Title

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Journal

Journal of Clinical Lipidology, 11(5)

ISSN

1933-2874

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Publication Date

2017-09-01

DOI

10.1016/j.jacl.2017.06.015

Peer reviewed

HHS Public Access

Author manuscript

J Clin Lipidol. Author manuscript; available in PMC 2019 February 28.

Published in final edited form as:

J Clin Lipidol. 2017 ; 11(5): 1223–1233. doi:10.1016/j.jacl.2017.06.015.

Residual Atherosclerotic Cardiovascular Disease Risk in Statin-Treated Adults: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Background: Residual atherosclerotic cardiovascular disease (ASCVD) risk in statin-treated U.S. adults without known ASCVD is not well-described.

Objective: To quantitate residual ASCVD risk and its predictors in statin-treated adults.

Methods: We studied 1,014 statin-treated adults (53.3% female, mean 66.0 years) free of clinical ASCVD in the Multiethnic Study of Atherosclerosis. We examined ASCVD event rates by National Lipid Association risk groups over 11-year follow-up and the relation of standard risk factors, biomarkers and subclinical atherosclerosis measures with residual ASCVD event risk.

Results: Overall, 5.3% of participants were at low, 12.2% at moderate, 60.3% at high, and 22.2% at very high baseline risk. Despite statin therapy, age-and-race standardized ASCVD rates per 1000 person years for men and women were both 4.9 for low/moderate risk, 19.1 and 14.2 for high risk and 35.6 and 26.7 for very high risk, respectively. Specific independent predictors of residual risk included current smoking, family history, diabetes, high sensitivity C-reactive protein, LDL-

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particle number, carotid intimal medial thickness, and especially coronary artery calcium score. Those on moderate or high intensity statins at baseline (compared to low intensity) had 39% lower risks, and those who increased statin intensity 62% lower ASCVD event risks ($p<0.01$).

Conclusion: Residual risk of ASCVD remains high despite statin treatment and is predicted by specific risk factors and subclinical atherosclerosis. These findings may be helpful for identifying those at highest risk needing more aggressive treatment.

Keywords

statins; risk factors; atherosclerosis; cardiovascular disease risk; dyslipidemia

Cardiovascular disease (CVD) remains the leading cause of death globally (1) and despite the availability of preventive therapies many CVD events still occur. Residual CVD risk has been defined as the risk of CVD events that persists despite treatment for or achievement of targets for risk factors such as low density lipoprotein (LDL) cholesterol, blood pressure, and glycemia (2). While current treatment regimens prevent up to half of CVD events (3, 4), many CVD events still occur despite optimal therapy. In major statin and non-statin trials (5–11) significant CVD risk remains even after reducing LDL-C, suggesting the need for intensified efforts at lifestyle management as well as newer treatment strategies to reduce this residual risk (12–14).

Most data on residual CVD risk has derived from statin trials which have strict inclusion criteria, limiting generalizability. The absolute risk remaining among statin-treated adults without known ASCVD at baseline as well as the predictors of residual risk have not been well-described in a population-based non-clinical trial population. In the Multi-Ethnic Study of Atherosclerosis (MESA), a longitudinal study of CVD, we examined the residual risk of ASCVD events in those on statin therapy and initially free of ASCVD, absolute and relative differences in ASCVD risk according to recently defined National Lipid Association risk groups (15), as well as the risk factor and subclinical atherosclerosis predictors of such residual risk.

Methods

Study population

MESA recruited 6,814 males and females aged 45 to 84 years and free of known CVD at baseline, including four race/ethnic groups: Caucasian, African-American, Caucasian, Chinese-American, and Hispanic. Baseline examinations were conducted from 2000 to 2002 at 6 field centers as previously described (16). MESA was approved by the institutional review boards and all participants provided written informed consent.

We included participants who reported statin therapy at the time of baseline examination and had measures of standard and novel risk factors/ biomarkers (see table 1 footnote) as well as measures for subclinical atherosclerosis [coronary artery calcium (CAC), carotid intima media thickness (CIMT), ankle-brachial index (ABI) and estimated glomerular filtration rate (eGFR)].

Baseline risk factor assessment

Information about participant demographics (including socioeconomic status measures of educational and income level), medical history, current medication use, and family history was collected using standardized questionnaires. Resting blood pressure was measured three times, averaging the last two measures. Body mass index (BMI) and waist circumference (WC) were also obtained. Glucose, total cholesterol and high-density lipoprotein cholesterol (HDL-C) were obtained after a 12-hour fast. The Friedewald equation was used to estimate LDL-C. We also examined as alternatives to LDL-C the total cholesterol/HDL-C ratio and non-HDL. Diabetes mellitus (DM) was defined as a fasting glucose ≥ 126 mg/dL (6.9 mmol/L) or use of insulin or oral hypoglycemic medications. HDL and LDL particle numbers (using Lipoprofile 3®) and glycan A (GlycA) were measured with nuclear magnetic resonance spectroscopy (Liposcience, Raleigh, NC)[17]; lipoprotein-associated phospholipase A2 ($LpPLA_2$) mass was measured using a sandwich enzyme immunoassay (PLAC™ Test; diaDexus, San Francisco, CA and $LpPLA_2$ activity by a high-throughput radiometric assay using tritium-labeled platelet activating factor (H3-PAF) as the substrate[18]. Plasma homocysteine was measured using a fluorescence polarization immunoassay (IMx Hcy assay, Axis Biochemicals ASA, Oslo, Norway) with the IMx analyzer (Abbott Diagnostics, Abbott Park, Illinois)[19].

CAC was assessed with an electron-beam CT scanner (Chicago, Los Angeles, and New York) or a multi-detector CT system (Baltimore, St. Paul, and Winston-Salem), with CAC scores calculated using Agatston method [20]. We categorized CAC into groups: 0, 1–99, 100–399 and 400+ but also examined CAC ≥300 as an alternative to the highest group. We also used CAC quartile rank in each age, sex and ethnicity/race group as previously defined in MESA [21] in a sensitivity analysis. CIMT was assessed using B-mode ultrasound (Logiq 700 ultrasound device; General Electric Medical Systems, Waukesha, WI). Mean CIMT is defined as mean of maximal common carotid IMT and maximal internal carotid IMT [22]. Carotid plaque presence defined as present if any stenosis was present. eGFR was calculated using the Modification of Diet in Renal Disease Study equation. For ABI, systolic blood pressure measurements in the bilateral brachial, dorsalis pedis, and posterior tibial arteries were obtained in the supine position using a handheld Doppler instrument with a 5-mHz probe. An abnormal ABI was defined as < 0.9 or ≥ 1.4 (1.3 in DM) [22].

