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Sex Differences in Lipid Profiles and Treatment Utilization Among Young Adults With Acute Myocardial Infarction: Results from the VIRGO Study

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Abstract

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Background—Young women with acute myocardial infarction (AMI) have higher mortality risk than similarly aged men. An adverse lipid profile is an important risk factor for cardiovascular outcomes after AMI, but little is known about whether young women with AMI have a higher-risk lipid pattern than men. We characterized sex differences in lipid profiles and treatment utilization among young adults with AMI.

Methods and Results—A total of 2,219 adults with AMI (1,494 women) aged 18–55 years were enrolled from 103 hospitals in the United States (2008–2012). Serum lipids and lipoprotein subclasses were measured 1 month after discharge. More than 90% of adults were discharged on a statin, but less than half received a high-intensity dose and 12% stopped taking treatments by 1 month. For both men and women, the median of low-density lipoprotein cholesterol (LDL-C) was reduced to <100 mg/dL 1 month after discharge for AMI, but high-density lipoprotein cholesterol (HDL-C) remained <40 mg/dL. Multivariate regression analyses showed that young women had favorable lipoprotein profiles compared with men: women had higher HDL-C and HDL large particle, but lower TC/HDL-C ratio and LDL small particle.

Conclusions—Young women with AMI had slightly favorable lipid and lipoprotein profiles compared with men, suggesting that difference in lipid and lipoprotein may not be a major contributor to sex differences in outcomes after AMI. In both men and women, statin remained inadequately utilized and low HDL-C level was a major lipid abnormality.

Keywords

myocardial infarction; lipids; lipoprotein; women

Introduction

Young women (≤55 years) with acute myocardial infarction (AMI) have higher rates of morbidity and mortality than similarly aged men, but the reasons have yet to be identified.[1, 2] An adverse lipid profile is an important risk factor for cardiovascular outcomes after AMI[3-5] and differences in lipid profile may account for sex differences in outcomes. However, little is known about whether young women and men with AMI have similar or distinct lipid profiles, particularly in an era of ubiquitous use of statins for secondary prevention. Understanding sex differences in post-AMI lipid profiles may provide important implications for treatment and guide strategies to reduce sex differences in outcomes.

Prior studies of post-AMI lipid profiles have been conducted in populations of predominately older patients.[6-9] Thus, there is limited evidence about the lipid profiles in younger patients and in particular young women, who are known to be at increased risk for mortality compared with their male counterparts.[1, 2] Evidence from the general population suggests young women have advantageous lipid profiles compared with men;[10] however, it is unclear if lipid advantages persist after AMI. In addition, prior studies have focused on standard measurements, such as cholesterol and triglyceride, and did not collect information on lipoprotein subclasses. Given that lipoproteins encompass heterogeneous subclasses that vary in composition and physiological function,[11] a comprehensive characterization of lipids and lipoprotein subclasses in young women is needed to better understand a potential risk factor for long-term outcomes.

Importantly, differences in lipid profiles may reflect variation in treatment patterns, patients' health behaviors, comorbidity, and biological susceptibility. As one of the most important factors affecting lipid and lipoprotein levels, lipid-lowering therapy (predominately statins) is recommended by clinical guidelines to all AMI patients at hospital discharge.[12] Evidence suggests that women are less likely than men to receive guideline-recommended therapies and appear to be less adherent to medications.[13, 14] Compared with men, young women with AMI also tend to exercise less, smoke more, and have higher rates of diabetes and obesity - all factors that are strongly associated with lipid abnormalities after AMI.[1, 15] There has yet to be any explanation as to whether these factors are associated with differences in post-AMI lipid and lipoprotein profiles among young men and women.

To address these gaps in knowledge, we utilized data from VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients), the largest prospective observational study of young men and women with AMI.[16] The objectives of this VIRGO analysis were (1) to characterize sex differences in lipid and lipoprotein profiles after hospital discharge among young men and women with AMI, (2) to describe use of statin and other lipid-lowering medications among young men and women with AMI, and (3) to assess the association between sex, patient characteristics, and post-AMI lipid profiles.

Methods

Participants and Study Design

VIRGO has been described previously.[16] In brief, VIRGO was a prospective, observational study designed to investigate the demographic, clinical, psychosocial, biological, and behavioral factors associated with higher mortality in young women with AMI.[1, 2] For this analysis of post-AMI lipid and lipoprotein profile, we included participants who were between the ages of 18-55 and enrolled from 103 hospitals in the United States (US) between August 21, 2008 and January 5, 2012. Participants were recruited using a 2:1 female to male enrollment design to enrich the study's inclusion of young women.

The diagnosis of AMI was confirmed by increased cardiac biomarkers (with at least 1 cardiac biomarker above the 99th percentile of the upper reference limit) within 24 hours of admission. Additional evidence of acute myocardial ischemia was also required, including at least 1 of the following: symptoms of ischemia, electrocardiogram changes indicative of new ischemia, or imaging evidence of infarction. We excluded participants if they met any of the following criteria: previous enrollment in VIRGO, neither English nor Spanish speaking, unable to provide informed consent, development of elevated cardiac markers due to elective coronary revascularization, or AMI caused by physical trauma.[16] For this analysis, we also excluded participants who had missing lipid and lipoprotein data at 1 month after hospital discharge or who were lost to follow-up by 1 month, as well as samples with duplicate VIRGO IDs (Figure 1). Institutional Review Board approval was obtained at each participating institution, and participants provided informed consent for study participation including baseline hospitalization and follow-up interviews.

Data Collection and Variables

We collected baseline information on patients' socio-demographics, clinical presentation, and treatment from medical chart abstraction and standardized in-person interviews administered by trained personnel during the index AMI admission. Follow-up telephone interviews and in-person blood tests were conducted at 1 month by the Yale Follow-Up Center.

