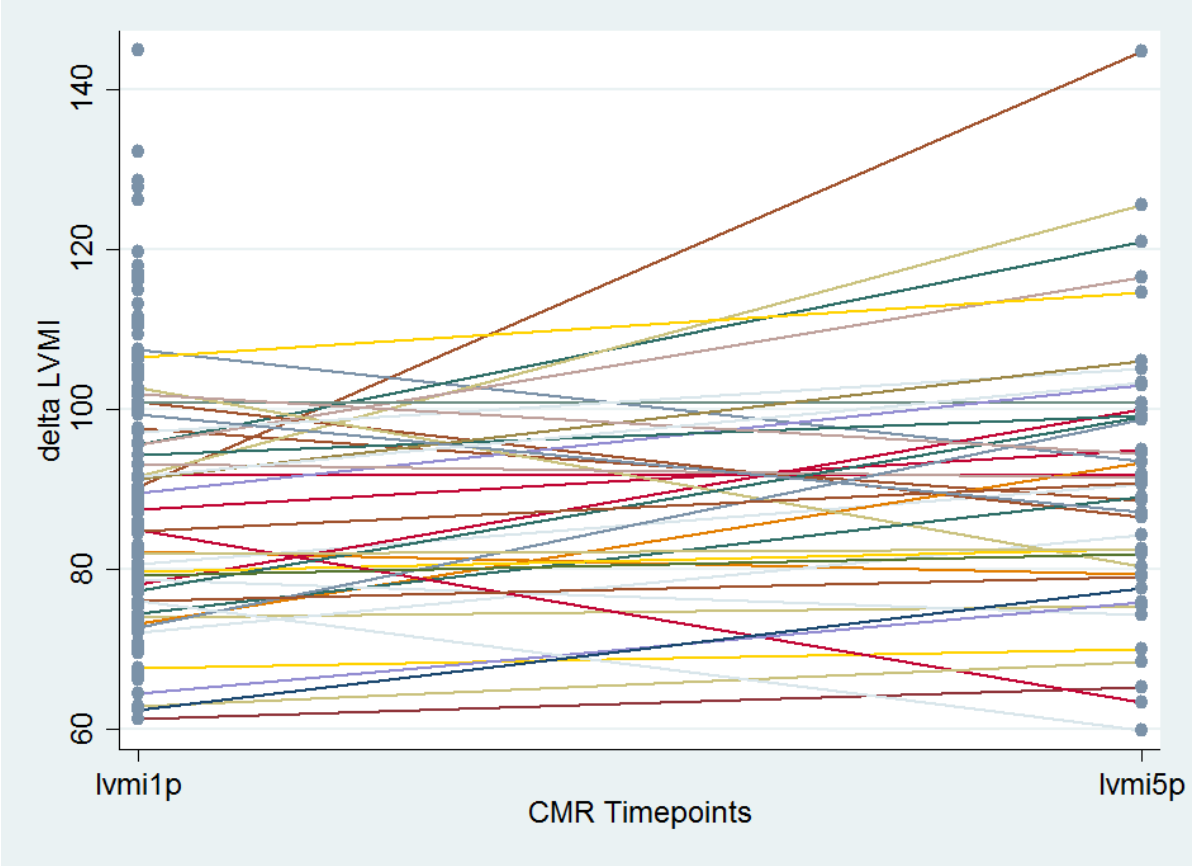
Figures & Tables

Suppl. Figure 1. Smoothed distribution of years of new statin use among MESA participants with no statin use at baseline



Statin use was estimated from positive reports at each of five MESA clinical exams. Cumulative years of statin use was defined as the sum of half of the preceding and subsequent exam intervals at each positive exam. When participants did not attend exams 3 or 4, it was assumed the participant was taking a statin at the missed exam if statins were recorded at the exam prior to and at the exam after the missed visit. Similarly, it was assumed the participant was not taking a statin at the missed exam if no statins were recorded at the exam prior to and at the exam after the missed visit. The mean number of years of statin use was 1.4 years (range 0 – 8; N=2431). Abbreviations: MESA = Multi-Ethnic Study of Atherosclerosis

Suppl. Figure 2. Ten year change in left ventricular mass index, among those with incident myocardial infarction



There were 42 MIs in total among those with follow-up CMR scan and valid years of statin exposure. The median time between scans was 9.4 years. The timing of statin use in relation to incident MI is not considered here.
Abbreviations: MESA = Multi-Ethnic Study of Atherosclerosis