At baseline we categorized participants into four National Lipid Association (NLA) risk groups as very high, high, moderate and low risk groups [15]. Definitions of NLA risk groups are summarized in Table 1. We further use optional additional measures recommended by the NLA guidelines to further refine risk group assignment in a sensitivity analysis (See Table 1 footnote). Detailed statin use information from MESA Exams 1–5 was obtained from questionnaires and the medication containers participants brought to the examination center from the MESA baseline examination and at four follow-up MESA exams conducted through 2012, with statin intensity defined according to the ACC/AHA Guideline for Management of Blood Cholesterol. [23]

ASCVD event ascertainment

Participants in MESA were followed up through December 2013. At intervals of 9–12 months, a telephone interviewer inquired about interim hospital admissions, cardiovascular diagnoses, and deaths. An adjudication committee received copies of all death certificates and medical records for hospitalizations and outpatient cardiovascular diagnoses and conducted next-of-kin interviews for out-of-hospital cardiovascular deaths for verification. Our primary endpoint was an incident ASCVD event, including angina, myocardial infarction, coronary revascularization, stroke, transient ischemic attack or peripheral arterial disease. We also defined a secondary endpoint of hard ASCVD to include myocardial infarction, CHD death, stroke and peripheral arterial disease. Follow-up stopped at the first ASCVD event, death, loss to follow-up, or the last follow-up call, whichever occurred first.

Statistical analysis

Descriptive data are presented as mean ± standard deviation (SD) for continuous variables and frequencies (percentage) for categorical variables. Continuous variables with skewness >1 were log transformed. ASCVD event rates are per 1000 person years by sex or ethnicity/race with age-ethnicity/race or age-sex standardization. Kaplan-Meier survival curves were created to show ASCVD event-free survival by NLA risk group with the log-rank test used to test group differences. Cox proportional hazards regression was used to calculate hazard ratios (HRs) for risk groups and demographic, clinical, novel, and subclinical disease risk predictors. Continuous variables were standardized by dividing the original value by their SD to obtain standardized HRs. The proportionality assumption was checked by including time-dependent variables for each predictor and the relative magnitude of each variable's contribution to ASCVD risk was based on the Wald Chi-square likelihood ratio change.

Each risk factor was examined separately in a Cox regression model (Model 1) adjusted for age, sex and race. Then a second model (Model 2) was constructed forcing age, sex, and race in the model and allowing stepwise selection of standard risk factors with $p<0.15$ and novel biomarkers with $p<0.15$ in Model 1. A final model 3 then forced age, sex, ethnicity/race, standard risk factors with $p<0.15$ and novel biomarkers with $p<0.15$ from Model 2 and allowed for stepwise selection of subclinical atherosclerosis measures. We separately added to this final model baseline statin intensity and statin intensity change between baseline and latest available MESA exam with statin information available in relation with incident ASCVD. Colinearity between inflammatory biomarkers were examined using Pearson correlation. Each of the biomarkers with $R^2>0.4$ and linear correlation on the graph were separately examined in the models as sensitivity analysis. Furthermore, we repeated main analysis in subgroups with LDL-C <100 mg/dL to see how results may differ in this subset with controlled LDL-C.

Analyses were performed using SAS version 9.3 (SAS Institute, NC) and p-values <0.05 were considered statistically significant.

Results

In total, 1,014 participants (46.8 % male, mean age 66.0 ± 8.7) were on statin therapy at baseline exam (2000–2002). Of these, 5.3% of participants (n=54) were at low, 12.2% (n=124) were at moderate, 60.3% (n=611) at high, and 22.2% (n=225) at very high baseline risk based on NLA risk group categorization (Table 1). If other factors for consideration as shown in Table 1 (elevated CAC, LDL-C, multiple pack smoking, elevated urine/creatine ratio, and hs-CRP) are used for risk reclassification, this resulted classification of 2.5% (n=25) at low, 5.7% (n=58) at moderate, 40.0% (n=406) at high, and 51.8% (n=525) at very high risk. Table 2 displays demographic and clinical risk factors, statin use by intensity, novel biomarkers, subclinical atherosclerosis measures, and NLA risk group distribution among those with versus without incident ASCVD. Overall, 173 participants (17.1%) developed an incident ASCVD event (35 MI, 54 angina, 26 revascularization procedure, 21 PVD, 7 TIA and 30 stroke) over a mean ± SD follow-up time of 11.1 ± 2.8 years (median 12.0 years); 67.6% and 4.8% of all participants were on a moderate or high intensity statin, respectively, at baseline. Those with vs. without incident ASCVD had similar LDL-C levels (49.7% and 48.1%, respectively had an LDL-C<100 mg/dl) but were older, more likely male, on antihypertensive medication, diagnosed with DM, cigarette smokers, and had lower HDL-C and higher systolic blood pressure. They also had higher LDL-P, hsCRP, IL-6, $LpPLA_2$ mass and activity, total homocysteine and GlycA and were more likely to have higher levels of CAC, CIMT, carotid plaque/stenosis, abnormal ABI, and to be in higher NLA risk groups.

ASCVD event rates by sex (age and race-standardized) or ethnicity (age and sex-standardized) with baseline NLA risk group are shown in Figure 1; women in the very high risk group had a rate of 26.7 and for men it was 35.6. ASCVD rates were highest in the very high risk group among Hispanics and Caucasians (35.1 and 39.7, respectively). For hard ASCVD, rates in low/moderate to very high risk groups ranged from 4.2 to 15.5 in women and 1.7 to 25.9 in men and as high as 24.1 in Caucasians and 22.3 in Hispanics in the very high risk group. Figure 2 shows the Kaplan-Meier survival curves; those in the high and very high risk groups had a lower ASCVD event-free survival than those in the low/moderate risk groups ($p < 0.001$ for log rank test).

