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Utility of lipoprotein particle measures for assessing coronary heart disease risk post-AHA/ACC guidelines: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Objective—The American College of Cardiology and American Heart Association have issued guidelines indicating that the contribution of apolipoprotein B-100 (ApoB) to cardiovascular risk assessment remains uncertain. The present analysis evaluates whether lipoprotein particle measures convey risk of coronary heart disease (CHD) in 4,679 Multi-Ethnic Study of Atherosclerosis (MESA) participants.

Approach and Results—Cox regression analysis was performed to determine associations between lipids or lipoproteins and primary CHD events. Following adjustment for non-lipid variables, lipoprotein particle levels in 4th quartiles were found to convey significantly greater risk of incident CHD compared to 1st quartile levels (hazard ratio (HR); 95% confidence interval (CI)): ApoB (HR: 1.84; CI: 1.25, 2.69), ApoB/ApoA-I (HR: 1.91; CI: 1.32, 2.76), total LDL-particles (LDL-P) (HR: 1.77; CI: 1.21, 2.58), and the LDL-P/HDL-P ratio (HR: 2.28; CI: 1.54, 3.37). Associations between lipoprotein particle measures and CHD were attenuated following adjustment for standard lipid panel variables. Using the AHA/ACC risk calculator as a baseline

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model for CHD risk assessment, significant net reclassification improvement (NRI) scores were found for ApoB/ApoA-I (0.18 p=0.007), and LDL-P/HDL-P (0.15, p<0.001). C-statistics revealed no significant increase in CHD event discrimination for any lipoprotein measure.

Conclusion—Lipoprotein particle measures ApoB/ApoA-I and LDL-P/HDL-P marginally improved NRI scores, but null findings for corresponding c-statistic are not supportive of lipoprotein testing. The attenuated associations of lipoprotein particle measures with CHD following adjustment for lipids indicate that their measurement does not detect risk that is unaccounted for by the standard lipid panel. However, the possibility that lipoprotein measures may identify CHD risk in a subpopulation of individuals with normal cholesterol but elevated lipoprotein particle numbers cannot be ruled out.

INTRODUCTION

The American College of Cardiology (ACC) and American Heart Association (AHA) have recently issued guidelines for calculating cardiovascular risk (1). The guidelines exclude a number of biomarkers whose value in identifying risk remains ambiguous, but leave open the possibility of their inclusion in future recommendations with more conclusive research. Among these biomarkers, apolipoprotein B-100 (ApoB) is cited as an assessment tool whose contribution to risk is uncertain, and no recommendation is given. It is the goal of the current study to test whether ApoB and other non-standard lipoprotein measurements may improve disease risk prediction using the new ACC/AHA 10-yr risk assessment calculator score as a baseline model.

Thus far, studies remain divided as to whether including apolipoproteins in risk models improves classification. Supporting their inclusion, ApoB and/or the ratio of ApoB to apolipoprotein A-I (ApoA-I) have been shown to associate with adverse cardiovascular outcomes and have been suggested to more accurately predict events than routine cholesterol measures such as low density lipoprotein-cholesterol (LDL-C), the ratio of total cholesterol (TC) to high density lipoprotein-cholesterol (HDL-C), or non-HDL-C (i.e., TC – HDL-C) in case-control (2-4), prospective (5-9) and interventional studies (10-12). In contrast, null findings have also been reported—prospective studies including the Women's Health study (13), Framingham Offspring Study (14), European Prospective Investigation into Cancer and Nutrition (15), and the Atherosclerosis Risk in Communities study (16, 17) showed that ApoB provides no additional risk information beyond the current lipid panel. Similar to ApoB, total LDL particle (LDL-P) concentrations derived from nuclear magnetic resonance (NMR) spectroscopy have also been shown to associate with risk of CVD and CHD (18-20), but may be equivalent to standard lipid measures in predicting future events (18, 20). Overall, evidence to support the clinical utility of NMR or apolipoprotein measurements is equivocal yet there may be a benefit of incorporating lipoprotein particle concentrations to risk profiles for a more complete assessment of lipoprotein phenotype, and by extension, disease risk.