Suppl. Table 1. Distribution of statin doses among 872 new users of statins

	New statin users		
	<4 years	**≥4 years**	**Overall**
Minimum statin dose during follow-up			
Low dose statin	91 (19.16)	94 (23.68)	185 (21.22)
Moderate dose statin	347 (73.05)	290 (73.05)	637 (73.05)
High dose statin	37 (7.79)	13 (3.27)	50 (5.73)
Maximum statin dose during follow-up			
Low dose statin	83 (17.47)	22 (5.54)	105 (12.04)
Moderate dose statin	344 (72.42)	290 (73.05)	634 (72.71)
High dose statin	48 (10.11)	85 (21.41)	133 (15.25)

Statin dose was defined according to the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. Values (SD) are minimum and maximum statin dose during follow-up.
Abbreviations: MESA = Multi-Ethnic Study of Atherosclerosis

Suppl. Table 2. Statin formulations used by MESA participants, 2000-2011 (doses are for the statin component of combinations)

Low dose statins	**Moderate dose statins**	**High dose statins**
Cerivastatin 0.2 mg*	Amlodipine & atorvastatin 10-20 mg	Amlodipine & atorvastatin 40-80 mg
Ezetimibe & simvastatin 10 mg	Atorvastatin 10-20 mg	Atorvastatin 40-80 mg
Fluvastatin 20-40 mg	Cerivastatin 0.3-0.4 mg*	Ezetimibe & simvastatin 80 mg
Lovastatin 10-20 mg (including XR)	Ezetimibe & simvastatin 20-40 mg	Lovastatin 60 mg (including XR)
Niacin & lovastatin 20 mg	Niacin & simvastatin 20 mg	Rosuvastatin 20-40 mg
Pravastatin 10-20 mg	Fluvastatin 80 mg	Simvastatin 80 mg
Simvastatin 5*-10 mg	Lovastatin 40 mg (including XR)	
	Pravastatin 40-80 mg	
	Rosuvastatin 5-10 mg	
	Simvastatin 20-40 mg	

*Removed from the US market in 2001.
Note: Groupings are based on the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults.
Abbreviations: XR = Extended release

Suppl. Table 3. Difference in 10-year change in left ventricular mass index and mass-to-volume ratio for the minimum and maximum statin dose relative to no statin, among those without an incident myocardial infarction (sensitivity analysis)

Model		**Min Statin Dose (N=2389)**				**Max Statin Dose (N=2389)**			
	Dose	**N**	**Est.**	**95%CI**	**p-value**	**N**	**Est.**	**95%CI**	**p-value**
Δ LVMI									
II. Model I† & age, gender, race	No statins	1554	--	--	--	1554	--	--	--
	Low dose	179	0.95	(-1.40,3.29)	0.43	103	-0.44	(-3.27,2.39)	0.76
	Moderate dose	612	-1.09	(-2.33,0.15)	0.08	612	-0.55	(-1.81,0.70)	0.39
	High dose	44	-0.6	(-4.82,3.63)	0.78	120	-1.18	(-3.87,1.51)	0.39
IV. Model III & lipid levels‡	No statins	1554	--	--	--	1554			
	Low dose	179	0.15	(-2.25,2.56)	0.9	103	-1.02	(-3.91,1.86)	0.49
	Moderate dose	612	-2.09	(-3.37,-0.81)	<0.01	612	-1.54	(-2.85,-0.24)	0.02
	High dose	44	-2.16	(-6.37,2.04)	0.31	120	-2.61	(-5.35,0.13)	0.06
VI. Fully Adjusted¥	No statins	1554	--	--	--	1554	--	--	--
	Low dose	179	0.13	(-2.29,2.55)	0.92	103	-1.02	(-3.91,1.87)	0.49
	Moderate dose	612	-2.09	(-3.38,-0.80)	<0.01	612	-1.55	(-2.86,-0.23)	0.02
	High dose	44	-2.14	(-6.37,2.09)	0.32	120	-2.63	(-5.39,0.14)	0.06
Δ MVR									
II. Model I† & age, gender, race	No statins	1554	--	--	--	1554	--	--	--
	Low dose	179	0.00	(-0.04,0.03)	0.88	103	-0.02	(-0.06,0.03)	0.41
	Moderate dose	612	0.00	(-0.02,0.02)	0.72	612	0.00	(-0.02,0.02)	0.72
	High dose	44	-0.04	(-0.11,0.02)	0.20	120	0.00	(-0.04,0.03)	0.83
IV. Model III & lipid levels‡	No statins	1554	--	--	--	1554	--	--	--
	Low dose	179	-0.02	(-0.05,0.02)	0.35	103	-0.03	(-0.08,0.01)	0.19
	Moderate dose	612	-0.01	(-0.04,0.01)	0.21	612	-0.01	(-0.04,0.01)	0.24
	High dose	44	-0.07	(-0.14,-0.00)	0.04	120	-0.03	(-0.07,0.01)	0.17
VI. Fully Adjusted¥	No statins	1554	--	--	--	1554	--	--	--