We examined each individual risk factor in relation with incident ASCVD (Table 2) adjusted for age, sex and ethnicity/race (Model 1) and found all traditional risk factors, biomarkers and subclinical measures except for LDL-C, HDL-P, eGFR, and $LpPla_2$ activity to be significantly associated with future events. Model 2 shows the results of stepwise regression allowing entry of standard risk factors and biomarkers, where besides age, lower LDL-C (inversely), current smoking, DM, higher LDL-P, higher hs-CRP, and higher plasma homocysteine were all associated with higher ASCVD event risk. In the final model after further selecting subclinical atherosclerosis measures (Model 3), current smoking, family history of premature CVD, DM, LDL-P, and hs-CRP remained predictive along with increased risks conferred by CIMT and CAC. CAC remained the strongest of the predictors followed by DM (Wald Chi-squares of 20.1, $p<0.0001$ and 14.9, $p<0.001$, respectively). For hard ASCVD (not shown in table), current smoking (vs. nonsmoking) (HR=2.11, 95% CI: 1.09–4.07, p=0.0258), systolic blood pressure (HR=1.33 per SD, 95% CI: 1.09–1.62,

p=0.0057), diabetes (HR=2.17, 95% CI: 1.38–3.39, p=0.0007), log-total plasma homocysteine (HR=1.25 per SD, p=0.02) were associated with ASCVD risk in model 2. Adding subclinical measures resulted in log-transformed mean CIMT (HR=1.32 per SD, 95% CI: 1.09–1.60, p=0.0039) and elevated CAC levels (HR=2.89, 95% CI: 1.60–5.22, p=0.02 for ≥400 vs. 0) being additionally predictive of events.

We also examined whether statin intensity at baseline was associated with ASCVD events. In the fully-adjusted model, those reporting moderate intensity statin use at baseline had a 39% lower ASCVD risk compared to those reporting low intensity statin use; those with high intensity statin use also had a 39% lower risk (Table 4). Moreover, in the same model containing baseline statin use, compared to those whose statin intensity stayed the same, those who increased statin intensity during follow-up had a significant 62% lower risk of subsequent ASCVD events, but those who decreased intensity or stopped their statin had no significant change in risk.

As we identified potential collinearity among hsCRP, IL-6 and glycan A, between $LpPla_2$ mass and $LpPla_2$ activity and between LDL-p and $LpPla_2$ activity, we examined these factors in separate models. Glyc A was significantly related to ASCVD events with a HR=1.20 (95% CI: 1.02–1.41) (p=0.0301) in model 3 while log-transformed IL-6 had a marginally significant HR (1.17, 95% CI: 1.00–1.38, p=0.0542). Also, in separate models (not shown in table), as an alternative to LDL-C the ratio of total cholesterol and HDL-C (HR=0.97 [0.79–1.19] or non-HDL-C [HR=0.90 [0.70–1.15] did not offer stronger prediction of future ASCVD events compared to LDL-C (HR=0.86 [0.67–1.10] in the above models. Furthermore we used CAC score ≥300 or CAC quartile group as alternative CAC measures in sensitivity analysis. A CAC score of ≥300 (compared to 0) had a HR=2.33 (2.01–2.70) (p<0.001) for future CVD events (compared to 3.38 [1.97–5.80] for CAC ≥400). Compared to those in the first age-sex-race specific quartile of CAC score, HR's for those in the 2^{nd}, 3^{rd}, and 4^{th} quartiles were 1.94, 2.02, and 1.89 (all p<0.05 to p=0.01) in fully adjusted models except for age, sex, and race since this information is already incorporated in the quartiles. Subgroup analysis in the 481 participants with LDL-C <100mg/dL is presented in Table 5. Only DM, LDL-P, hsCRP and CAC >=400 was significantly associated future ASCVD risk. Log-transformed HDL-C was marginally significant in the models.

Discussion

This report from MESA is the first population-based cohort without prior ASCVD to report on residual ASCVD risk in statin-treated adults over a period of more than 10 years. Overall, 17% of participants developed an initial ASCVD event; in those classified as high risk, the 10-year estimated event rate was 14% in women and 19% in men, and among those at very high risk, 27% and 36%, respectively. Residual risk was greatest in Caucasians compared to other ethnic groups. Moreover, DM, LDL-P, hsCRP, and increased levels of CAC, in particular, were the most important predictors of residual ASCVD risk, even in the subset with a baseline LDL-C<100 mg/dl.

The ACC/AHA Cholesterol Management Guideline (23) recommends moderate or high intensity statin therapy for those with ASCVD, LDL-C ≥190 mg/dl (4.9 mmol/L), diabetes,

or 10-year ASCVD risk of ≥7.5%. In our study, among those who suffered a subsequent ASCVD event, only 5% were on a high intensity statin at baseline. We also showed lower future ASCVD risks in those on moderate or high intensity statins, or those who increased statin intensity, although these results should be interpreted cautiously due to possible treatment biases present due to the observational nature of our study.

Studies quantifying and examining predictors of residual risk have been mainly limited to clinical trials of persons with pre-existing ASCVD. The Cholesterol Treatment Trialists' Collaboration showed 22% of those with and 9.5% of those without prior ASCVD developed ASCVD events within 5 years (24, 25). The Treat to New Targets (TNT) trial showed predictors of subsequent ASCVD events were older age, increased body mass index, male sex, DM, apolipoprotein B, and blood urea nitrogen levels (26); those on 80 mg atorvastatin had a CVD event rate of 8.7% over 5 years (27). Other trials of secondary prevention show event rates of 11–17% within 5 years or less (28). More recently, the IMPROVE-IT investigators (11) showed after 7 years, that despite combined simvastatin and ezetimibe resulting in an LDL-C averaging 54 mg/dl in high-risk acute coronary syndrome patients, 32.7% of patients still suffered events.

Poorly controlled LDL-C and remaining atherogenic dyslipidemia from apolipoprotein B containing lipoproteins, low HDL-C and high triglycerides have been proposed as principal causes of residual ASCVD risk in statin treated patients. We have shown among US adults on statin therapy only 64% to be at LDL-C targets (20% in those with CHD), but only 52% for apolipoprotein B (29). In the current study, less than half of our participants on statin therapy had an LDL-C <100 mg/dl (2.6 mmol/L). The presence of DM in our study was also a potent and consistent predictor of residual ASCVD risk, and while our study was not intended to look at residual risk after multiple risk factor control, we have recently documented 60% lower risks of CVD events in those with DM at target for LDL-C, blood pressure, and glycated hemoglobin (30).