At baseline, patients' serum lipid levels were derived from medical chart abstraction. For 97% of patients, baseline serum lipid levels were obtained prior to arrival or within 24 hours of admission. At 1 month after hospital discharge, we measured serum lipids and lipoprotein subclasses by standardized assay. Specifically, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglyceride levels were measured by a blood draw according to standard procedures. Low-density lipoprotein cholesterol (LDL-C) was calculated by Friedewald equation[17] if triglycerides were <400 mg/dL and was measured directly if triglycerides were ≥400 mg/dL. Lipoprotein subclasses were measured by a high-resolution ion mobility technique that physically separated lipoprotein particles by size.[18] These subclasses comprise the full spectrum of lipoprotein particles, including very low-density lipoprotein (VLDL) particle, intermediate-density lipoprotein (IDL) particle, low-density lipoprotein (LDL) particle, and high-density lipoprotein (HDL) particle. We used the ion mobility technique to measure lipoprotein subclasses because it measures particle size accurately and counts the particles present at each size, providing a direct measurement of lipoprotein particle size and concentration for each lipoprotein subclass.[18] All serum lipids and lipoprotein subclasses were measured at Quest Diagnostics using the Beckman Coulter Olympus AU series instruments. The laboratory was certified by the National Heart, Lung, and Blood Institute and Centers for Disease Control and Prevention Lipid Standardization Program.

We obtained information on lipid-lowering medications at admission and discharge from medical records, and medications at 1 month from patient interviews. We identified patients who were taking high-intensity statins vs. low- and moderate-intensity statins based on the type and dosage of statin therapy (Supplemental Table 1). High-intensity statins were defined as statins dosed at a level expected to lower LDL-C by at least 50% according to the American College of Cardiology (ACC)/American Heart Association (AHA) recommendation.[19] We also considered lipid-lowering therapies other than statins, including ezetimibe, niacin, fibrate, and fish oil.

We quantified patients' socioeconomic status by defining marital status, highest education, health insurance, employment status, and financial hardship (not having enough money to make ends meet or having just enough money to make ends meet versus having some money left over at the end of the month). We assessed the clinical severity of AMI presentations by final AMI diagnosis (ST-elevation AMI), left ventricular ejection fraction <40%, Global Registry of Acute Coronary Events (GRACE) risk score,[20] and length of hospital stay. We included other cardiac risk factors and comorbidities, such as menopausal status for women, physician diagnosis of hypertension, diabetes, dyslipidemia, and history of heart disease extracted from the medical record, obesity (body mass index ≥30 kg/m^2), prospectively measured waist circumference (high classified as >88 cm for women, >102 cm for men),

smoking, and physical activity. Self-reported physical activity was measured with the Behavioral Risk Factor Surveillance Survey physical activity instrument,[21] which has high reliability and validity among young adults.[22]

Statistical Analyses

Descriptive statistics of patient characteristics at baseline and 1 month were calculated for the overall population and compared between men and women. We calculated frequencies for categorical variables and medians with interquartile ranges for continuous variables. We determined statistical differences between women and men using chi-squared, Student's t and Wilcoxon Rank Sum tests, where appropriate.

To describe lipid and lipoprotein profile by sex, we estimated the distributions of various biomarkers for women and men separately. For the standard lipid profile, we plotted the distributions at baseline and 1 month by sex. We also compared the distributions at both periods in VIRGO with those in a nationally representative sample of the population in the US based on the National Health and Nutrition Examination Survey (NHANES) 2011-2012. NHANES used a multi-stage, stratified, clustered probability sampling design and provided a representative sample of the non-institutionalized population in the US.[23] We included individuals aged 40-55 years (median age of 47) in order to have an age distribution similar to that of VIRGO. We accounted for the complex survey design in NHANES to make lipid estimates representative of the corresponding sex group in the national population. For lipoprotein subclasses, while the clinical thresholds have not yet been determined, we used a convenience sample of healthy employees from Quest Diagnostics as the reference population and compared their lipoprotein subclasses with those in VIRGO. This sample consisted of volunteers who were aged 18-66 years (median age 28 for men and 34 for women), had no history of heart disease or diabetes, and were not on heart-related medications.

To further examine the association of sex, clinical characteristics, and lipoprotein biomarkers, we conducted multivariable linear regression analyses. We considered LDL-C, HDL-C, TC/HDL-C ratio, HDL large particle, LDL small particle, and lipoprotein (a) as the dependent variables because they are known to be strong predictors of cardiovascular outcomes.[24] Explanatory variables included patient sex, age, race, marital status, employment, AMI type, diabetes and obesity at baseline, smoking, physical activity, and statin use at 1 month. We did not include menopausal status in the model because this variable was applicable to only women and missing for men. For each dependent variable, 2 models were developed: model 1 included sex only and model 2 included sex and all other covariates. We also tested the interactions between sex and diabetes on each lipid parameter. We considered a 2-sided $p < 0.05$ as statistically significant. All analyses were conducted with SAS 9.3 (SAS Institute Inc., Cary, North Carolina) and the most recent version of the VIRGO database.

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and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Results

Sample Characteristics

There were 2,219 adults with AMI in VIRGO included in this analysis (725 men and 1,494 women; Figure 1). The median age was similar for both sexes (48 years for men and 49 for women). The majority of patients were white (78%), married (52%), had more than a high school education (59%), and had health insurance (79%). About half presented with ST-elevation AMI (STEMI) and one third had prior heart disease. Cardiovascular risk factors (e.g., hypertension, diabetes, dyslipidemia, and obesity) were common in these patients (Table 1).

Compared with men, women were more likely to be black, single, have diabetes mellitus, obesity, high waist circumference, prior stroke, congestive heart failure, and longer wait times from symptom onset of AMI to hospital arrival, but were less likely to have dyslipidemia and present with STEMI. The clinical severity of the AMI was similar for men and women: 8.5% of men and 9.1% of women had a GRACE risk score >99 (p=0.66). There were 10.0% of men and 10.1% of women with an ejection fraction <40% (p=0.91). Nearly half of the women were post-menopausal, of which 2.3% used estrogen therapy.

At 1-month follow-up, women were more likely to be unemployed and have not enough money to make ends meet compared with men (Table 2). In addition, women were more likely to be current smokers and to be physically inactive.