	Low dose	179	-0.02	(-0.05,0.02)	0.34	103	-0.03	(-0.08,0.01)	0.19
	Moderate dose	612	-0.01	(-0.04,0.01)	0.21	612	-0.01	(-0.04,0.01)	0.24
	High dose	44	-0.07	(-0.14,-0.00)	0.05	120	-0.03	(-0.07,0.01)	0.18

These sensitivity analyses are based on the minimum statin dose reported and the maximum statin dose reported among new users during the study period.

† Model I is unadjusted. ‡ At baseline: Smoking status (former, never, current), BMI (kg/m^2), diabetes status (normal, impaired fasting glucose, untreated diabetes, treated diabetes), hypertension status (normal, untreated hypertension, treated hypertension), waist circumference (cm), systolic and diastolic blood pressure (mmHg), HDL cholesterol (mg/dl), triglycerides (mg/dl), and total cholesterol (mg/dl).

¥ At baseline: Age, gender, race, smoking status (former, never, current), BMI (kg/m^2), diabetes status (normal, impaired fasting glucose, untreated diabetes, treated diabetes), waist circumference (cm), antihypertensive agent use (yes/no for diuretics, calcium channel blockers, beta-blockers, ace-inhibitors, and angiotensin type 2 antagonists), systolic and diastolic blood pressure (mmHg), HDL cholesterol (mg/dl), triglycerides (mg/dl), total cholesterol (mg/dl), intentional exercise defined as moderate and vigorous physical activity total (met-min per week), no health insurance, and log-transformed CAC Score.

Abbreviations: CI = Confidence interval; LVEF = Left ventricular ejection fraction; LVEDV = Left ventricular end diastolic volume; LVM-BSA = Left ventricular mass that is indexed by body surface area; LVMI = Left ventricular mass index; MI = Myocardial infarction; MVR = Mass-to-volume ratio

Suppl. Table 4. Difference in 10-year change in in left ventricular mass index and mass-to-volume ratio with duration and dose of statin interaction, among those without an incident myocardial infarction

Model	**Mean Statin Dose (N=2389)**			
	Dose	**Estimate**	**95%CI**	**P-value**
Δ LVMI				
II. Model I† & age, gender, race	No statins	--	--	--
	Low dose	-0.85	(-6.62, 4.92)	0.77
	Moderate dose	-0.44	(-2.62, 1.73)	0.69
	High dose	-0.32	(-6.76, 6.12)	0.92
	Statin Exposure Years	-0.32	(-1.64, 1.00)	0.64
	Low*years	0.51	(-1.66, 2.69)	0.64
	Mod*years	0.28	(-1.13, 1.70)	0.69
	High*years	Omitted	Omitted	Omitted
IV. Model III & lipid levels‡	No statins	--	--	--
	Low dose	-1.13	(-6.95, 4.69)	0.70
	Moderate dose	-1.25	(-3.43, 0.92)	0.26
	High dose	-2.71	(-8.85, 3.43)	0.39
	Statin Exposure Years	-0.05	(-1.24, 1.15)	0.94
	Low*years	0.15	(-1.98, 2.28)	0.89
	Mod*years	-0.05	(-1.33, 1.24)	0.94
	High*years	Omitted	Omitted	Omitted
VI. Fully Adjusted¥	No statins	--	--	--
	Low dose	-1.17	(-7.00, 4.65)	0.69
	Moderate dose	-1.25	(-3.42, 0.93)	0.26
	High dose	-2.68	(-8.83, 3.47)	0.39
	Statin Exposure Years	-0.05	(-1.24, 1.14)	0.93
	Low*years	0.16	(-1.97, 2.30)	0.88
	Mod*years	-0.05	(-1.34, 1.24)	0.94
	High*years	Omitted	Omitted	Omitted
Δ MVR				
II. Model I† & age, gender, race	No statins	--	--	--
	Low dose	0.00	(-0.08, 0.09)	0.93
	Moderate dose	-0.02	(-0.06, 0.02)	0.31

