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ORIGINAL INVESTIGATIONS

Effect of Alirocumab on Lipoprotein(a) and Cardiovascular Risk After Acute Coronary Syndrome

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ABSTRACT

BACKGROUND Lipoprotein(a) concentration is associated with cardiovascular events. Alirocumab, a proprotein convertase subtilisin/kexin type 9 inhibitor, lowers lipoprotein(a) and low-density lipoprotein cholesterol (LDL-C).

OBJECTIVES A pre-specified analysis of the placebo-controlled ODYSSEY Outcomes trial in patients with recent acute coronary syndrome (ACS) determined whether alirocumab-induced changes in lipoprotein(a) and LDL-C independently predicted major adverse cardiovascular events (MACE).

METHODS One to 12 months after ACS, 18,924 patients on high-intensity statin therapy were randomized to alirocumab or placebo and followed for 2.8 years (median). Lipoprotein(a) was measured at randomization and 4 and 12 months thereafter. The primary MACE outcome was coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, or hospitalization for unstable angina.

RESULTS Baseline lipoprotein(a) levels (median: 21.2 mg/dl; interquartile range [IQR]: 6.7 to 59.6 mg/dl) and LDL-C [corrected for cholesterol content in lipoprotein(a)] predicted MACE. Alirocumab reduced lipoprotein(a) by 5.0 mg/dl (IQR: 0 to 13.5 mg/dl), corrected LDL-C by 51.1 mg/dl (IQR: 33.7 to 67.2 mg/dl), and reduced the risk of MACE (hazard ratio [HR]: 0.85; 95% confidence interval [CI]: 0.78 to 0.93). Alirocumab-induced reductions of lipoprotein(a) and corrected LDL-C independently predicted lower risk of MACE, after adjustment for baseline concentrations of both lipoproteins and demographic and clinical characteristics. A 1-mg/dl reduction in lipoprotein(a) with alirocumab was associated with a HR of 0.994 (95% CI: 0.990 to 0.999; $p = 0.0081$).

CONCLUSIONS Baseline lipoprotein(a) and corrected LDL-C levels and their reductions by alirocumab predicted the risk of MACE after recent ACS. Lipoprotein(a) lowering by alirocumab is an independent contributor to MACE reduction, which suggests that lipoprotein(a) should be an independent treatment target after ACS. (ODYSSEY Outcomes: Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; NCT01663402) (J Am Coll Cardiol 2020;75:133–44) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Lipoprotein(a), a genetically determined low-density lipoprotein particle that contains apolipoprotein(a) and apolipoprotein B-100 moieties, is believed to possess pro-atherogenic, pro-thrombotic, pro-inflammatory, and pro-oxidative properties (1). High levels of lipoprotein(a) have been associated with incident cardiovascular disease in most, but not all, population-based epidemiological analyses (1,2) and in patients with established coronary heart disease (3,4). Moreover, Mendelian randomization analysis supports a linear relationship between lipoprotein(a) concentration and incident coronary heart disease in the general population (5). Based on available data, European (but not United States) guidelines suggest that lipoprotein(a) is a potential target for treatment if concentrations are ≥50 mg/dl (6,7).

Although observational data with apheresis suggest a possible benefit of lipoprotein(a) lowering on cardiovascular outcomes (8), no randomized data to date indicate that medications that lower lipoprotein(a) reduce cardiovascular risk through that mechanism. Niacin reduces lipoprotein(a) by 15% to 25% but does not reduce death or ischemic cardiovascular events (9,10), and anacetrapib lowers