Lipid-lowering Medications on Admission, at Discharge, and at 1 Month

One third of adults hospitalized with AMI were already treated with statins at admission; this proportion increased to >90% at discharge (Table 3). Less than 3% of patients had a contraindication to statins. Among adults treated with statins, 42.7% were on high-intensity statins and 57.3% were on low- and moderate-intensity statins. At 1 month after discharge for AMI, statin use decreased; 12.3% of adults (11.1% of women and 12.9% of men, p = 0.25) were no longer taking statins. As a result, approximately 1 in 5 adults (17.6%) were not on a statin at 1 month after discharge.

Compared with men, women had similar use of any statins on admission (30.3% vs. 31.6%, p=0.52) and at 1 month (75.5% vs. 78.6%, p=0.10), but had slightly less use at discharge (90.0% vs. 95.3%, p<0.01). Among those on statins, women were less likely to report being treated with a high-intensity dose at 1 month (39.0% vs. 45.1%, p=0.02) but the absolute differences were modest (6 percentage points).

Sex Differences in Lipids and Lipoprotein subclasses at Baseline and 1 Month

At baseline, TC and LDL-C levels were similar between men and women, and were slightly lower than the levels in the US general population (Supplemental Table 2). Even for adults not treated with statins on admission (70% of the cohort), the LDL-C level was lower than that of the general population (median of 112 mg/dL vs. 122 mg/dL, results not shown). The

baseline HDL-C level was very low for both sexes, with medians ≤40 mg/dL. Due to the low HDL-C levels, the ratios of TC to HDL-C were higher for both sexes compared with those of the general population. Figure 2 shows how the distributions of lipid biomarkers changed between baseline and 1-month post AMI by sex. There were substantial reductions in TC and LDL-C levels between baseline and 1 month for both men and women, but only minimal change in HDL-C and triglyceride levels (Figure 2). The reductions in TC and LDL-C levels were smaller in women than in men (median reduction of 10% vs. 13% for TC, 11% vs. 16% for LDL-C, results not shown).

At 1 month, TC and LDL-C had been reduced to low levels in both men and women: the median (interquartile range) of TC was 145 (126-174) mg/dL for men and 157 (132-185) mg/dL for women, whereas LDL-C was 81 (65-104) mg/dL for men and 86 (67-107) mg/dL for women (Supplemental Table 2). These values were substantially lower than those in the similarly aged general population. HDL-C levels remained very low for both sexes (33 (28-39) mg/dL for men and 39 (32-48) mg/dL for women) and were lower than those of the general population (44 (37-52) mg/dL for men and 56 (47-66) mg/dL for women). Compared with men, women had slightly higher TC, LDL-C, and HDL-C levels, but had lower triglyceride levels ($p<0.05$ for all).

The results of lipoprotein subclasses generally paralleled these findings and showed statistically significant sex differences. The concentrations of LDL particles (total and all subclasses) in VIRGO were lower compared with those of the sample of healthy volunteers for both men and women (Supplemental Table 3). This was consistent with the finding of low LDL-C levels. Similarly, the concentrations of HDL particles were also lower in VIRGO and consistent with the finding of low HDL-C levels. Compared with men, women had higher concentrations of total HDL particles because of higher concentrations of large and small HDL subclasses. However, despite a slightly higher LDL-C level for women, there were no sex differences in the concentration of total LDL particles (1221 (972-1570) nmol/L for men and 1205 (961-1525) nmol/L for women, $P=0.45$). This is because women had higher concentrations of large LDL particles, but lower concentrations of small and very small LDL particles compared with men. The median LDL particle size for women was slightly larger than that for men.

Sex, Patient Characteristics, and Lipid and Lipoprotein Profiles at 1 Month

Fully adjusted analyses demonstrated that young women had slightly favorable lipid and lipoprotein profiles compared with men. Women had higher levels of HDL-C and HDL large particle, but had lower levels of TC/HDL-C ratio and LDL small particle than men in the unadjusted models (Table 4). These sex differences persisted even after adjusting for socio-demographic and clinical characteristics ($p<0.05$ for all). The higher LDL-C level in women in the unadjusted model was no longer significant in the fully adjusted model. The difference in LDL-C levels was explained largely by differences in statin use, socio-demographic factors, and comorbidities. A lower level of HDL-C at 1 month was associated with younger age, male sex, white race, receiving high-intensity statins, being unemployed, having comorbidities and unhealthy lifestyles (diabetes, obesity, smoking, and physical inactivity), and STEMI. We also tested the interactions between diabetes and sex for all six models

presented in Table 4. A significant sex by diabetes interaction was found only for the model of LDL small particle (p=0.0002): having diabetes was significantly associated with higher concentration of LDL small particle in women (estimate of 33.61; P<0.001), but not in men (estimate of -12.15; P=0.23). Non-diabetic women had lower concentration of LDL small particle than non-diabetic men (estimate of -66.12; P<0.001), but there was not a significant sex difference for diabetes individuals (estimate of -20.35; P =0.15).

Discussion

In this large study of young adults with AMI, we found small sex differences in lipid biomarkers. Women had slightly favorable lipid and lipoprotein profiles compared with men at baseline hospitalization and at 1-month post-AMI. More than 90% of adults were discharged on a statin, but less than half received a high-intensity dose. Treatment decreased at 1 month and about 1 in 5 patients were not on statins at 1 month after discharge for AMI. For most men and women, LDL-C levels were reduced to <100 mg/dL by 1 month, but the low HDL-C of <40 mg/dL was a major lipid abnormality.