	High dose	-0.03	(-0.13, 0.07)	0.60
	Statin Exposure Years	0.00	(-0.02, 0.02)	0.91
	Low*years	-0.01	(-0.04, 0.02)	0.58
	Mod*years	0.01	(-0.02, 0.03)	0.67
	High*years	Omitted	Omitted	Omitted
IV. Model III & lipid levels‡	No statins	--	--	--
	Low dose	0.00	(-0.08, 0.08)	0.98
	Moderate dose	-0.03	(-0.07, 0.01)	0.14
	High dose	-0.06	(-0.16, 0.04)	0.24
	Statin Exposure Years	0.00	(-0.02, 0.03)	0.71
	Low*years	-0.01	(-0.04, 0.01)	0.34
	Mod*years	0.00	(-0.02, 0.02)	0.96
	High*years	Omitted	Omitted	Omitted
VI. Fully Adjusted¥	No statins	--	--	--
	Low dose	0.00	(-0.08, 0.09)	0.97
	Moderate dose	-0.03	(-0.07, 0.01)	0.14
	High dose	-0.06	(-0.16, 0.04)	0.24
	Statin Exposure Years	0.00	(-0.02, 0.03)	0.72
	Low*years	-0.01	(-0.04, 0.01)	0.33
	Mod*years	0.00	(-0.02, 0.02)	0.96
	High*years	Omitted	Omitted	Omitted

* Values are 10^{-3}

† Model I is unadjusted. ‡ At baseline: Smoking status (former, never, current), BMI (kg/m^2), diabetes status (normal, impaired fasting glucose, untreated diabetes, treated diabetes), hypertension status (normal, untreated hypertension, treated hypertension), waist circumference (cm), systolic and diastolic blood pressure (mmHg), HDL cholesterol (mg/dl), triglycerides (mg/dl), and total cholesterol (mg/dl).

¥ At baseline: Age, gender, race, smoking status (former, never, current), BMI (kg/m^2), diabetes status (normal, impaired fasting glucose, untreated diabetes, treated diabetes), waist circumference (cm), antihypertensive agent use (yes/no for diuretics, calcium channel blockers, beta-blockers, ace-inhibitors, and angiotensin type 2 antagonists), systolic and diastolic blood pressure (mmHg), HDL cholesterol (mg/dl), triglycerides (mg/dl), total cholesterol (mg/dl), intentional exercise defined as moderate and vigorous physical activity total (met-min per week), no health insurance, and log-transformed CAC Score.

Abbreviations: CI = Confidence interval; LVEF = Left ventricular ejection fraction; LVEDV = Left ventricular end diastolic volume; LVM-BSA = Left ventricular mass that is indexed by body surface area; LVMI = Left ventricular mass index; MI = Myocardial infarction; MVR = Mass-to-volume ratio

Suppl. Table 5. Difference in 10-year change in cardiac indices of left ventricular structure and function for statin dose relative to no statin, among those without an incident myocardial infarction

Model	**Statin Dose (N=2389)**				
	Dose	**N**	**Estimate**	**95%CI**	**p-value**
Δ LVMI					
II. Model I† & age, gender, race	No statins	1554	--	--	--
	Low dose	118	-0.21	(-2.85,2.43)	0.88
	Moderate dose	640	-0.58	(-1.84,0.68)	0.37
	High dose	77	-1.69	(-4.82,1.44)	0.29
IV. Model III & lipid levels‡	No statins	1554	--	--	--
	Low dose	118	-0.8	(-3.50,1.90)	0.56
	Moderate dose	640	-1.63	(-2.93,-0.32)	0.01
	High dose	77	-2.9	(-6.05,0.25)	0.07
VI. Fully Adjusted¥	No statins	1554	--	--	--
	Low dose	118	-0.79	(-3.51,1.92)	0.57
	Moderate dose	640	-1.64	(-2.95,-0.33)	0.01
	High dose	77	-2.88	(-6.05,0.29)	0.07
Δ MVR					
II. Model I† & age, gender, race	No statins	1554	--	--	--
	Low dose	118	-0.02	(-0.06,0.02)	0.37
	Moderate dose	640	0.01	(-0.01,0.03)	0.58
	High dose	77	-0.02	(-0.07,0.03)	0.37
IV. Model III & lipid levels‡	No statins	1554	--	--	--
	Low dose	118	-0.03	(-0.07,0.01)	0.14
	Moderate dose	640	-0.01	(-0.03,0.01)	0.29
	High dose	77	-0.04	(-0.09,0.01)	0.09
VI. Fully Adjusted¥	No statins	1554	--	--	--
	Low dose	118	-0.03	(-0.07,0.01)	0.13
	Moderate dose	640	-0.01	(-0.03,0.01)	0.29
	High dose	77	-0.04	(-0.09,0.01)	0.08
Δ LVM Unindexed					
	No statins	1554	--	--	--