In the present analysis of 4,679 Multi-Ethnic Study of Atherosclerosis (MESA) participants over an 8.5-year follow-up period, we first compared the standard lipid panel with non-standard measurements ApoB and the ratio of ApoB/ApoA-I as well as nuclear magnetic

resonance (NMR) spectroscopy-derived measures of total LDL particles (LDL-P) and the ratio of LDL-P to high density lipoprotein particles (HDL-P) for evaluating CHD risk. We then determined whether these lipoprotein measures may impart risk independent of cholesterol measures. Finally, we used the AHA/ACC risk calculator score as a baseline prediction model and determined whether individual additions of ApoB, ApoB/ApoA-I, LDL-P, or LDL-P/HDL-P improved CHD risk prediction.

MATERIALS AND METHODS

Materials and Methods are available in the online-only Data Supplement.

RESULTS

Unadjusted demographic, clinical, and lifestyle characteristics of 4,679 MESA participants are shown in Table 1.

Estimated hazard ratios (HRs) for CHD outcomes by quartiles of LDL-C, non-HDL-C, TC/HDL-C, ApoB, ApoB/ApoA-I, total LDL-P, and LDL-P/HDL-P are presented in Table 2. Adjustments were made for non-lipid measures including sex, systolic blood pressure, hypertension medication use, age, and race/ethnicity. Lipid-lowering medication that began after baseline did not significantly alter results and was not included in the model. All lipid and apolipoprotein measures were found to be significantly associated with risk of incident CHD. Individuals with lipid or apolipoprotein levels in the 4th quartiles were found to be at significantly greater risk of incident CHD than those in the 1st quartile: LDL-C (HR: 1.62; CI: 1.11, 2.35); non-HDL-C (HR: 1.99; CI: 1.36, 2.90); total cholesterol (TC)/HDL-C (HR: 2.24; CI: 1.50, 3.33); ApoB (HR: 1.84; CI: 1.25, 2.69); ApoB/ApoA-I (HR: 1.91; CI: 1.32, 2.76); total LDL-particles (HR: 1.77; CI: 1.21, 2.58); LDL-P/HDL-P (HR: 2.28 CI: 1.54, 3.37). Given the presence of four ethnicities/races in this subcohort, an interaction analysis was performed (supplementary tables I and II). No modifying influence of race was observed.

Given the similarity of HRs among lipid and lipoprotein variables, it was then determined whether ApoB, ApoB/ApoA-I, LDL-P, LDL-P/HDL-P would associate with CHD event outcomes independent of LDL-C, non-HDL-C, TC/HDL-C, or all lipid panel variables TC, LDL-C, HDL-C, and triglycerides (TGs) (Table 3). Cox proportional hazards analyses were conducted, and adjustments were made for sex, hypertension medication, systolic blood pressure, age, diabetes, smoking, and race/ethnicity, with individual adjustments for LDL-C, non-HDL-C, or TC/HDL-C, followed by a combination of TC, LDL-C, HDL-C, and TGs. Following adjustment for LDL-C, significant associations with incident CHD were observed for individuals in the 4th quartiles for ApoB (HR= 1.99; CI: 1.18, 3.36), ApoB/ApoA-I (HR=1.86; CI: 1.21, 2.85), total LDL-P (HR=1.75; CI: 1.11, 2.75); and LDL-P/HDL-P (HR: 2.303 CI: 1.49, 3.57). Following adjustment for non-HDL-C, associations with future incident CHD were observed for the top quartiles of ApoB (HR: 1.83; CI: 1.01, 3.34), ApoB/ApoA-I (HR: 1.72; CI: 1.10, 2.70), and LDL-P/HDL-P (HR: 2.25; CI: 1.43, 3.55). No significant associations were found between total LDL-P and CHD following adjustment for non-HDL-C. Only the association of LDL-P/HDL-P with CHD was observed for individuals

in the 4th quartiles following adjustment for TC/HDL-C (HR: 2.02; CI: 1.19, 3.42). Finally, upon adjusting for all variables in the standard lipid panel (TC, LDL-C, HDL-C, and TGs), no significant associations were observed with CHD.