Our finding of slightly favorable lipid profiles in women compared with men allowed us to exclude the hypothesis that a high-risk lipid pattern explains why young women with AMI have higher mortality than men. Even our comprehensive assessment of lipoprotein subclasses showed favorable profiles in women, adding to the evidence that lipoprotein abnormality may not be a major contributor to sex difference in outcomes. The favorable lipid and lipoprotein profiles in women were only partially explained by socio-demographic and clinical confounders, and remained statistically significant in the fully adjusted model. The unexplained differences might be caused by other factors not analyzed here such as genetic variants associated with lipoprotein subclass distributions and response to statins.[25]

Our analysis of lipid-lowering treatment suggests statin was inadequately utilized in both men and women. We found that more than half of patients were not prescribed high-intensity statins at discharge even though it is recommended in guidelines for all AMI patients.[26] A potential reason could be that the baseline LDL-C levels of these young patients were not high enough (median of <110 mg/dL) and physicians may consider low- or moderate-intensity statins sufficient. Consistent with previous studies,[13] we also found a significant proportion of patients discontinued statin treatment by 1 month with no appreciable difference between men and women. It is possible that patients with lower education level, lack of health insurance, or lack of money to pay for medications were more likely to stop treatments,[14, 27] resulting in a decrease in treatment adherence. It is also possible that the LDL-C level has been substantially reduced to <100 mg/dL at 1 month and physicians still consider treating LDL-C according to target levels as opposed to patient's overall risk (as endorsed by the recent ACC/AHA guideline).[26]

Furthermore, our findings of the low HDL-C levels of <40 mg/dL in both men and women raise concern. Several clinical trials have identified a low HDL-C level as an independent predictor of major cardiovascular events in patients treated with statins.[28, 29] This relationship remains significant even among patients with LDL-C <70 mg/dL.[29] However, whether increasing HDL-C level could translate into benefits of cardiovascular outcomes is

still uncertain. Recent randomized clinical trials showed that effective agents for increasing HDL-C levels, such as niacin, fibrates, and cholesteryl ester transfer protein inhibitors, failed to reduce mortality and cardiovascular outcomes when statin treatment was already in place.[30-32] The mechanism is not clear, but a number of explanations have been proposed. For example, the overall HDL-C level alone may be an inadequate marker for lipoprotein functionality and certain HDL sub-fractions may be more important determinants of cardiovascular risk.[32]

This paper contributes to the literature in several key ways. First, it is the largest comprehensive analysis of sex differences in lipid and lipoprotein profiles in young adults with AMI. Previous studies were based predominantly on elderly individuals and only included sex as a covariate in the model rather than explicitly addressing sex differences in lipid profile as the primary objective. Second, our comprehensive evaluation of lipoprotein subclasses adds to our understanding of the subclass profiles in young adults with AMI. Previous studies focused on standard measurements (e.g., cholesterol and triglyceride),[6-9] which alone may have been insufficient to reveal other markedly different patterns in this population. Finally, we are able identify the pattern of lipid-lowering treatment in men and women on admission, at discharge, and at 1 month.

Our study has important implications for treatment of young women with AMI. As a majority of women did not receive high-intensity statins at discharge and medication adherence remained suboptimal, targeted interventions to promote statin use and adherence are needed to reduce cardiovascular risk in this population. In addition, substantial residual risks persist in women with AMI despite that LDL-C levels were well controlled after discharge.[33] This underscores the importance of treating patients according to their overall cardiovascular risks rather than LDL-C target alone. As residual risks in young women are affected by multiple factors, improving outcomes in this population may require risk modification that extends beyond LDL lowering with a combination of medications and lifestyle interventions. These efforts might include adding medications such as high-intensity statins, antiplatelet agents, beta-blockers, and angiotensin-converting enzyme inhibitors, as well as smoking cessation, physical activity, and improvement in other factors that have impaired outcomes in these patients.

There are some limitations to this study. First, VIRGO was an observational study that required patients to be healthy enough at baseline to participate; thus, we were unable to capture those who were too ill to be enrolled. Second, baseline serum lipid levels were extracted from medical records rather than measured according to standard protocol. However, the lipid levels for 97% of patients were obtained before arrival to the hospital or within 24 hours of admission, which is consistent with the Adult Treatment Panel III guidelines of using the initial (<24 hours after admission) LDL values to guide therapy.[34] The evidence on lipid stability after AMI is mixed, but many studies suggest lipid profiles within 24 hours of admission are not influenced or only influenced to a limited degree by the acute phase reaction, so should be representative of the patients' typical levels.[6, 35-37] Third, we did not measure lipoprotein subclasses at baseline and were unable to examine change in lipoprotein subclasses during follow-up. It is possible that atherogenic lipoproteins at 1 month have been eliminated due to statin treatment after the AMI event. Fourth, we used

data from a convenience sample of healthy employees as the reference ranges for lipoprotein subclasses, which might limit the interpretability of our results for subclasses. Finally, our measure of statin adherence is indirect because we calculated adherence by comparing the difference in treatment rates at discharge and 1 month. This approach may overestimate adherence in patients who did not take medications between the two periods.

In conclusion, young women with AMI had slightly favorable lipid and lipoprotein profiles compared with similarly aged men, suggesting that difference in lipids and lipoproteins may not be a major contributor to the sex differences in outcomes among young adults with AMI. In both men and women, statin remained inadequately utilized and low HDL-C level was a major lipid abnormality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Vaccarino V, Horwitz RI, Meehan TP, Petrillo MK, Radford MJ, Krumholz HM. Sex differences in mortality after myocardial infarction: evidence for a sex-age interaction. Arch Intern Med. 1998; 158:2054–62. [PubMed: 9778206]
2. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based differences in early mortality after myocardial infarction. National Registry of Myocardial Infarction 2 Participants. N Engl J Med. 1999; 341:217–25. [PubMed: 10413733]
3. van de Woestijne AP, Wassink AM, Monajemi H, Liem AH, Nathoe HM, van der Graaf Y, Visseren FL. Smart Study Group. Plasma triglyceride levels increase the risk for recurrent vascular events independent of LDL-cholesterol or nonHDL-cholesterol. Int J Cardiol. 2013; 167:403–8. [PubMed: 22265582]
4. Patel A, Woodward M, Campbell DJ, Sullivan DR, Colman S, Chalmers J, Neal B, MacMahon S. Plasma lipids predict myocardial infarction, but not stroke, in patients with established cerebrovascular disease. Eur Heart J. 2005; 26:1910–5. [PubMed: 16006443]
5. Pekkanen J, Linn S, Heiss G, Suchindran CM, Leon A, Rifkind BM, Tyroler HA. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. N Engl J Med. 1990; 322:1700–7. [PubMed: 2342536]
6. Khan HA, Alhomida AS, Sobki SH. Lipid profile of patients with acute myocardial infarction and its correlation with systemic inflammation. Biomark Insights. 2013; 8:1–7. [PubMed: 23400110]
7. Bergmann A, Schulze J, Hubner D, Weizel A, Julius U, Kreuzer J. Lipid-lowering therapy and cholesterol levels following acute myocardial infarction: a German study of 5361 patients. Eur J Epidemiol. 2003; 18:407–11. [PubMed: 12889686]
8. Martin SS, Gosch K, Kulkarni KR, Spertus JA, Mathews R, Ho PM, Maddox TM, Newby LK, Alexander KP, Wang TY. Modifiable factors associated with failure to attain low-density lipoprotein

cholesterol goal at 6 months after acute myocardial infarction. Am Heart J. 2013; 165:26–33 e3. [PubMed: 23237130]