II. Model I† & age, gender, race	Low dose	118	0.8	(-2.80,4.40)	0.66
	Moderate dose	640	-0.25	(-1.99,1.48)	0.77
	High dose	77	0.14	(-5.30,5.57)	0.96
IV. Model III & lipid levels‡	No statins	1554	--	--	--
	Low dose	118	0.15	(-3.55,3.85)	0.94
	Moderate dose	640	-1.25	(-3.09,0.60)	0.19
	High dose	77	-0.83	(-6.20,4.55)	0.76
VI. Fully Adjusted¥	No statins	1554	--	--	--
	Low dose	118	0.18	(-3.53,3.89)	0.92
	Moderate dose	640	-1.25	(-3.10,0.60)	0.19
	High dose	77	-0.75	(-6.17,4.67)	0.79
Δ LVM-BSA Adjusted					
II. Model I† & age, gender, race	No statins	1554	--	--	--
	Low dose	118	0.06	(-1.90,2.01)	0.95
	Moderate dose	640	-0.39	(-1.32,0.53)	0.41
	High dose	77	-0.87	(-3.34,1.60)	0.49
IV. Model III & lipid levels‡	No statins	1554	--	--	--
	Low dose	118	-0.37	(-2.37,1.64)	0.72
	Moderate dose	640	-1.11	(-2.08,-0.14)	0.02
	High dose	77	-1.67	(-4.13,0.79)	0.18
VI. Fully Adjusted¥	No statins	1554	--	--	--
	Low dose	118	-0.36	(-2.37,1.65)	0.73
	Moderate dose	640	-1.12	(-2.09,-0.14)	0.02
	High dose	77	-1.65	(-4.12,0.82)	0.19
Δ LVM-EDV					
II. Model I† & age, gender, race	No statins	1554	--	--	--
	Low dose	118	-2.45	(-6.14,1.24)	0.19
	Moderate dose	640	-0.02	(-2.08,2.03)	0.98

	High dose	77	-1.37	(-7.38,4.63)	0.65
IV. Model III & lipid levels‡	No statins	1554	--	--	--
	Low dose	118	-2.93	(-6.68,0.83)	0.13
	Moderate dose	640	-0.62	(-2.93,1.69)	0.60
	High dose	77	-2.25	(-8.47,3.97)	0.48
VI. Fully Adjusted¥	No statins	1554	--	--	--
	Low dose	118	-2.99	(-6.76,0.78)	0.12
	Moderate dose	640	-0.6	(-2.94,1.73)	0.61
	High dose	77	-2.33	(-8.52,3.86)	0.46
Δ LVEF^					
II. Model I† & age, gender, race	No statins	1553	--	--	--
	Low dose	118	1.17	(-0.14,2.48)	0.08
	Moderate dose	640	0.4	(-0.30,1.10)	0.26
	High dose	77	-1.99	(-3.94,-0.04)	0.05
IV. Model III & lipid levels‡	No statins	1553	--	--	--
	Low dose	118	1.09	(-0.23,2.41)	0.11
	Moderate dose	640	0.32	(-0.46,1.09)	0.42
	High dose	77	-2.01	(-4.01,-0.02)	0.05
VI. Fully Adjusted¥	No statins	1553	--	--	--
	Low dose	118	1.1	(-0.23,2.43)	0.10
	Moderate dose	640	0.33	(-0.45,1.10)	0.41
	High dose	77	-1.98	(-3.98,0.01)	0.05

^ One participant missing LVEF change, thus the analysis consists of 2388 participants.

† Model I is unadjusted. ‡ At baseline: Smoking status (former, never, current), BMI (kg/m^2), diabetes status (normal, impaired fasting glucose, untreated diabetes, treated diabetes), hypertension status (normal, untreated hypertension, treated hypertension), waist circumference (cm), systolic and diastolic blood pressure (mmHg), HDL cholesterol (mg/dl), triglycerides (mg/dl), and total cholesterol (mg/dl).