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CI = confidence interval

HR = hazard ratio

IQR = interquartile range

LDL-C = low-density lipoprotein cholesterol

MACE = major adverse cardiovascular events

non–HDL-C = non–high-density lipoprotein cholesterol

PCSK9 = proprotein convertase subtilisin/kexin type 9

Sanofi, AstraZeneca, Patient Centered Outcomes Research Institute, Ferring Pharmaceuticals, Myokardia, Familial Hypercholesterolemia Foundation, and Bayer; and has received consulting fees or honoraria from AstraZeneca, Amgen, Cytokinetics, Eli Lilly, Roche-Genentech, Janssen Pharmaceuticals, Regeneron, Novo Nordisk, Pfizer, Sanofi, Signal Path, and Elsevier Publishers. Dr. Sinnaeve has received personal fees from Sanofi, Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, and Amgen; has received personal fees and nonfinancial support from AstraZeneca and Merck Sharp Dohme; and has received grants and personal fees from Daiichi-Sankyo and Bayer. Dr. Tsimikas has served as a consultant to Boston Heart Diagnostics; is a co-inventor and receives royalties from patents owned by UCSD on oxidation-specific antibodies and of biomarkers related to oxidized lipoproteins; has a dual appointment at UCSD and Ionis Pharmaceuticals; and is a co-founder of and has an equity interest in Oxitope, Inc. and Kleanthi Diagnostics, LLC; (Although these relationships have been identified for conflict of interest management based on the overall scope of the project and its potential benefit to Oxitope and Kleanthi Diagnostics LLC, the research findings included in this particular publication may not necessarily relate to the interests of Oxitope, Inc. and Kleanthi Diagnostics, LLC. The terms of this arrangement have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies.). Dr. Vogel has received grants and personal fees from Sanofi. Dr. White has received grant support paid to the institution and fees for serving on a steering committee for the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) from Sanofi and Regeneron Pharmaceuticals, for the ACCELERATE study (A Study of Evacetrapib in High-Risk Vascular Disease) from Eli Lilly, for the STRENGTH trial (Outcomes Study to Assess Statin Residual Risk Reduction With EpaNova in High CV Risk Patients With Hypertriglyceridemia) from Omthera Pharmaceuticals, for the SPIRE trial (The Evaluation of Bococizumab [PF-04950615; RN 316] in Reducing the Occurrence of Major Cardiovascular Events in High Risk Subjects) from Pfizer USA, for the HEART-FID study (Randomized Placebo-Controlled Trial of FCM as Treatment for Heart Failure With Iron Deficiency) from American Regent, for the CAMELLIA-TIMI study (A Study to Evaluate the Effect of Long-term Treatment With BELVIQ [Lorcaserin HC] on the Incidence of Major Adverse Cardiovascular Events and Conversion to Type 2 Diabetes Mellitus in Obese and Overweight Subjects With Cardiovascular Disease or Multiple Cardiovascular Risk Factors) from Eisai Inc, for the dal-GenE study (Effect of Dalcetrapib vs Placebo on CV Risk in a Genetically Defined Population With a Recent ACS) from DalCor Pharma UK Inc., for the AEGIS-II study from CSL Behring, for the SCORED trial (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk) and the SOLOIST-WHF trial (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure) from Sanofi-Aventis Australia Pty. Ltd., and for the CLEAR Outcomes Study (Evaluation of Major Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated With Bempedoic Acid [ETC-1002] or Placebo) from Esperion Therapeutics Inc.; has served on the Advisory Board for Acetelion, Sirtex, and Genentech, Inc. (an affiliate of F. Hoffmann-La Roche Ltd., "Roche"; Lytics Post-PCI Advisory Board at European Society of Cardiology); and has received lecture fees from AstraZeneca. Dr. Zahger serves as National Coordinator for the ODYSSEY OUTCOMES trial and the SCORED trial, both funded by Sanofi; and has consulted for Bayer, AstraZeneca, Boehringer Ingelheim, NovoNordisk, and Sanofi. Dr. Zeiher has received fees for serving on a steering committee for the ODYSSEY OUTCOMES trial from Sanofi; and has received Advisory Board and speaker fees from Sanofi, Amgen, Boehringer Ingelheim, Bayer, Novartis, Pfizer, AstraZeneca, and Vifor. 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Dr. Steg has received grants and nonfinancial support (co-chair of the ODYSSEY OUTCOMES trial; as such he received no personal fees, but his institution has received funding for the time he has devoted to trial coordination, and he has received support for some travel related to trial meetings) from Sanofi; has received research grants and personal fees from Bayer (Steering Committee MARINER, grant for epidemiological study), Merck (speaker fees, grant for epidemiological studies), Sanofi (co-chair of the ODYSSEY OUTCOMES trial; cochair of the SCORED trial; consulting, speaking), Servier (Chair of the CLARIFY registry; grant for epidemiological research), and Amarin (executive steering committee the REDUCE-IT trial [Disease Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial]; consulting); has received personal fees from Amgen, Bristol-Myers Squibb, Boehringer Ingelheim, Pfizer, Novartis, Regeneron Pharmaceuticals, Lilly, and AstraZeneca; and has a European application number/patent number, issued on October 26, 2016 (No. 15712241.7), for a method for reducing cardiovascular risk. Dr. Schwartz has received research grants to the University of Colorado from Resverlogix, Roche, Sanofi, and The Medicines Company; and is co-inventor of pending U.S. patent 62/806313 "Methods for Reducing Cardiovascular Risk," assigned in full to University of Colorado. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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lipoprotein(a) by 25% with only modest cardiovascular benefits, which are likely explained by other effects on the lipid profile (11). Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors lower lipoprotein(a) concentrations by approximately 25% (12,13) and reduce cardiovascular events (14–16), but it is uncertain whether, and to what extent, reduction of lipoprotein(a) contributes to this benefit, independent of the concurrent reduction of low-density lipoprotein cholesterol (LDL-C).