9. Melloni C, Shah BR, Ou FS, Roe MT, Smith SC Jr, Pollack CV Jr, Ohman M, Gibler WB, Peterson ED, Alexander KP. Lipid-lowering intensification and low-density lipoprotein cholesterol achievement from hospital admission to 1-year follow-up after an acute coronary syndrome event: results from the Medications ApplIed aNd SusTAINed Over Time (MAINTAIN) registry. Am Heart J. 2010; 160:1121–9. 1129 e1. [PubMed: 21146667]
10. Swiger KJ, Martin SS, Blaha MJ, Toth PP, Nasir K, Michos ED, Gerstenblith G, Blumenthal RS, Jones SR. Narrowing sex differences in lipoprotein cholesterol subclasses following mid-life: the very large database of lipids (VLDL-10B). J Am Heart Assoc. 2014; 3:e000851. [PubMed: 24755154]
11. Superko HR. Advanced lipoprotein testing and subfractionation are clinically useful. Circulation. 2009; 119:2383–95. [PubMed: 19414656]
12. Smith SC Jr, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, Grundy SM, Hiratzka L, Jones D, Krumholz HM, Mosca L, Pasternak RC, Pearson T, Pfeffer MA, Taubert KA. AHA/ACC, National Heart, Lung, and Blood Institute. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. Circulation. 2006; 113:2363–72. [PubMed: 16702489]
13. Smolina K, Ball L, Humphries KH, Khan N, Morgan SG. Sex disparities in post-acute myocardial infarction pharmacologic treatment initiation and adherence: problem for young women. Circ Cardiovasc Qual Outcomes. 2015; 8:586–92. [PubMed: 26462876]
14. Lewey J, Shrank WH, Bowry AD, Kilabuk E, Brennan TA, Choudhry NK. Gender and racial disparities in adherence to statin therapy: a meta-analysis. Am Heart J. 2013; 165:665–78. 678 e1. [PubMed: 23622903]
15. Dreyer RP, Smolderen KG, Strait KM, Beltrame JF, Lichtman JH, Lorenze NP, D'Onofrio G, Bueno H, Krumholz HM, Spertus JA. Gender differences in pre-event health status of young patients with acute myocardial infarction: A VIRGO study analysis. Eur Heart J Acute Cardiovasc Care. 2016; 5:43–54. [PubMed: 25681487]
16. Lichtman JH, Lorenze NP, D'Onofrio G, Spertus JA, Lindau ST, Morgan TM, Herrin J, Bueno H, Mattera JA, Ridker PM, Krumholz HM. Variation in recovery: Role of gender on outcomes of young AMI patients (VIRGO) study design. Circ Cardiovasc Qual Outcomes. 2010; 3:684–93. [PubMed: 21081748]
17. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972; 18:499–502. [PubMed: 4337382]
18. Mora S, Caulfield MP, Wohlgemuth J, Chen Z, Superko HR, Rowland CM, Glynn RJ, Ridker PM, Krauss RM. Atherogenic lipoprotein subfractions determined by ion mobility and first cardiovascular events after random allocation to high-intensity statin or placebo: the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) Trial. Circulation. 2015; 132:2220–9. [PubMed: 26408274]
19. Stone NJ, Robinson JG, Lichtenstein AH, Goff DC Jr, Lloyd-Jones DM, Smith SC Jr, Blum C, Schwartz JS. ACC/AHA Cholesterol Guideline Panel. Treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: synopsis of the 2013 American College of Cardiology/American Heart Association cholesterol guideline. Ann Intern Med. 2014; 160:339–43. [PubMed: 24474185]
20. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, Goodman SG, Granger CB, Steg PG, Gore JM, Budaj A, Avezum A, Flather MD, Fox KA. GRACE Investigators. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. JAMA. 2004; 291:2727–33. [PubMed: 15187054]
21. Centers for Disease Control and Prevenetion. [accessed on June 7, 2016] Behavioral risk factor surveillance system users guide. 2009. Available at http://www2.cdc.gov/nccdphp/brfss2/training_gu/