¥ At baseline: Age, gender, race, smoking status (former, never, current), BMI (kg/m^2), diabetes status (normal, impaired fasting glucose, untreated diabetes, treated diabetes), waist circumference (cm), antihypertensive agent use (yes/no for diuretics, calcium channel blockers, beta-blockers, ace-inhibitors, and angiotensin type 2 antagonists), systolic and diastolic blood pressure (mmHg),

HDL cholesterol (mg/dl), triglycerides (mg/dl), total cholesterol (mg/dl), intentional exercise defined as moderate and vigorous physical activity total (met-min per week), no health insurance, and log-transformed CAC Score.
Abbreviations: CI = Confidence interval; LVEF = Left ventricular ejection fraction; LVEDV = Left ventricular end diastolic volume; LVM-BSA = Left ventricular mass that is indexed by body surface area; LVMI = Left ventricular mass index; MI = Myocardial infarction; MVR = Mass-to-volume ratio

Suppl. Table 6. Difference in 10-year change in cardiac indices of left ventricular structure and function for each additional year of new statin use, among those without an incident myocardial infarction

Model	**Complete Case (N=2389)**			**IPCW (N=2389)**		
	Estimate	**95%CI**	**p-value**	**Estimate**	**95%CI**	**p-value**
Δ LVMI						
II. Model I† & age, gender, race	-0.13	(-0.40,0.14)	0.35	-0.11	(-0.37,0.16)	0.43
IV. Model III & lipid levels‡	-0.30	(-0.59,-0.02)	0.04	-0.29	(-0.57,-0.01)	0.04
VI. Fully Adjusted¥	-0.30	(-0.59,-0.02)	0.04	-0.29	(-0.58,-0.01)	0.04
Δ MVR						
II. Model I† & age, gender, race	0.00	(-0.00,0.01)	0.48	0.02	(-0.02,0.06)	0.31
IV. Model III & lipid levels‡	0.00	(-0.01,0.00)	0.42	-0.01	(-0.05,0.03)	0.50
VI. Fully Adjusted¥	0.00	(-0.01,0.00)	0.42	-0.01	(-0.06,0.03)	0.50
Δ LVM-Unindexed						
II. Model I† & age, gender, race	-0.03	(-0.41,0.34)	0.86	-0.02	(-0.40,0.35)	0.9
IV. Model III & lipid levels‡	-0.20	(-0.60,0.19)	0.31	-0.16	(-0.56,0.23)	0.42
VI. Fully Adjusted¥	-0.20	(-0.60,0.19)	0.32	-0.17	(-0.57,0.23)	0.41
Δ LVM-BSA indexed						
II. Model I† & age, gender, race	-0.08	(-0.28,0.12)	0.43	-0.07	(-0.27,0.13)	0.49
IV. Model III & lipid levels‡	-0.20	(-0.41,0.01)	0.06	-0.19	(-0.40,0.02)	0.07
VI. Fully Adjusted¥	-0.20	(-0.42,0.01)	0.06	-0.19	(-0.41,0.02)	0.07
Δ LVEDV						
II. Model I† & age, gender, race	0.09	(-0.31,0.49)	0.65	0.13	(-0.27,0.52)	0.53
IV. Model III & lipid levels‡	0.00	(-0.44,0.45)	0.99	-0.03	(-0.48,0.41)	0.89
VI. Fully Adjusted¥	0.00	(-0.44,0.45)	0.99	-0.03	(-0.48,0.42)	0.91
*Δ LVEF^*						
II. Model I† & age, gender, race	0.06	(-0.08,0.20)	0.41	0.04	(-0.11,0.18)	0.62
IV. Model III & lipid levels‡	0.04	(-0.11,0.20)	0.57	0.04	(-0.12,0.20)	0.62
VI. Fully Adjusted¥	0.05	(-0.11,0.20)	0.54	0.04	(-0.12,0.20)	0.61

Both an unweighted complete case analysis and an analysis weighted by the inverse probability of censoring over the study period are presented above.

† Model I is unadjusted.‡ At baseline: Smoking status (former, never, current), BMI (kg/m^2), diabetes status (normal, impaired fasting glucose, untreated diabetes, treated diabetes), hypertension status (normal, untreated hypertension, treated hypertension), waist circumference (cm), systolic and diastolic blood pressure (mmHg), HDL cholesterol (mg/dl), triglycerides (mg/dl), and total cholesterol (mg/dl).
¥ At baseline: Age, gender, race, smoking status (former, never, current), BMI (kg/m^2), diabetes status (normal, impaired fasting glucose, untreated diabetes, treated diabetes), waist circumference (cm), antihypertensive agent use (yes/no for diuretics, calcium channel blockers, beta-blockers, ace-inhibitors, and angiotensin type 2 antagonists), systolic and diastolic blood pressure (mmHg), HDL cholesterol (mg/dl), triglycerides (mg/dl), total cholesterol (mg/dl), intentional exercise defined as moderate and vigorous physical activity total (met-min per week), no health insurance, and log-transformed CAC Score. ^ One participant missing LVEF change, thus the analysis consists of 2388 participants.
Abbreviations: CAC = Coronary artery calcium; CI = Confidence interval; IPCW = Inverse probability of censoring weighted; LVEF = Left ventricular ejection fraction; LVEDV = Left ventricular end diastolic volume; LVM-BSA = Left ventricular mass that is indexed by body surface area