We also showed LDL-P to be strongly associated with future ASCVD events, suggesting the need for therapies that lower LDL-P beyond LDL-C lowering. Consistent with our observations, Toth et al. (31) showed those achieving both LDL-C and LDL-P targets were not only on greater intensity of treatment, but also had the lowest event rates. Also, while $LpPla_2$ mass predicted ASCVD events in age, gender, and ethnicity-adjusted analyses, this relation was attenuated further after adjustment for other factors in our statin-treated sample. While $LpPla_2$ is an established measure of vascular inflammation which has been previously shown to relate to ASCVD risk, its role as a target of therapy remains uncertain given the recent negative clinical trial findings (32). We show in this report CAC, in particular remains an important predictor of residual ASCVD risk despite statin therapy, consistent with findings from the overall MESA cohort where CAC (but not family history, hsCRP, nor ankle brachial index) improved risk prediction for ASCVD events beyond the Pooled Cohort Risk Score (33). An earlier analysis of statin-treated participants in MESA with only 4.4 years of follow-up showed CAC but not traditional risk factors to predict future CVD events (34). Current guidelines (23) indicate an hsCRP>2 mg/L (19.0 nmol/L), CAC score ≥300 or ≥75th percentile for age, sex, and ethnicity, an ABI<0.9, as well as a positive family history may inform the treatment decision if uncertain based on global risk assessment alone. Our

findings of nearly two-fold greater risk if at least some CAC is present might warrant intensification of statin therapy (if not already on high intensity statin) for such individuals.

Our study comprised participants free of ASCVD at baseline recruited without selection for certain risk factors; prior studies reporting on residual ASCVD risk have been in selected clinical trials of persons with hypercholesterolemia and/or ASCVD. In addition, MESA had standardized assessment of risk factors, novel biomarkers, subclinical atherosclerosis measures, and ASCVD events. Limitations include the absence of information on duration of statin use prior to the baseline examination, decisions that led to statin use, and measures of other potentially important predictors such as lipoprotein (a) levels. Our observed risks are specific to the participants in MESA, which while more generalizable to the population as a whole than prior reports from clinical trials, may not be entirely representative of the US population on statin therapy. Not surprisingly, our MESA participants on statins were at higher risk than those not on statins and tended to be older, and with more diabetes, higher levels of systolic blood pressure, LDL-cholesterol, LDL particle number, $LpPla_2$ mass and activity, family history of cardiovascular disease, coronary calcium, carotid IMT and carotid plaques (data not shown). Importantly, the implications of our analyses relating changes in statin intensity to outcomes need to be treated with caution given the observational nature of our study. Finally, our report was intended to describe residual risk in a statin-treated population-based cohort only; it was beyond the scope of this report nor was there an adequate sample size available to examine residual risk among those controlled for other risk factors (e.g., diabetes or hypertension).

Conclusions

In conclusion, among a population-based cohort of persons on statin therapy free of ASCVD at baseline, residual ASCVD event risk approaches 20% in only a decade and is as high as 40% in certain subgroups (e.g., very high risk Caucasians). Moreover, DM, LDL-P, hs-CRP, and increased levels of CAC, in particular, are strong predictors of residual ASCVD events. These measures may be valuable in assessing future risk of ASCVD events in statin-treated adults and potentially targeting those needing more intensive therapy to reduce such risk.

Acknowledgements

This research was supported by contracts HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168 and N01-HC-95169 from the National Heart, Lung, and Blood Institute and by grants UL1-TR-000040 and UL1-TR-001079 from NCRR. The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org. This analysis and manuscript was supported by a contract from Amgen Inc. to the University of California, Irvine. Drs. Quek and Lopez are employees of Amgen Inc., Dr. Budoff serves on the speakers bureau of Amgen Inc., and Dr. Wong is a consultant for Amgen Inc. and Pfizer and has received speakers fees from Sanofi and Regeneron Pharmaceuticals. Dr. Cushman has research funding and has received speaking fees from Diadexus. Dr. Nathan Wong and Dr. Yanglu Zhao had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Abbreviation List

ABI	ankle brachial index

ASCVD	atherosclerotic cardiovascular disease
BMI	body mass index
CAC	coronary artery calcium
CIMT	carotid intima-media thickness
CHD	coronary heart disease
CVD	cardiovascular disease
DBP	diastolic blood pressure
DM	diabetes mellitus
eGFR	estimated glomerular filtration rate
GlycA	glycan A
HDL-C	high density lipoprotein-cholesterol
HDL-P	high density lipoprotein-particle
HR	hazard ratio
hsCRP	high-sensitivity C-reactive protein
IL-6	interluekin-6
LDL-C	low density lipoprotein-cholesterol
LDL-P	low density lipoprotein-particle
$LpPLA_2$	lipoprotein-associated phospholipase A2
MESA	Multiethnic Study of Atherosclerosis
SBP	systolic blood pressure