22. Yore MM, Ham SA, Ainsworth BE, Kruger J, Reis JP, Kohl HW 3rd, Macera CA. Reliability and validity of the instrument used in BRFSS to assess physical activity. Med Sci Sports Exerc. 2007; 39:1267–74. [PubMed: 17762359]
23. Centers for Disease Control and Prevention. [accessed on June 7, 2016] US National Health and Nutrition Examination Survey. Available at http://www.cdc.gov/nchs/nhanes.htm
24. Mora S, Otvos JD, Rifai N, Rosenson RS, Buring JE, Ridker PM. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. Circulation. 2009; 119:931–9. [PubMed: 19204302]
25. Shim H, Chasman DI, Smith JD, Mora S, Ridker PM, Nickerson DA, Krauss RM, Stephens M. A multivariate genome-wide association analysis of 10 LDL subfractions, and their response to statin treatment, in 1868 Caucasians. PLOS ONE. 2015; 10:e0120758. [PubMed: 25898129]
26. Stone NJ, Robinson JG, Lichtenstein AH, Goff DC Jr, Lloyd-Jones DM, Smith SC Jr, Blum C, Schwartz JS. ACC/AHA Cholesterol Guideline Panel. Treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: synopsis of the 2013 American College of Cardiology/American Heart Association cholesterol guideline. Ann Intern Med. 2014; 160:339–43. [PubMed: 24474185]
27. Mann DM, Woodward M, Muntner P, Falzon L, Kronish I. Predictors of nonadherence to statins: a systematic review and meta-analysis. Ann Pharmacother. 2010; 44:1410–21. [PubMed: 20702755]
28. Sacks FM, Tonkin AM, Shepherd J, Braunwald E, Cobbe S, Hawkins CM, Keech A, Packard C, Simes J, Byington R, Furberg CD. Effect of pravastatin on coronary disease events in subgroups defined by coronary risk factors: the Prospective Pravastatin Pooling Project. Circulation. 2000; 102:1893–900. [PubMed: 11034935]
29. Barter P, Gotto AM, LaRosa JC, Maroni J, Szarek M, Grundy SM, Kastelein JJ, Bittner V, Fruchart JC. Treating to New Targets Investigators. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. N Engl J Med. 2007; 357:1301–10. [PubMed: 17898099]
30. Landray MJ, Haynes R, Hopewell JC, Parish S, Aung T, Tomson J, Wallendszus K, Craig M, Jiang L, Collins R, Armitage J. HPS2 Thrive Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med. 2014; 371:203–12. [PubMed: 25014686]
31. Kaur N, Pandey A, Negi H, Shafiq N, Reddy S, Kaur H, Chadha N, Malhotra S. Effect of HDL-raising drugs on cardiovascular outcomes: a systematic review and meta-regression. PLOS ONE. 2014; 9:e94585. [PubMed: 24728455]
32. Martin SS, Khokhar AA, May HT, Kulkarni KR, Blaha MJ, Joshi PH, Toth PP, Muhlestein JB, Anderson JL, Knight S, Li Y, Spertus JA, Jones SR. Lipoprotein Investigators C. HDL cholesterol subclasses, myocardial infarction, and mortality in secondary prevention: the Lipoprotein Investigators Collaborative. Eur Heart J. 2015; 36:22–30. [PubMed: 24980493]
33. Dreyer RP, Wang Y, Strait KM, Lorenze NP, D'Onofrio G, Bueno H, Lichtman JH, Spertus JA, Krumholz HM. Gender differences in the trajectory of recovery in health status among young patients with acute myocardial infarction: Results from the VIRGO Study. Circulation. 2015; 131:1971–80. [PubMed: 25862743]
34. Expert Panel on Detection Evaluation Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA. 2001; 285:2486–97. [PubMed: 11368702]
35. Rosenson RS. Myocardial injury: the acute phase response and lipoprotein metabolism. J Am Coll Cardiol. 1993; 22:933–40. [PubMed: 7689082]
36. Sewdarsen M, Vythilingum S, Jialal I, Nadar R. Plasma lipids can be reliably assessed within 24 hours after acute myocardial infarction. Postgrad Med J. 1988; 64:352–6. [PubMed: 3200776]
37. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial Investigators. N Engl J Med. 1996; 335:1001–9. [PubMed: 8801446]