In a pre-specified analysis of the ODYSSEY Outcomes (ODYSSEY Outcomes: Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial, we tested the hypotheses that baseline lipoprotein(a) predicted recurrent major adverse cardiovascular events (MACE) following an index acute coronary syndrome (ACS) in patients who received intensive statin therapy. We also examined if the decrease in lipoprotein(a) concentration with treatment using the PCSK9 inhibitor, alirocumab, was associated with a decreased risk of MACE, independent of the concurrent reduction of LDL-C.

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METHODS

PATIENTS. Details of the ODYSSEY OUTCOMES trial design and results have been previously published (16,17). In brief, the trial included 18,924 patients age 40 years or older who experienced an ACS 1 to 12 months before randomization and who had a LDL-C level of ≥70 mg/dl (1.81 mmol/l), non–high-density lipoprotein cholesterol (non–HDL-C) level of ≥100 mg/dl (2.59 mmol/l), or an apolipoprotein B level of ≥80 mg/dl on high-intensity statin therapy (atorvastatin 40 to 80 mg daily, rosuvastatin 20 to 40 mg daily, or the maximum tolerated dose of either). Study inclusion was not based on lipoprotein(a) concentrations. The trial was approved by the institutional review board of each site, and all patients provided informed consent.

TREATMENTS. Patients were randomly assigned to treatment with alirocumab 75 mg subcutaneously every 2 weeks or matching placebo. Among patients assigned to alirocumab, the dose was blindly increased to 150 mg in patients who did not achieve an LDL-C level of <50 mg/dl (1.29 mmol/l). Placebo was blindly substituted for alirocumab in patients who had 2 consecutive LDL-C measurements of <15 mg/dl (0.39 mmol/l).

ENDPOINTS. The primary endpoint (MACE) was a composite of coronary heart disease death, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina that required hospitalization. Secondary endpoints considered in the present analysis were coronary heart disease death or nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, cardiovascular death, and all-cause death. Unstable angina was not considered individually because of a small number of events. All endpoints were adjudicated by a committee blinded to treatment assignment and lipid levels under the auspices of the Duke Clinical Research Institute.

MEASUREMENT OF LIPOPROTEINS. Lipoprotein(a) mass was measured once at randomization, at 4 months, and at 12 months at COVANCE Central Laboratories (Los Angeles, California) using an automated immunoturbidimetric assay on a Siemens BNII (Siemens, Healthcare Diagnostics, Malvern, Pennsylvania) validated against the International Federation of Clinical Chemistry and World Health Organization standards (18). The interassay coefficient of variation ranged from 3.1% to 4.8%, depending on the lipoprotein(a) concentration. Apolipoprotein(a) size heterogeneity had only a moderate effect on lipoprotein(a) recovery with this assay. LDL-C was calculated by the Friedewald formula (19), except when triglycerides were >400 mg/dl (4.52 mmol/l) or when the Friedewald-calculated LDL-C was <15 mg/dl (0.39 mmol/l). In these cases, LDL-C was measured by beta-quantification.

Calculated or directly measured LDL-C levels include cholesterol contained in lipoprotein(a), which corresponds to approximately 30% of the lipoprotein(a) mass (20,21). To account for this and derive an estimate of cholesterol contained in LDL particles, we calculated corrected LDL-C (referred to herein as LDL-C_{corr}) using the formula (21):

$$\text{LDL-C}_{\text{corr}} = \text{LDL-C} - 0.3 \times \text{lipoprotein(a) mass}$$

Similarly, to derive an estimate of cholesterol carried in all apolipoprotein-B–containing particles other than lipoprotein(a), corrected non–HDL-C was calculated using the relationship:

$$\text{non} - \text{HDL-C}_{\text{corr}} = (\text{total cholesterol} - \text{HDL-C}) - 0.3 \times \text{lipoprotein(a) mass}$$

STATISTICAL ANALYSIS. Lipoprotein(a), LDL-C, and non–HDL-C distributions were assessed for the overall population and by treatment group at baseline and at months 4 and 12 (±4 weeks) after randomization. If a patient had multiple values within each of these periods, the last value was analyzed. Missing values were imputed by prespecified methods.