NRI and c-statistics were employed to evaluate the performance of each lipid or lipoprotein marker when added to a baseline 2013 AHA/ACC cardiovascular risk calculator score. The total NRI represents the combination of reclassifications for CHD cases or 'events' (M_{event}) and 'non-events' ($M_{nonevent}$). M_{event} is the proportion of event subjects whose calculated probability of having an event in the new model is greater than that in the baseline model; a positive M_{event} represents an improvement in sensitivity of the new model. In contrast, $M_{nonevent}$ is the proportion of non-event subjects whose predicted probability of having an event in the new model is greater than that in the baseline model; a negative $M_{nonevent}$ represents an improvement in model specificity while a positive $M_{nonevent}$ represents a greater number of false-positives and decrease in specificity. All NRI reclassifications, i.e. total, events (M_{event}), and nonevents ($M_{nonevent}$) are reported in Table 4. TC/HDL-C, LDL-P/HDL-P, and ApoB/ApoA-I ratios were found to significantly improve the AHA/ACC risk score for incident CHD. ApoB/ApoA-I improved reclassification of events (M_{event}=0.43) but incorrectly reclassified nonevents ($M_{nonevent}$=0.24), resulting in a total NRI of 0.18 (p=0.007). LDL-P/HDL-P improved reclassification of events (M_{event}=0.39) but incorrectly reclassified nonevents ($M_{nonevent}$=0.25), resulting in a total NRI of 0.145 (p<0.001). Likewise, TC/HDL-C improved reclassification of events (M_{event}=0.58) but incorrectly reclassified nonevents ($M_{nonevent}$=0.46), resulting in a total NRI of 0.12 (p=0.03).

In contrast to NRI scores, c-statistics revealed no significant improvements with the addition of any lipid or lipoprotein to the AHA/ACC baseline model. Respective c-statistics for the baseline AHA/ACC model and with the addition of each lipid/lipoprotein were as follows: AHA/ACC = 0. 730; LDL-C = 0. 727; non-HDL-C = 0. 724; TC/HDL-C ratio = 0.726; LDL-P = 0. 725; LDL-P/HDL-P = 0.727; ApoB = 0. 728; ApoB/ApoA-I ratio = 0.736.

DISCUSSION

A 2013 report from the AHA/ACC task force on risk assessment states that there is insufficient evidence to include ApoB or ApoB/ApoA-I to current risk guidelines (1). We found that elevated levels of ApoB, ApoB/ApoA-I, as well as NMR-derived total LDL-P and LDL-P/HDL-P were significantly associated with future CHD events, though only the association of LDL-P/HDL-P remained significant following adjustment for TC/HDL-C. Upon adjusting for traditional lipid panel variables of TC, LDL-C, HDL-C, and TGs, no associations remained significant. NRI analysis revealed that including TC/HDL-C, ApoB/ApoA-I, or LDL-P/HDL-P to the 2013 AHA/ACC risk score significantly reclassified individuals by improving sensitivity; however the improvement of sensitivity comes at the expense of decreased specificity in all cases. C-statistics revealed that neither apolipoproteins nor NMR measures significantly improved event prediction.