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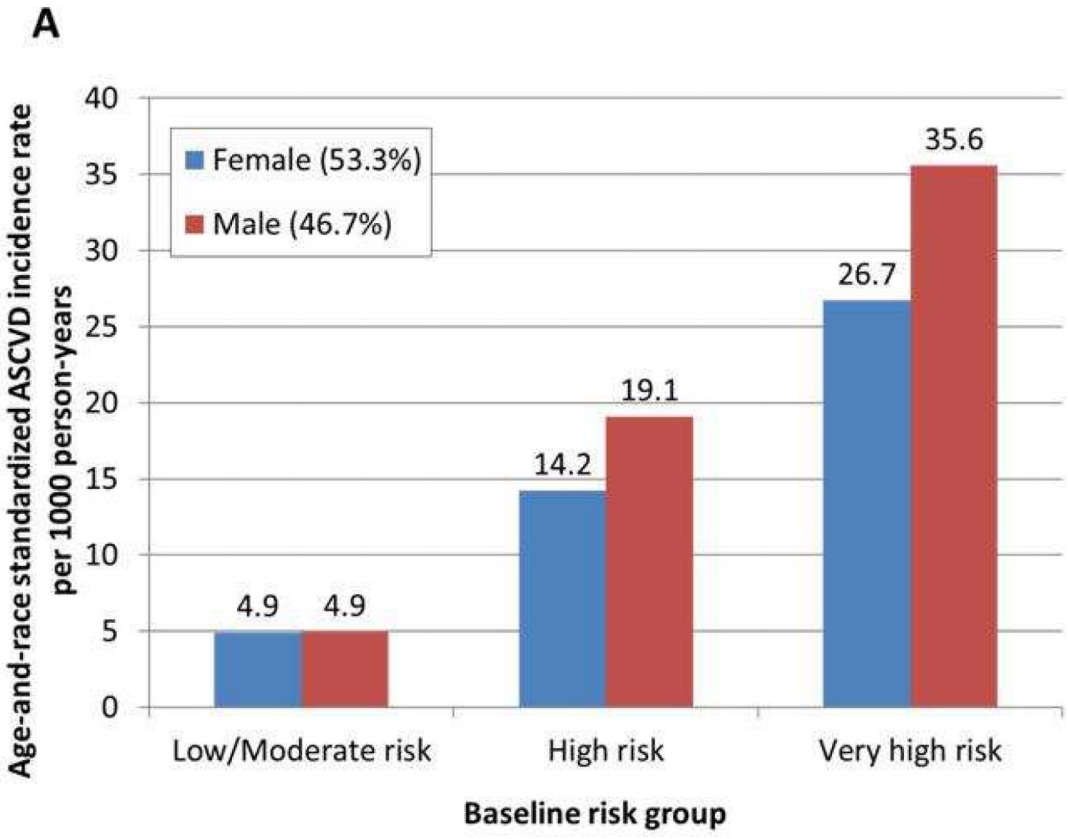
- Residual ASCVD risk in statin-treated adults without CVD is not well-quantified.
- We examined ASCVD event rates and predictors of ASCVD event risk.
- 60% of our subjects on statins were at high, and 22% at very high baseline risk.
- Predictors of residual risk included diabetes, hs-CRP, and LDL-particle number.
- Coronary artery calcium remained the most important predictor of residual risk.



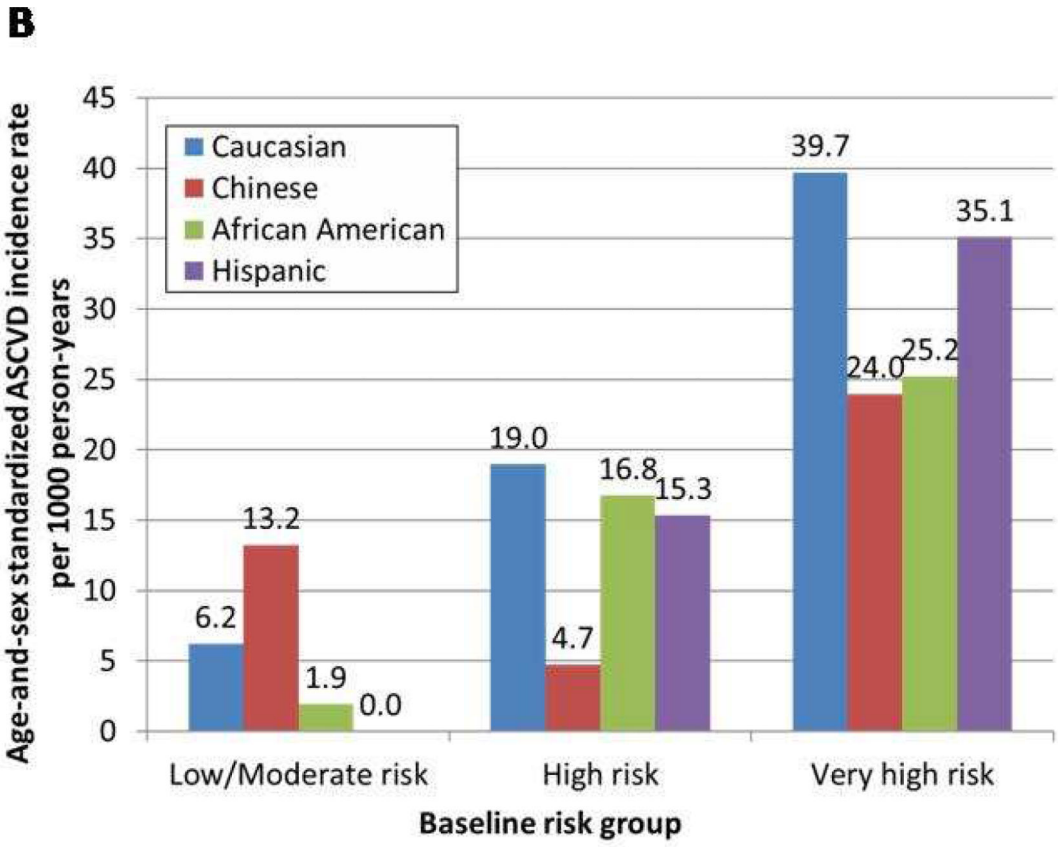


Figure 1.

Observed ASCVD Event Rate (per 1000 person years) by a) Sex (adjusted for age and ethnicity) and b) Ethnicity (adjusted for age and sex) According to National Lipid Association Risk Group

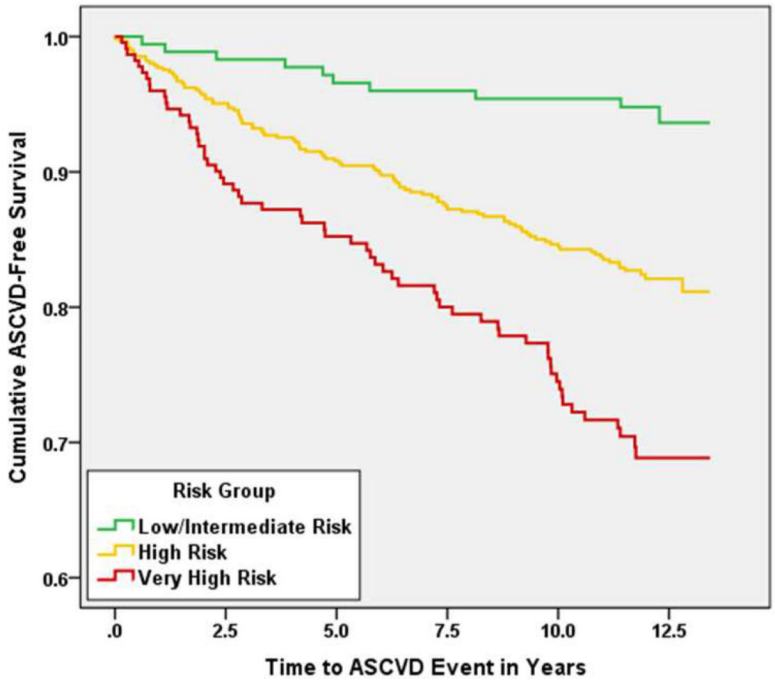


Figure 2.