Suppl. Table 7. Previous studies that evaluated changes in left ventricular mass and statin use

Author Year	Study Design	Population	Time Frame	LVM Measure	N	Comparison Groups	BL Measure	Change	Unit
Su 2000	Cohort - age and BSA-matched	Hyperlipidemia/essential hypertension	6 m	LVMI (indexed BSA)	20	(I) PRAVASTATIN 10 mg/day + AHA	143 (12)	-36	g/m2
					20	(II) AHA + Diet control	142 (18)	-20	g/m2
					20	(III) AHA (normolipedmia group)	142 (17)	-20	g/m2
Warita 2012	Cohort	Elderly with hypertension and LVH, with need for Statin based on Japanese guidelines	1 y	LVMI (indexed BSA)	110	Continued AHA + PITAVASTATIN 1-2 mg/day	139 (25)	-9	g/m2
					110	Continued AHA	140 (25)	-3	g/m2
Pan 2010	RCT	Essential hypertension and LVH	12 m	LVMI (indexed BSA)	20	Telmisartan	122 (33)	-15	g/m2
					21	SIMVASTATIN 10 mg + Telmisartan	137 (55)	-36	g/m2
Teixeira 2010	RCT	Primary (essential) hypertension	12 m	LVMI (indexed BSA)	19	FLUVASTATIN 20 mg	99	-17	g/m2
					20	Placebo	116	-16	g/m2
Folkering a 2010	RCT	Hypertension and LVH	6 m	LVMI (indexed BSA)	71	ROSUVASTATIN 20 mg	114	-3 (17)	g/m2
					71	Control	118	-5 (15)	g/m2
Andersse n 2005; HYRIM Trial	RCT	Hypertension + high BMI + drug treated	2 y	LVM	183	FLUVASTATIN 40 mg	272 (73)	2	g
					185	Placebo	261 (68)	25	g

Lee 2002	RCT	Hypercholesterolemia	6 m	LVMI (indexed with correction formula)	25	PRAVASTATIN 10 mg or 20 mg	127 (8)	-18 (8)	g/m2
					25	Control	123 (7)	-4 (8)	g/m2

Abbreviations: AHA = Antihypertensive agent; BMI = Body mass index; BSA = Body surface area; HYRIM = Hypertension High Risk Management (trial); LVH = Left ventricular hypertrophy; LVM = Left ventricular mass; LVMI = Left ventricular mass index; RCT = Randomized controlled trial

Suppl. Table 8. Timing of myocardial infarction and use of statins at any time

MI Timing	All participants	Non-statin user	Statin user	Unclear or missing use
No adjudicated MI during study period	4151	1826	1223	1090
MI between baseline and exam 2	18	0	12	6
MI between exam 2 and exam 3	16	1	10	6
MI between exam 3 and exam 4	26	5	13	12
MI between exam 4 and exam 5	54	12	31	18
Total	4265	1844	1289	1132

Of the 66 participants with any years of statin use and incident MI, 21 had evidence of statin use prior to the MI. The remaining 45 had unclear statin use before or after MI. Among the 42 MIs reported among those with valid statin use data and covariates (i.e. those included in the study analyses), 5 did not have any reported statin use, 11 had evidence of use before the MI, and 26 had unclear timing of statin use in relation to the MI.

Suppl. Table 9. Difference in 10-year change in indices of left ventricular structure and function for each additional year of new statin use, among 42 participants with incident myocardial infarction