Previous studies have reported inconsistent findings as to whether apolipoproteins identify disease risk more effectively than traditional lipid measures. Results from two of the largest studies to date, Apolipoprotein MOrtality RISk study (AMORIS, n=175,553) and

INTERHEART (n=9,345 acute MI cases, n=12,120 controls) indicate that respective measures of ApoB/ApoA-I and ApoB may improve CHD risk assessment (2, 5). Conducted across 52 countries in 12,461 cases and 14,637 controls, the INTERHEART study showed that the ratio of ApoB/ApoA-I was significantly associated with MI risk (OR=1.59)—greater than either non-HDL-C (OR=1.21) or TC/HDL-C (OR=1.17) (2). In the prospective AMORIS study, investigators found that ApoB was more accurate in predicting fatal MI than LDL-C over an approximate 5.5 year follow up (5). In agreement with AMORIS and INTERHEART, a host of additional studies (3, 4, 6-8) including the National Health and Nutrition Examination Survey (9) as well as clinical trials for statin therapies, Air Force Coronary/Texas Atherosclerosis Prevention Study (11) and Long-term Intervention with Pravastatin in Ischemic Disease (12), have indicated that apolipoprotein measurement may either be a useful addition to or replacement of standard lipid measures in evaluating disease risk. Particularly noteworthy, the Air Force Coronary/Texas Atherosclerosis Prevention Study showed that ApoB, but not LDL-C, predicted primary coronary events at baseline and on statin therapy—demonstrating that it may have value over LDL-C measurement (11). A recent and comprehensive meta-analysis of twelve epidemiological studies (n=233,455; events=22,950) conducted by Sniderman et al. (21) confirmed the above study findings. The authors concluded that ApoB (RR=1.43; CI=1.35, 1.51) ‘is superior’ to non-HDL-C (RR=1.34; CI=1.24, 1.44) and LDL-C (RR=1.25; CI=1.18, 1.33) in associating with future fatal or nonfatal ischemic cardiovascular events.

Contrary to the above evidence, other studies have demonstrated that ApoB and ApoB/ApoA-I do not improve risk assessment over the standard lipid panel. An early prospective study conducted over a 10-year follow-up period in Atherosclerosis Risk in Communities participants was one of the first to show that ApoB and ApoA-I are not associated with higher CHD risk in models that accounted for LDL-C, HDL-C, and TG levels (16). Subsequent studies have since compared ApoB with non-HDL-C. Framingham Offspring (15-year follow up) (14), European Prospective Investigation into Cancer and Nutrition (11.4 year follow up) (15), and the Women’s Health Study (11-year follow up) (13) found that ApoB and non-HDL-C were equivalent in their associations with CHD risk. This last prospective study by Mora et al. (13) further reported that the ApoB/ApoA-I ratio conferred a 2.79-fold higher risk for incident CVD, similar to that of the TC/HDL-C ratio, HR=2.82. Calculation of NRI for apolipoprotein measures demonstrated limited improvement in CVD risk assessment compared to the TC/HDL-C ratio (<2%). Finally, a 2009 meta-analysis composed of 22 studies (n= 91,307, events=4,449) reported that the ratio of ApoB to ApoA-I showed a similar association with future CHD as non-HDL-C/HDL-C (22). Our findings largely agree with these latter studies that ApoB, ApoB/ApoA-I, and standard lipid measures are comparably associated with future CHD outcomes.

The core reasons for the disparities among studies remain unclear, but differences in study populations, statistical models and covariates, assay methodologies, CHD endpoints, length of study follow-up periods, or a combination of these and other factors may be involved. In the Women’s Health Study cohort, Mora et al. (13) suggested that fully adjusted models with lifestyle and demographic information may result in study differences. This observation is particularly relevant, as sex (16), age (6), and the presence of diabetes (23) may influence the association of ApoB with CVD risk, though an effect of age has also been refuted (21).

These differences may contribute to the incongruent associations with CVD/CHD incidence, and should be considered when evaluating the clinical utility of apolipoproteins. A final possibility remains that the value in apolipoprotein measurements relies on identifying individuals with uncommon lipid profiles where cholesterol is normal but lipoprotein particle numbers are high—a so-called discordant phenotype (24). Most studies, including MESA, do not have an adequate number of CHD outcomes to test this hypothesis.