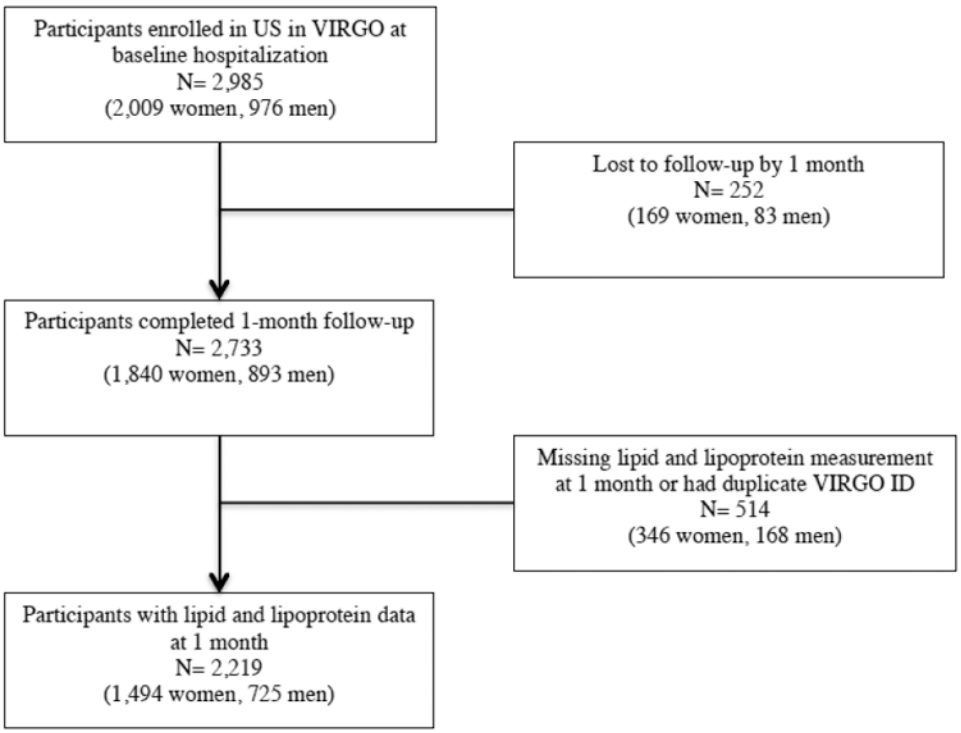

Figure 1. Flowchart of sample selection for post-AMI lipid analysis in VIRGO

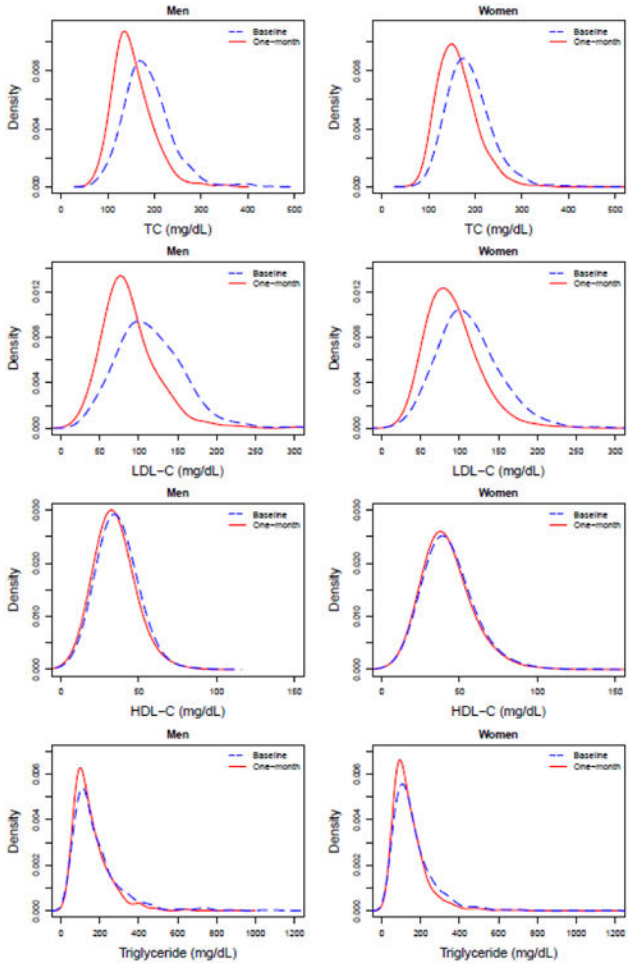

Figure 2. Distributions of standard lipid profile at baseline hospitalization and at 1 month after discharge for AMI, by sex (baseline =blue, 1 month=red)

Table 1
Baseline patient characteristics, stratified by sex

Characteristics	Overall (N=2219)	Men (N=725)	Women (N=1494)	P-value
Socio-demographics				
Age, median (IQR), year	49 (44-52)	48 (44-52)	49 (44-52)	0.05
Race, n (%)				
White	1720 (77.7%)	610 (84.3%)	1110 (74.4%)	<0.01
Black	358 (16.2%)	60 (8.3%)	298 (20.0%)	
Other	137 (6.2%)	54 (7.5%)	83 (5.6%)	
Married/living with a partner as if married, n (%)	1161 (52.4%)	430 (59.3%)	731 (49.0%)	<0.01
Education, n (%)				
< High school	42 (1.9%)	11 (1.5%)	31 (2.1%)	0.64
High school	858 (38.9%)	279 (38.7%)	579 (39.0%)	
>High school	1304 (59.2%)	431 (59.8%)	873 (58.9%)	
Health insurance, n (%)				
Yes	1738 (78.6%)	560 (77.7%)	1178 (79.0%)	0.47
No	474 (21.4%)	161 (22.3%)	313 (21.0%)	
History of cardiovascular condition, n (%)				
Heart disease (%), composite of prior CAD, prior angina and prior heart failure	690 (31.1%)	214 (29.5%)	476 (31.9%)	0.26
Coronary artery disease	456 (20.5%)	154 (21.2%)	302 (20.2%)	0.57
Angina pectoris	586 (26.5%)	185 (25.6%)	401 (26.9%)	0.52
Congestive heart failure	91 (4.1%)	18 (2.5%)	73 (4.9%)	<0.01
Stroke	100 (4.5%)	22 (3.0%)	78 (5.2%)	0.02
AMI severity				
AMI type, n (%)				
NSTEMI	1109 (50.0%)	312 (43.0%)	797 (53.3%)	<0.01
STEMI	1110 (50.0%)	413 (57.0%)	697 (46.7%)	
Ejection fraction <40%, n (%)	214 (10.1%)	70 (10.0%)	144 (10.1%)	0.91
GRACE risk score >99, n (%)	194 (8.9%)	61 (8.5%)	133 (9.1%)	0.67
Length of hospital stay, median (IQR), d	3 (2-4)	3 (2-4)	3 (2-4)	0.26
Comorbid conditions, n (%)				
Hypertension	1441 (64.9%)	456 (62.9%)	985 (65.9%)	0.16
Diabetes	664 (29.9%)	153 (21.1%)	511 (34.2%)	<0.01
Dyslipidemia	1128 (50.9%)	397 (54.9%)	731 (49.0%)	0.01
Obesity (BMI ≥30 kg/m^2)	1162 (52.4%)	346 (47.7%)	816 (54.6%)	<0.01
High waist circumference (women >88 cm, men >102 cm)	1270 (71.1%)	321 (53.3%)	949 (80.1%)	<0.01
Menopause status, n (%)				
Pre-menopause	-	-	350 (24.6%)	-
Peri-menopause	-	-	385 (27.0%)	-
Post-menopause	-	-	690 (48.4%)	-
Estrogen use at discharge, n (%)	-	-	35 (2.3%)	-
Time interval from symptom onset of AMI to arrival (min)	238 (75-1209)	187 (65-847)	281 (80-1380)	<0.01

All percentages were calculated by excluding missing, don't know and patient refused.
AMI= acute myocardial infarction, BMI= body mass index, CAD= coronary artery disease, IQR= interquartile range; NSTEMI= non ST-elevation AMI; STEMI= ST-elevation AMI

Table 2

Patient factors measured at 1 month that may influence lipid levels, stratified by sex

Factor	Overall (N=2219)	Men (N=725)	Women (N=1494)	P-value
Ability to pay for medication, n (%)				
Health insurance	1308 (71.9%)	423 (71.1%)	885 (72.4%)	0.57
Employed (work full or part time)	1312 (59.2%)	498 (68.9%)	814 (54.5%)	<0.01
Finances at end of month				
Some money left over	564 (26.0%)	228 (32.5%)	336 (22.9%)	<0.01
Just enough to make ends meet	780 (36.0%)	255 (36.3%)	525 (35.8%)	
Not enough to make ends meet	825 (38.0%)	219 (31.2%)	606 (41.3%)	
Health behavior, n (%)				
Smoking status				
Current	749 (34.1%)	219 (30.8%)	530 (35.7%)	0.06
Former	821 (37.4%)	286 (40.2%)	535 (36.1%)	
Never	626 (28.5%)	207 (29.1%)	419 (28.2%)	
Physical activity				
Recommended	806 (36.8%)	306 (43.1%)	500 (33.7%)	<0.01
Insufficient	744 (33.9%)	216 (30.4%)	528 (35.6%)	
Inactive	643 (29.3%)	188 (26.5%)	455 (30.7%)	

All percentages were calculated by excluding missing, don't know and patient refused.