Kaplan-Meier Survival Curve of ASCVD-Free Survival by National Lipid Association Risk Group. Log-rank p<0.0001 between groups (unadjusted).

Table 1.

Definition of National Lipid Association (NLA) Risk Groups (15).

Very high risk	a. ASCVD b. Diabetes mellitus with ≥ 2 other major ASCVD risk factors[a] or end-organ damage[b]
High risk	a. Diabetes mellitus with 0–1 other major ASCVD risk factors b. Chronic kidney disease stage 3B or 4 c. LDL-C ≥ 190 mg/dL (severe hypercholesterolemia phenotype) d. ≥ 3 major ASCVD risk factors e. quantitative risk scoring reaches the high-risk threshold[c]
Moderate risk	No diabetes mellitus, 2 major ASCVD risk factors and no other major indicators of higher risk
Low risk	0–1 and no other major indicators of higher risk

[a] Major ASCVD risk factors include: 1. Age ≥45 y for male and ≥55 y for female; 2. Family history of early CHD; 3. Current cigarette smoking; 4. High blood pressure (≥ 140/90 mm Hg, or on blood pressure medication) 5. Low HDL-C <40 mg/dL for male and < 50 mg/dL for female.

[b] End-organ damage indicated by increased albumin-to-creatinine ratio (≥30 mg/g), chronic kidney disease (eGFR < 60 mL/min/1.73m^2), or retinopathy.

[c] High-risk threshold is defined as >10% using Adult Treatment Panel III Framingham Risk Score for hard coronary heart disease (CHD; myocardial infarction or CHD death), >15% using the 2013 Pooled Cohort Equations for hard ASCVD (myocardial infarction, stroke or death from CHD or stroke.

ASCVD = atherosclerotic cardiovascular disease; CHD= coronary heart disease

Other risk indicators are used to reclassify participants:

If any of below are presented then risk will be reclassified into the next higher risk group:
1. > 1 pack per day smoking
2. LDL-C >=160 mg/dL and/or non-HDL-C >=190 mg/dL
3. High-sensitivity C-reactive protein >=2.0 mg/L
4. Urine albumin-to-creatinine ratio >=30 mg/g

Low or moderate risk participants with CAC >=300 are reclassified to high risk; MESA does not have information on premature family history of ASCVD so this information is not included.

Table 2.

Descriptive Characteristics of Statin Users in MESA According to Incident ASCVD

	Incident ASCVD (n=173)	No ASCVD (n=841)	P value
Age, years	67.6 ± 8.2	65.6 ± 8.8	0.008
Male	94 (54.3)	380 (45.2)	0.028
Ethnicity/Race			0.469
Caucasian	81 (46.8)	358 (42.6)	
African American	46 (26.6)	245 (29.1)	
Hispanic	33 (19.1)	148 (17.6)	
Chinese American	13 (7.5)	90 (10.7)	
Smoking status			
Previous smoker	86 (20.7)	329 (79.3)	0.002
Current smoker	21 (12.1)	76 (9.1)	0.032
SBP, mmHg	134.4 ± 21.6	129.2 ± 21.6	0.004
Antihypertensive medication	126 (72.8)	493 (58.6)	0.0005
Diabetes Mellitus	63 (36.4)	173 (20.6)	<0.0001
BMI, kg/m^2	29.8 ± 5.3	28.8 ± 5.3	0.903
Waist circumference, cm			
Family history of CVD	110 (63.6)	470 (55.9)	0.062
Triglycerides, mg/dL (mmol/L)	148±97 (1.7±1.1)	136± 82 (1.5±0.9)	0.112
HDL-C, mg/dL (mmol/L)	48.7 ± 13.8 (1.3±0.3)	51.3 ± 13.5 (1.3±0.4)	0.019
LDL-C, mg/dL (mmol/L)	104.2 ± 29.4 (2.7±0.8)	103.2 ± 28.0 (2.7±0.7)	0.674
eGFR, $mL/min/1.73m^2$	75.7 ±19.0)	77.4±17.4)	
Urine albumin creatinine ratio	7.5 (4.7–20.7)	5.8 (3.6–13.4)	
Statin intensity at baseline			0.494
Low	54 (31.2)	225(26.8)	
Moderate	111 (64.2)	574 (68.3)	
High	8 (4.6)	41(4.9)	
Statin intensity change*			0.015
Reduced intensity/stopped	32(20.0)	221(27.6)	
Remained the same intensity	99(61.9)	395(49.4)	
Increased intensity	29(18.1)	184(23.0)	
Novel biomarkers			
HDL-P, umol/L	34.6 ± 7.0	35.6 ± 6.4	0.053
LDL-P, nmol/L	1222.2 ± 318.0	1157.5 ± 299.3	0.011
hsCRP, mg/L (nmol/L)	4.1 ± 5.8 (39.0±55.2)	3.1 ± 4.9 (29.5±46.7)	0.043
IL-6, pg/mL	1.7 ± 1.2	1.5 ± 1.2	0.027
$LpPLA_2$ mass, ng/mL	170.3 ± 40.5	161.7 ± 37.7	0.015
$LpPLA_2$ activity, nmol/min/mL	141.9 ± 30.5	136.1 ± 31.8	0.045