NMR-Derived Total LDL Particle Number

NMR has also been proposed as a more accurate means of identifying CHD risk by quantifying the sizes and total concentrations of lipoproteins including LDL and HDL. Though NMR measures are not as well-studied as apolipoproteins, it is generally accepted that elevated LDL-P concentrations convey risk of CVD or CHD (13, 18, 24, 25). It has further been reported that LDL-P is superior to LDL-C in assessing disease risk (13, 18, 19), but more recent studies suggest that LDL-P is equivalent to LDL-C and/or non-HDL-C (13, 24, 25). Our findings agree with the latter studies that total LDL-P is similar to non-HDL-C as a relationship was not observed following its adjustment.

In contrast, the ratio of LDL-P/HDL-P was found to associate with CHD independent of LDL-C, non-HDL-C, or TC/HDL-C. To date, we are the first to demonstrate that it conveys risk of CHD *independent* of these cholesterol measures; however, very few studies have examined LDL-P/HDL-P in relation to CHD events (26). Given the paucity of data, the significance of this result remains highly uncertain until further studies either confirm or refute our finding in this regard.

CHD Risk Classification

The 2013 AHA/ACC risk calculator score served as the baseline model, and improvement in event prediction was tested with the addition of each lipid and lipoprotein variable. NRI analysis revealed that adding ApoB/ApoA-I, LDL-P/HDL-P, or TC/HDL-C ratios modestly improved the prediction of future CHD events (myocardial infarction, resuscitated cardiac arrest, or CHD death); however, interpreting these results is not straightforward. For instance, the addition of ApoB/ApoA-I identified 42.8% of the population that suffered a CHD event (or 60 individuals) as being at higher risk compared to the baseline model. However, this increased sensitivity comes at the expense of specificity—adding ApoB/ApoA-I to the baseline model predicted higher CHD risk for 24.5% of those that did not suffer events (or 1102 individuals). Supplementing these findings, the c-statistic revealed no improvement in event prediction with the addition of any measure to the AHA/ACC baseline model, though this finding was expected as it is a more conservative test than NRI. Taken together, the addition of ApoB/ApoA-I or LDL-P/HDL-P may modestly improve sensitivity for detecting CHD risk but reduces specificity—potentially explaining the null findings for their respective c-statistics. Further studies are warranted to determine whether the higher sensitivity but lower specificity offered by NMR or apolipoprotein testing is cost effective.

Strengths and Limitations

The present analysis contains a number of limitations. First, it must be acknowledged that the AHA/ACC guidelines were developed using CHD and ischemic stroke as outcome variables. Our analysis restricted outcomes to CHD alone using a broader definition to include instances of angina when followed by coronary artery bypass and/or where obstruction was found to be ≥70%. In addition, there may be a selection bias in the present study as individuals taking lipid-lowering medication at baseline were excluded, potentially skewing results toward the null finding. In our statistical model, we adjusted for multiple variables; however, we cannot discount the presence of residual confounding. Apart from potential confounding, we recognize the importance of sub-analyses by sex, race, and other subgroups, but did not have the statistical power to stratify the population. Though our analysis was limited by the relatively few CHD events, statistically significant findings were still apparent.

Conclusions

The present analysis represents a comprehensive evaluation of lipoprotein and apolipoprotein measurements and their associations with future CHD events. The association of LDL-P/HDL-P ratio with CHD independent of individual standard lipid measures may be a novel finding, but requires confirmation by other large prospective studies. By comparison, our findings for ApoB/ApoA-I were largely equivocal. Though ApoB/ApoA-I increased sensitivity, the lower specificity and C-statistic results do not support its measurement. Moreover, the attenuated associations following adjustment for lipid variables indicate that lipoprotein particle measures do not detect risk that is unaccounted for by the standard lipid panel. Lipoprotein measurement may yet be useful in identifying risk in a subgroup of individuals, but a larger population of those with a discordant lipid-lipoprotein phenotype is necessary to determine whether such testing is cost effective.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
AMORIS	Apolipoprotein MOrtality RISk study