Baseline characteristics were assessed by lipoprotein(a) quartile and compared across quartiles by chi-square tests for categorical variables and Kruskal-Wallis tests for continuous variables. Relationships between baseline lipoprotein(a) and endpoint events in the placebo group were determined by Cox proportional hazards models using the baseline lipoprotein(a) quartile as the predictor variable. We constructed unadjusted models and models that adjusted for demographic and clinical variables (age, sex, race, geographic region, body mass index, smoking history, diabetes, time from index ACS to randomization) and baseline LDL-C_{corr}. p Values were computed for linear trends across baseline lipoprotein(a) quartiles. A spline analysis of degree 3 (piecewise cubic curve) of the relationship between continuous baseline lipoprotein(a) and MACE in the placebo group was performed, setting the hazard ratio (HR) to 1.00 at the overall baseline median (21.2 mg/dl) concentration of lipoprotein(a) with natural cubic basis and 3 knots, located at the overall 25th percentile (6.7 mg/dl), median (21.2 mg/dl), and 75th percentile (59.6 mg/dl). The p value for the spline effect was based on the score test.

Heterogeneity in the relative and absolute effects of alirocumab treatment on MACE were assessed according to baseline lipoprotein(a) quartile. To assess the former, we constructed a Cox proportional hazards model with baseline lipoprotein(a) quartile, treatment, and their interaction as predictors, as well as a baseline hazard stratification by geographic region. To assess the latter, absolute risk reductions with alirocumab treatment, quantified as differences in observed incidences between treatment groups, were compared across baseline lipoprotein(a) quartiles using a Gail-Simon test (22).

To determine the association between modification of lipoprotein(a) levels by alirocumab treatment and MACE, the relationships between the change in lipoprotein(a) from baseline to month 4 and the risk of MACE after month 4 were described using Cox proportional hazards models in the alirocumab group. The following models were developed: a model without covariates (model 1); a model adjusted for baseline lipoprotein(a) (model 2); a model additionally adjusted for either baseline LDL-C_{corr} and change from baseline to month 4 in LDL-C_{corr} (model 3A) or baseline non–HDL-C_{corr} and change from baseline to month 4 in non–HDL-C_{corr} (model 3B); and a model adjusted for all variables in model 3, as well as the previously mentioned demographic and clinical variables with either LDL-C_{corr} (model 4A) or non–HDL-C_{corr} (model 4B). A comparison of models 2 and 3A indicated whether the relationship between the change in lipoprotein(a) and MACE was modified by adjustment for the simultaneous change in LDL-C_{corr}. Similarly, a comparison of models 2 and 3B indicated whether the relationship between the change in lipoprotein(a) and MACE was modified by adjustment for the simultaneous change in all other apolipoprotein-B–containing lipoproteins. Effects are summarized by HRs per 1-mg/dl reduction and the observed median reduction in lipoprotein(a) (all models) and in LDL-C_{corr} or non–HDL-C_{corr} (models 3A, 3B, 4A, and 4B) at month 4. The predicted absolute reduction in the risk of MACE with alirocumab attributable to lowering of lipoprotein(a) and to simultaneous lowering of LDL-C_{corr} (model 3A) or non–HDL-C_{corr} (model 3B) 4 years after randomization was calculated at the 25th (6.7 mg/dl), 50th (21.2 mg/dl), and 75th (59.6 mg/dl) percentiles of baseline lipoprotein(a), using the relationships between the variables and baseline lipoprotein(a) described in the Online Appendix. Attribution for each parameter was based on its contribution to the predicted absolute risk reduction relative to no change in lipoprotein(a) and LDL-C_{corr} or non–HDL-C_{corr}.