	Incident ASCVD (n=173)	No ASCVD (n=841)	P value
Homocysteine, umol/L	10.5 ± 4.9	9.4 ± 3.1	0.0052
GlycA, umol/L	399.2 ± 65.9	386.5 ± 59.1	0.012
Subclinical Atherosclerosis measures			
CAC			<0.0001
0	25 (14.5)	304 (36.2)	
1–99	51 (29.5)	272 (32.3)	
100–399	37 (21.4)	147 (17.5)	
400+	60 (34.7)	118 (14.0)	
Mean CIMT, mm	1.23 ± 0.42	1.06 ± 0.36	<0.0001
Abnormal ABI	20 (11.6)	50 (6.0)	0.008
eGFR, mL/min	75.7 ± 19.0	77.4 ± 17.4	0.255
Carotid Stenosis			0.001 †
No	51 (30.4)	363 (43.9)	
Yes	117 (69.6)	463 (56.1)	
1–24%	66 (39.3)	314 (38.0)	
25–49%	46 (27.3)	137 (16.6)	
50–74%	3 (1.8)	6 (0.7)	
75–99%	2 (1.2)	5 (0.6)	
100%	0 (0)	1 (0.1)	
NLA risk group			
Low/moderate risk	10(5.8)	168 (20.0)	reference
High risk	102(59.0)	509(60.5)	0.0004
Very High risk	61(35.3)	164(19.5)	<0.0001

Continuous variables are presented as mean ± standard deviation and categorical variables are presented as frequencies (percentage). Abbreviation: ABI = ankle brachial index; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CAC = coronary artery calcium; CIMT = carotid intima-media thickness; DBP = diastolic blood pressure; DM = diabetes mellitus; eGFR = glomerular filtration rate; GlycA = glycan A; HDL-C = high density lipoprotein-cholesterol; HDL-P = high density lipoprotein-particle; hsCRP = high-sensitivity C-reactive protein; IL-6 = interluekin-6; LDL-C = low density lipoprotein-cholesterol; LDL-P = low density lipoprotein-particle; $LpPLA_2$ = lipoprotein-associated phospholipase A2; SES = socioeconomic status; SBP = systolic blood pressure. NLA=National Lipid Association.

* Statin intensity change information missing for 91 persons.

† Comparing stenosis yes vs. no.

Table 3.

Cox Regression of Risk of Atherosclerotic Cardiovascular Disease (ASCVD) Events Including Demographic and Standard Risk Markers with Novel Biomarkers, and Subclinical Atherosclerosis Measures

	Model 1		Model 2		Model 3	
	HR	**95%CI**	**HR**	**95%CI**	**HR**	**95%CI**
Age, per SD	1.32	1.13–1.54***	1.22	1.00–1.48*	1.06	0.88–1.29
Male vs. female	1.48	1.09–2.00*	1.38	0.95–1.99	1.32	0.94–1.86
Chinese vs. Caucasian	0.64	0.36–1.15	0.73	0.38–1.39	1.00	0.54–1.88
African American vs. Caucasian	0.92	0.64–1.33	0.70	0.45–1.09	0.83	0.55–1.24
Hispanic vs. Caucasian	1.00	0.67–1.50	0.71	0.44–1.09	0.90	0.58–1.40
LDL-C, per SD	1.04	0.89–1.21	0.73	0.54–0.99*	0.85	0.66–1.10
Log-HDL-C, per SD	0.81	0.69–0.95*				
Log-Triglycerides, per SD	1.21	1.03–1.42*				
Prior smoker vs. non smoker	1.54	1.10–2.15*	1.35	0.93–1.96	1.38	0.98–1.95
Current smoker vs. non smoker	2.04	1.23–3.38**	1.98	1.11–3.54*	1.77	1.05–3.00*
Family history of CVD, yes vs. no	1.38	1.01–1.90*	1.38	0.96–1.97	1.45	1.04–2.03*
SBP per SD	1.23	1.06–1.43**	1.16	0.98–1.39	1.14	0.98–1.33
Hypertension med, yes vs. no	1.80	1.28–2.54***	1.37	0.90–2.09	1.45	0.99–2.11
DM, yes vs. no	2.41	1.74–3.34****	2.45	1.68–3.57****	1.97	1.40–2.78***
BMI per SD	1.27	1.09–1.48**				
Waist Circumference, per SD	1.22	1.06–1.40**				
eGFR, per SD	0.98	0.83–1.15				
Novel biomarkers						
HDL-P, per SD	0.89	0.74–1.06	0.97	0.79–1.20		
LDL-P, per SD	1.27	1.10–1.48**	1.22	1.03–1.44*	1.30	1.12–1.51***
Log-hsCRP, per SD	1.35	1.15–1.58***	1.30	1.09–1.55**	1.31	1.11–1.54**
Log-IL-6, per SD	1.26	1.09–1.47**			1.17	1.00–1.38
$LpPLA_2$ mass, per SD	1.18	1.01–1.69*	1.12	0.89–1.40		
$LpPLA_2$ activity, per SD	1.16	0.98–1.38	1.07	0.81–1.42		
Log-Homocysteine, per SD	1.23	1.06–1.44**	1.22	1.03–1.44*		
GlycA, per SD	1.33	1.14–1.56***	1.11	0.90–1.38		
Subclinical atherosclerosis measures						
CAC 1–99 vs. 0	2.14	1.31–3.49**			1.88	1.15–3.09*
CAC 100–399 vs. 0	2.88	1.70–4.89****			2.27	1.32–3.89**
CAC 400+ vs. 0	5.58	3.33–9.34****			3.38	1.97–5.80****
Log-Mean CIMT, per SD	1.50	1.28–1.77****			1.24	1.04–1.48*
Abnormal ABI, yes vs. no	1.88	1.16–3.04*			1.43	0.84–2.44

	Model 1		Model 2		Model 3	
	HR	**95%CI**	**HR**	**95%CI**	**HR**	**95%CI**
Carotid stenosis	1.63	1.16–2.30**			0.91	0.58–1.42

Model 1 shows HR for each measure adjusted for age, sex, ethnicity/race (HR for age, sex and ethnicity/race were adjusted for each other);

Model 2 forces age, sex, and race in the model and allows stepwise selection of standard risk factors with p<0.15 and novel biomarkers with p<0.15 in model 1;

Model 3 forces for age, sex, ethnicity/race, standard risk factors with p<0.15 and novel biomarkers with p<0.15 from Model 2 in the model and allows stepwise selection of subclinical atherosclerosis measures Likelihood Ratio Chi-square contributions for the final model (model 3) were 0.39 for age, 2.56 for sex, 0.96 for race, 5.76 for smoking, 4.81 for family history, 14.85 for DM, 12.18 for LDL-P,10.46 for CRP, 3.83 for homocysteine, 20.07 for CAC categories and 5.96 for CIMT.