ApoA-I	apolipoprotein A-I
ApoB	apolipoproteins B-100
CHD	coronary heart disease
CVD	cardiovascular disease
HDL-C	high density lipoprotein cholesterol
HDL-P	HDL particle
LDL-C	low density lipoprotein cholesterol
LDL-P	LDL particle
MESA	Multi-ethnic Study of Atherosclerosis
NRI	Net Reclassification Improvement
TC	total cholesterol
TGs	triglycerides

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Significance

Blood levels of total cholesterol, LDL-C, and HDL-C have been used for decades to evaluate risk for developing coronary heart disease (CHD). However, these measurements give an incomplete picture of an individual's lipid profile, as cholesterol is carried in the blood by lipoprotein particles. We hypothesized that lipoprotein measurements provide CHD risk information independent of cholesterol measures. Indeed, we observed that the ratio of LDL-particles to HDL-particles was associated with incident CHD independent of cholesterol measures including total cholesterol/HDL-C; however, findings were attenuated following adjustment for total cholesterol, LDL-C, HDL-C and triglyceride levels. Upon including these lipoprotein measures in the 2013 AHA/ACC risk calculator, we found that the ratios of LDL-particles to HDL-particles and apolipoprotein B (a surrogate measure of LDL particles) to apolipoprotein A-I (a surrogate measure of HDL particles) improved the sensitivity of the risk calculator, but the lower specificity and C-statistic results did not support their measurement.

Table 1

Unadjusted baseline demographic, lifestyle, and clinical characteristics of the Multi-Ethnic Study of Atherosclerosis subcohort (n=4,679)

Demographics	
Age (SD)	61.9 (10.4)
Sex, n (%) female	2457 (52.5)
Race/ethnicity	
Black, n (%)	1347 (28.8)
Caucasian n (%)	1709 (36.5)
Chinese, n (%)	559 (12.0)
Hispanic, n (%)	1064 (22.7)
Lifestyle	
Current smoker, n (%)	607 (13.0)
Alcohol current use, n (%)	2551 (68.2)
Clinical characteristics	
Hypertension, n (%)	1952 (41.7)
Body Mass Index (SD)	28.2 (5.5)
Total cholesterol, mg/dL (SD)	196.3 (35.5)
LDL-C, mg/dL (SD)	119.7 (31.4)
HDL-C, mg/dL (SD)	51.1 (15.1)
TG levels, mg/dL (SD)	128.5 (87.5)

Table 2

Risk of incident CHD are expressed as hazard ratios followed by 95% confidence intervals and *P* values for LDL-C, non-HDL-C, TC/HDL-C, ApoB, ApoB/ApoA-I, total LDL-P concentration (NMR) or the ratio of LDL-P to HDL-P in 4,679 MESA participants adjusted for non-lipid variables*

	Qrt	LDL-C	Non-HDL-C	TC/HDL-C	ApoB	ApoB/ApoA	LDL-P	LDL-P/HDL-P
CHD	1	ref	ref	ref	ref	ref	ref	ref
233 events	2	0.93 (0.63, 1.38) 0.73	1.16 (0.78, 1.73) 0.48	1.37 (0.90, 2.09) 0.15	1.06 (0.70, 1.58) 0.79	0.85 (0.56, 1.30) 0.46	1.01 (0.67, 1.52) 0.95	1.15 (0.74 - 1.77) 0.54
	3	1.35 (0.93, 1.97) 0.11	1.28 (0.87, 1.88) 0.21	1.10 (0.71, 1.71) 0.67	1.33 (0.90, 1.96) 0.16	1.03 (0.69, 1.53) 0.90	1.18 (0.79, 1.74) 0.42	1.29 (0.85 - 1.96) 0.22
	4	**1.62 (1.11, 2.35) 0.012**	**1.99 (1.36, 2.90) <0.001**	**2.24 (1.50, 3.33) <0.001**	**1.84 (1.25, 2.69) 0.0019**	**1.91 (1.32, 2.76) <0.001**	**1.77 (1.21, 2.58) 0.003**	**2.28 (1.54 - 3.37) <0.001**