Model	**Complete Case (N=42)**			**IPCW (N=42)**		
	Estimate	**95%CI**	**p-value**	**Estimate**	**95%CI**	**p-value**
Δ LVMI						
I. Unadjusted	-1.63	(-3.11,-0.14)	0.03	-2.19	(-3.85,-0.52)	0.01
II. Model I & age, gender, race	-2.35	(-3.44,-0.49)	0.01	-2.63	(-4.16, -1.11)	0.001
Δ MVR						
I. Unadjusted	0.00	(-0.03,0.04)	0.92	0.04	(-0.30, 0.39)	0.8
II. Model I & age, gender, race	0.00	(-0.04,0.04)	0.88	0.00	(-0.38, 0.38)	0.99
Δ LVM-Unindexed						
I. Unadjusted	-1.91	(-4.18,0.37)	0.1	-2.52	(-5.01,-0.03)	0.05
II. Model I & age, gender, race	-2.66	(-5.04,-0.27)	0.03	-3.47	(-5.83,-1.12)	0.005
Δ LVM-BSA indexed						
I. Unadjusted	-1.12	(-2.26,0.02)	0.05	-1.51	(-2.76,-0.26)	0.02
II. Model I & age, gender, race	-1.43	(-2.57,-0.29)	0.02	-1.91	(-3.06,-0.76)	0.002
Δ LVEDV						
I. Unadjusted	1.47	(-3.81,6.75)	0.58	2.37	(-2.94,7.67)	0.37
II. Model I& age, gender, race	1.76	(-4.44,7.97)	0.57	2.87	(-3.30,9.03)	0.35
Δ LVEF						
I. Unadjusted	0.88	(-0.42,2.18)	0.18	0.83	(-0.46,2.12)	0.20
II. Model I & age, gender, race	1.06	(-0.56,2.69)	0.19	0.99	(-0.65,2.64)	0.23

Both an unweighted complete case analysis and an analysis weighted by the inverse probability of censoring are presented above.
Abbreviations: CI = Confidence interval; IPCW = inverse probability of censoring weighted; LVEF = Left ventricular ejection fraction; LVEDV = Left ventricular end diastolic volume; LVM-BSA = Left ventricular mass that is indexed by body surface area; LVMI = Left ventricular mass index; MI = Myocardial infarction; MVR = Mass-to-volume ratio

Suppl. Table 10. Myocardial scar at follow-up magnetic resonance imaging by myocardial infarction status during study follow-up

MI status	No myocardial scar	Myocardial scar	N/A (No Gadolinium)	No second scan
None	1427	103	988	1632
MI	7	17	19	71

The presence of myocardial scar was based on visual assessment of any size scar using late GAD enhancement images.
Abbreviations: MI = Myocardial infarction; N/A = Not applicable

Suppl. Table 11. Difference in 10-year change left ventricular mass index and mass-to-volume ratio for each additional year of new statin use, among those without an incident myocardial infarction who were new statin users

Model	**Complete Case without prevalent users at baseline (N=835)**			**Complete Case with prevalent users at baseline (N=1236)**		
	Estimate	**95%CI**	**p-value**	**Estimate**	**95%CI**	**p-value**
Δ LVMI						
II. Model I† & age, gender, race	-0.06	(-0.53,0.42)	0.82	-0.08	(-0.36,0.19)	0.56
IV. Model III & lipid levels‡	-0.07	(-0.56,0.42)	0.77	-0.06	(-0.34,0.22)	0.66
VI. Fully Adjusted¥	-0.07	(-0.57,0.42)	0.77	-0.06	(-0.33,0.20)	0.69
Δ MVR						
II. Model I† & age, gender, race	0.00	(-0.00, 0.01)	0.24	0.00	(-0.00,0.01)	0.56
IV. Model III & lipid levels‡	0.00	(-0.00, 0.00)	0.28	0.00	(-0.00,0.01)	0.51
VI. Fully Adjusted¥	0.00	(-0.00, 0.01)	0.26	0.00	(-0.00,0.01)	0.50

Analyses with and without prevalent users of statins at baseline are presented.

† Model I is unadjusted. ‡ At baseline: Smoking status (former, never, current), BMI (kg/m^2), diabetes status (normal, impaired fasting glucose, untreated diabetes, treated diabetes), hypertension status (normal, untreated hypertension, treated hypertension), waist circumference (cm), systolic and diastolic blood pressure (mmHg), HDL cholesterol (mg/dl), triglycerides (mg/dl), and total cholesterol (mg/dl). ¥ At baseline: Age, gender, race, smoking status (former, never, current), BMI (kg/m^2), diabetes status (normal, impaired fasting glucose, untreated diabetes, treated diabetes), waist circumference (cm), antihypertensive agent use (yes/no for diuretics, calcium channel blockers, beta-blockers, ace-inhibitors, and angiotensin type 2 antagonists), systolic and diastolic blood pressure (mmHg), HDL cholesterol (mg/dl), triglycerides (mg/dl), total cholesterol (mg/dl), intentional exercise defined as moderate and vigorous physical activity total (met-min per week), no health insurance, and log-transformed CAC Score.

Abbreviations: CAC = Coronary artery calcium; CI = Confidence interval; IPCW = Inverse probability of censoring weighted; LVEF = Left ventricular ejection fraction; LVEDV = Left ventricular end diastolic volume; LVM-BSA = Left ventricular mass that is indexed by body surface area; LVMI = Left ventricular mass index; MVR = Mass-to-volume ratio