Age (SD) =8.7 year, LDL-C (SD) =28.3mg/dL (0.74 mmol/L), SBP (SD) = 21.7mmHg, HDL- P (SD) =6.5umol/L, LDL-P (SD) =303.4 nmol/L, $LpPLA_2$ mass (SD) = 38.4ng/mL, $LpPLA_2$ activity (SD) = 31.7 nmol/min/mL, GlycA (SD) =60.5 umol/L, eGFR (SD) = 17.7 mL/min/1.73m^2.

*p<0.05

†p<0.01

‡p<0.001

§p<0.0001.

Abbreviation: ABI = ankle brachial index; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CAC = coronary artery calcium; CIMT = carotid intima-media thickness; DBP = diastolic blood pressure; DM = diabetes mellitus; eGFR = glomerular filtration rate; GlycA = glycan A; HDL-C = high density lipoprotein-cholesterol; HDL-P = high density lipoprotein-particle; HR = hazard ratio; hsCRP = high-sensitivity C-reactive protein; IL-6 = interluekin-6; LDL-C = low density lipoprotein-cholesterol; LDL-P = low density lipoprotein-particle; $LpPLA_2$ = lipoprotein-associated phospholipase A2; SBP = systolic blood pressure.

Sample sizes vary by model based on included covariates

Table 4.

Association of Baseline Statin Intensity and Statin Intensity Change During Follow-up with Future ASCVD events.

	HR	95%CI	P value
Baseline statin intensity			
Low intensity	ref	/	/
Moderate intensity	0.61	0.39–0.97 *	0.0344
High intensity	0.61	0.24–1.54	0.2954
Statin intensity change			
Stayed the same	ref	/	/
Stopped or reduced	0.65	0.41–1.03	0.0647
Increased	0.38	0.21–0.67	0.0008

The model was adjusted for all risk factors in Model 4 of table 3, including age, sex, race, smoking, family history of premature CVD, SBP, diabetes, hypertension medication, LDL-P, hs-CRP, total homocysteine, CAC categories and mean CIMT

* p<0.05

† p<0.01

‡ p<0.001

§ p<0.0001.

Table 5.

Cox Regression of Risk of Atherosclerotic Cardiovascular Disease (ASCVD) Events Including Demographic and Standard Risk Markers with Novel Biomarkers, and Subclinical Atherosclerosis Measures in Participants with Baseline LDL-C< 100 mg/dl

	Model A		**Model B**	
	HR	**95%CI**	**HR**	**95%CI**
Age, per SD	1.51	1.17–1.96**	1.28	0.96–1.70
Male vs. female	0.97	0.59–1.60	0.87	0.51–1.47
Chinese vs. Caucasian	0.68	0.29–1.61	0.81	0.34–1.94
African American vs. Caucasian	0.60	0.33–1.07	0.79	0.42–1.47
Hispanic vs. Caucasian	0.86	0.48–1.55	1.11	0.59–1.47
LDL-C, per SD				
Log-HDL-C, per SD	0.78	0.60–1.01	0.83	0.63–1.10
Log-Triglycerides, per SD				
Prior smoker vs. non smoker				
Current smoker vs. non smoker				
Family history of CVD, yes vs. no	1.57	0.98–2.50	1.37	0.84–2.23
SBP per SD				
Hypertension med, yes vs. no				
DM, yes vs. no	2.72	1.72–4.32****	2.24	1.38–3.63**
BMI per SD				
Waist Circumference, per SD				
eGFR, per SD				
Novel biomarkers				
HDL-P, per SD				
LDL-P, per SD	1.45	1.01–2.08 *	1.68	1.16–2.45**
Log-hsCRP, per SD	1.40	1.12–1.75**	1.39	1.11–1.75**
Log-IL-6, per SD				
$LpPLA_2$ mass, per SD				
$LpPLA_2$ activity, per SD				
Log-Homocysteine, per SD	1.22	0.98–1.53	1.16	0.92–1.48
GlycA, per SD				
Subclinical atherosclerosis measures				
CAC 1–99 vs. 0			1.91	0.92–3.98
CAC 100–399 vs. 0			2.07	0.89–4.85
CAC 400+ vs. 0			3.94	1.80–8.62***
Log-Mean CIMT, per SD				
Abnormal ABI, yes vs. no			1.72	0.92–3.21
Carotid stenosis				

Model A forces age, sex, and race in the model and allows stepwise selection of standard risk factors with $p<0.15$ and novel biomarkers with $p<0.15$ in model 1 of table 3;

Model B forces for age, sex, ethnicity/race, SES, standard risk factors with $p<0.15$ and novel biomarkers with $p<0.15$ from Model A and allows stepwise selection of subclinical atherosclerosis measures;

Age (SD) =8.7 year, LDL-C (SD) =28.3mg/dL (0.74 mmol/L), SBP (SD) = 21.7mmHg, HDL- P (SD) =6.5umol/L, LDL-P (SD) =303.4 nmol/L, $LpPLA_2$ mass (SD) = 38.4ng/mL, $LpPLA_2$ activity (SD) = 31.7 nmol/min/mL, GlycA (SD) =60.5 umol/L, eGFR (SD) = 17.7 mL/min/1.73m^2.

* $p<0.05$

† $p<0.01$

‡ $p<0.001$

§ $p<0.0001$.

Abbreviation: ABI = ankle brachial index; ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CAC = coronary artery calcium; CIMT = carotid intima-media thickness; DBP = diastolic blood pressure; DM = diabetes mellitus; eGFR = glomerular filtration rate; GlycA = glycan A; HDL-C = high density lipoprotein-cholesterol; HDL-P = high density lipoprotein-particle; HR = hazard ratio; hsCRP = high-sensitivity C-reactive protein; IL-6 = interluekin-6; LDL-C = low density lipoprotein-cholesterol; LDL-P = low density lipoprotein-particle; $LpPLA_2$ = lipoprotein-associated phospholipase A2; SBP = systolic blood pressure.

Sample sizes vary by model based on included covariates