CHD = coronary heart disease; Qrt = quartile; TC = total cholesterol; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; ApoB = apolipoproteins B-100; ApoA-I = apolipoprotein A-I; LDL-P = LDL particle; HDL-P = HDL particle; NMR= nuclear magnetic resonance spectroscopy; MESA = Multi-ethnic Study of Atherosclerosis

*Adjusted for sex, hypertension meds, systolic blood pressure, age (category), diabetes, smoking, and race/ethnicity.

Table 3

Risk of incident CHD for lipoprotein particle markers in 4,679 MESA participants are adjusted for non-lipid variables* + ***specified lipid measure(s)†.*** Results for each marker are presented as hazard ratios for individuals in 4th quartiles, using respective 1st quartiles as referents; 95% confidence intervals and *P* values are specified.

Outcome	† Lipid adjustment	ApoB	ApoB/ApoA-I	LDL-P	LDL-P/HDL-P
CHD 233 events	LDL-C	**1.99 (1.18, 3.36) 0.01**	**1.86 (1.21, 2.85) 0.005**	**1.75 (1.11, 2.75) 0.016**	**2.3 (1.49, 3.57) <0.001**
	Non-HDL-C	**1.83 (1.01, 3.34) 0.048**	**1.72 (1.10, 2.70) 0.018**	1.60 (0.98, 2.62) 0.06	**2.25 (1.43, 3.55) <0.001**
	TC/HDL-C	1.48 (0.94, 2.32) 0.089	1.32 (0.81, 2.15) 0.27	1.36 (0.85, 2.17) 0.20	**2.02 (1.19, 3.42) 0.009**
	TC+ LDL-C + HDL-C + TG	1.23 (0.63, 2.41) 0.55	1.12 (0.64, 1.98) 0.69	1.08 (0.62, 1.91) 0.78	1.76 (0.95, 3.27) 0.072

CHD = coronary heart disease; TC = total cholesterol; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; TG = triglycerides; ApoB = apolipoproteins B-100; ApoA-I = apolipoprotein A-I; LDL-P = LDL particle; HDL-P = HDL particle; MESA = Multi-ethnic Study of Atherosclerosis

*Adjusted for non-lipid risk factors including sex, hypertension meds, systolic blood pressure, age (category), diabetes, smoking, and race/ethnicity.

Table 4

Net Reclassification Improvement of predicted risk for myocardial infarction, resuscitated cardiac arrest, or CHD death over 8.5 years with the singular addition of the specified lipid or lipoprotein measure to a baseline model of the 2013 AHA/ACC risk calculator. Total NRI with *P* values as well as sub-categories of reclassified events and non-events are shown.

	LDL-C	Non-HDL-C	TC/HDL-C	ApoB	ApoB/ApoA	LDL-P	LDL-P/HDL-P
NRI (total)	0.065	0.073	**0.12**	0.093	**0.18**	0.14	**0.15**
p-value	NS	NS	**0.03**	NS	**0.007**	NS	**<0.001**
M (event)	30.9%	60.0%	58.4%	33.5%	42.8%	45.1%	39.2%
M (non-event)	24.4%	47.7%	46.3%	24.2%	24.4%	30.9%	24.7%

CHD = coronary heart disease; TC = total cholesterol; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; ApoB = apolipoproteins B-100; ApoA-I = apolipoprotein A-I; LDL-P = LDL particle; HDL-P = HDL particle; MESA = Multi-ethnic Study of Atherosclerosis; NRI = Net Reclassification Improvement