Table 3
Sex differences in lipid-lowering therapies on admission, at discharge and 1 month

	Overall (N=2219)	Men (N=725)	Women (N=1494)	P-value
Lipid-lowering therapy on admission	681 (30.7%)	229 (31.6%)	452 (30.3%)	0.52
Non-statin *	0	0	0	0.52
Statin	681 (100%)	229 (100%)	452 (100%)	
Lipid-lowering therapy at discharge	2067 (93.3%)	696 (96.1%)	1371 (92.0%)	<0.01
Non-statin *	32 (1.5%)	5 (0.7%)	27 (2.0%)	0.03
Statin	2035 (98.5%)	691 (99.3%)	1344 (98.0%)	
High intensity	868 (42.7%)	310 (44.9%)	558 (41.5%)	0.15
Low and moderate intensity	1167 (57.3%)	381 (55.1%)	786 (58.5%)	
Lipid-lowering therapy at 1 month *	1730 (84.0%)	576 (87.0%)	1154 (82.5%)	0.01
Non-statin †	32 (1.8%)	6 (1.0%)	26 (2.3%)	0.08
Statin	1698 (98.2%)	570 (99.0%)	1128 (97.7%)	
High intensity	697 (41.0%)	257 (45.1%)	440 (39.0%)	0.02
Low and moderate intensity	1001 (59.0%)	313 (54.9%)	688 (61.0%)	
Statin discontinued by 1 month				
Yes	233 (12.3%)	70 (11.1%)	163 (12.9%)	0.25
No	1662 (87.7%)	562 (88.9%)	1100 (87.1%)	
Contraindications to lipid therapy, n (%)	59 (2.7%)	17 (2.3%)	42 (2.8%)	0.20

* This shows the number of patients taking only non-statin therapy so that the numbers of statin and non-statin therapy sum up to the total sample. If a patient takes both statin and non-statin therapy at the same time, he/she would be counted in the “statin” category.

† 36 patients who were not prescribed statin at discharge were on statin at 1 month.

All percentages were calculated by excluding missing, don't know, and patient refused.

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Table 4

Associations between sex, clinical characteristics, and (A) standard lipid profile and (B) lipoprotein subclasses 1 month after hospital discharge

(A)

Models	Covariates	LDL-cholesterol, mg/dL (N= 2053)		HDL-cholesterol, mg/dL (N= 2121)		Total cholesterol/HDL-cholesterol ratio (N= 2110)	
		Estimates	P-value	Estimates	P-value	Estimates	P-value
Model 1: Sex only	Women (vs. men)	3.41	0.04	7.64	<0.01	-0.57	<0.01
Model 2: Sex and all covariates	Women (vs. men) Statin use at 1 month	1.65	0.32	8.29	<0.01	-0.73	<0.01
	Non-statin	Reference category		Reference category		Reference category	
	Low or moderate intensity	-10.25	<0.01	-0.89	0.20	-0.47	<0.01
	High intensity	-18.55	<0.01	-2.11	<0.01	-0.61	<0.01
	Age at baseline (per 5-year increase)	-0.29	0.65	0.49	0.03	-0.05	0.21
	White race (vs. non-white)	1.68	0.37	-2.71	<0.01	0.47	<0.01
	Married at baseline	-5.95	<0.01	-1.02	0.07	-0.18	0.06
	Employed	-4.56	0.01	1.43	0.01	-0.42	<0.01
	Diabetes at baseline	-4.87	0.01	-2.35	<0.01	0.26	0.01
	Obesity at baseline	-1.84	0.24	-6.43	<0.01	0.40	<0.01
	Current smoker at 1 month	7.85	<0.01	-3.55	<0.01	0.67	<0.01
	Physical activity at 1 month						
	Inactive	Reference category		Reference category		Reference category	
	Insufficient	1.72	0.37	0.78	0.25	0.02	0.85
	Sufficient	0.15	0.94	2.14	<0.01	-0.16	0.17
	STEMI (vs. NSTEMI)	-0.51	0.74	-1.43	0.01	0.05	0.56

(B)

Models	Covariates	LDL small particle, nmol/L (N= 2150)		HDL large particle, nmol/L (N= 2150)		Lipoprotein (a), nmol/L (N= 1573)	
		Estimates	P-value	Estimates	P-value	Estimates	P-value
Model 1: Sex only	Women (vs. men)	-20.52	<0.01	915.99	<0.01	2.06	0.49

(A)

Models	Covariates	LDL-cholesterol, mg/dL (N= 2053)		HDL-cholesterol, mg/dL (N= 2121)		Total cholesterol/HDL-cholesterol ratio (N= 2110)	
		Estimates	P-value	Estimates	P-value	Estimates	P-value
Model 2: Sex and all covariates	Women (vs. men) Statin use at 1 month	-27.96	<0.01	836.03	<0.01	0.20	0.95
	Non-statin	Reference category		Reference category		Reference category	
	Low or moderate intensity	-13.23	0.03	-194.46	0.05	1.76	0.62
	High intensity	-32.30	<0.01	-402.37	<0.01	9.66	0.01
	Age at baseline (per 5-year increase)	-4.47	0.02	22.07	0.49	1.09	0.35
	White race (vs. non-white)	28.89	<0.01	-352.60	<0.01	-18.52	<0.01
	Married at baseline	-9.57	0.06	-138.38	0.09	-0.52	0.86
	Employed	-16.84	<0.01	-44.28	0.59	1.00	0.74
	Diabetes at baseline	22.24	<0.01	136.47	0.13	-4.10	0.21
	Obesity at baseline	14.91	<0.01	-201.08	0.01	6.93	0.02
	Current smoker at 1 month	34.40	<0.01	-146.41	0.08	7.00	0.02
	Physical activity at 1 month						
	Inactive	Reference category		Reference category		Reference category	
	Insufficient	-0.51	0.93	-43.69	0.66	-3.40	0.35
	Sufficient	-0.79	0.89	102.07	0.30	-4.76	0.19
	STEMI (vs. NSTEMI)	2.15	0.65	-160.70	0.04	1.31	0.65

The models were developed based on cohorts that excluded missing values in all variables.
LDL= low-density lipoprotein, HDL= high-density lipoprotein