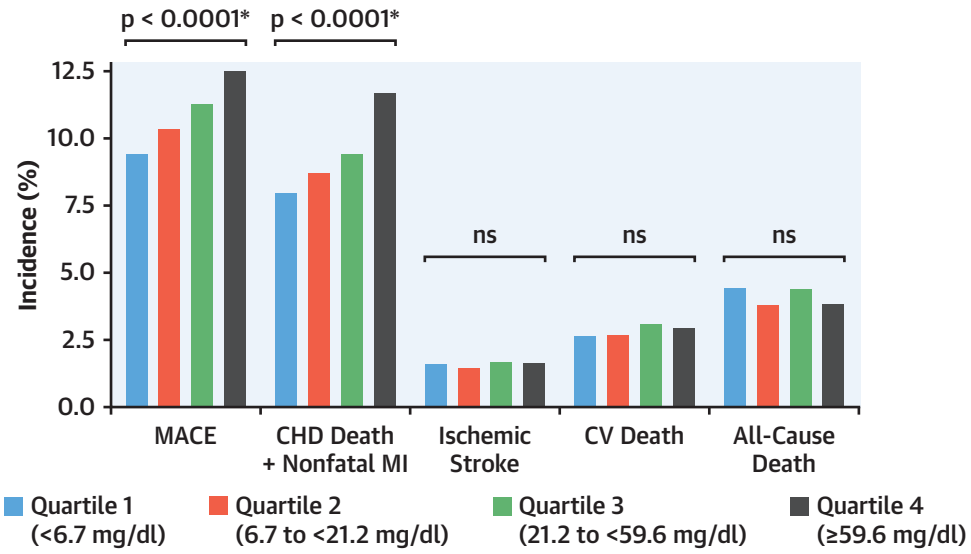
All analyses were conducted by an independent academic statistical team at the State University of New York Downstate School of Public Health using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS. The distribution of baseline lipoprotein(a) was highly skewed, with a median of 21.2 mg/dl (interquartile range [IQR]: 6.7 to 59.6 mg/dl) (Online Figure 1); 16% of patients had the minimum value for the assay of 2.0 mg/dl. Baseline characteristics of the patients by lipoprotein(a) quartile are shown in Online Table 1. Participants in the upper lipoprotein(a) quartiles were more likely to be women, black, and from North America but less likely to smoke or have diabetes. LDL-C and non–HDL-C concentrations and the percentage of patients treated with high-intensity statin were highest in the highest quartile of lipoprotein(a). Conversely, LDL-C_{corr} and non–HDL-C_{corr} decreased across increasing quartiles of lipoprotein(a). Participants in the higher lipoprotein(a) quartiles were more likely to have had blinded up titration of alirocumab and less likely to have had blinded substitution of placebo for alirocumab.

BASELINE LIPOPROTEIN(A), CARDIOVASCULAR EVENTS, AND MORTALITY IN THE PLACEBO GROUP. Median follow-up was 2.8 years (IQR: 2.3 to 3.4 years). The relationship between baseline lipoprotein(a)

FIGURE 1 Baseline Lipoprotein(a) Quartile as a Predictor of Events in the Placebo Group



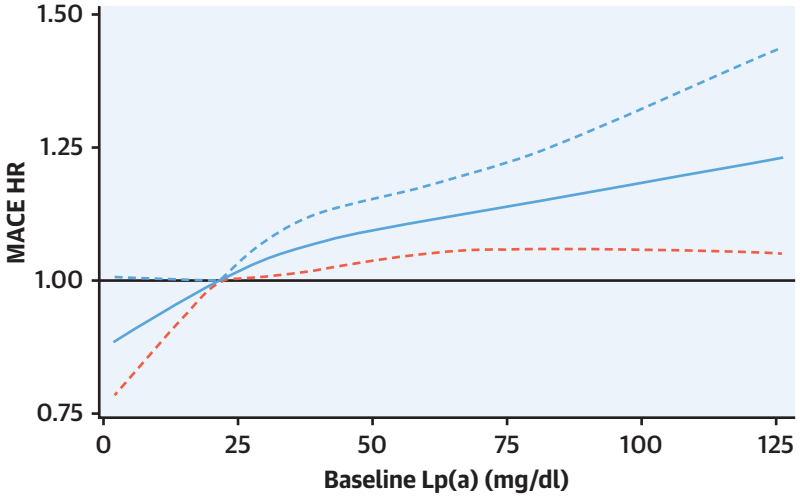
Incidence of major adverse cardiovascular events (MACE) and secondary endpoints are shown by baseline lipoprotein(a) quartiles for the placebo group. MACE and coronary heart disease (CHD) death and nonfatal myocardial infarction (MI) incidence were greater at higher lipoprotein(a) levels. There were no significant relationships between lipoprotein(a) quartile and ischemic stroke, cardiovascular (CV) death, or all-cause death. *$p < 0.0001$ for linear trend across quartiles in unadjusted Cox proportional hazards model for MACE and coronary heart disease death and nonfatal myocardial infarction. $p > 0.05$ for other endpoints.

quartile and incidence of events in the placebo group is shown in **Figure 1**, and modeling of this relationship is shown in Online Table 2. The occurrence of MACE and coronary heart disease death and/or nonfatal myocardial infarction increased significantly from the lowest to the highest lipoprotein(a) baseline quartile. In unadjusted Cox proportional hazards models, participants in the highest, compared with the lowest, baseline quartile of lipoprotein(a) were 46% and 54% more likely to experience MACE and nonfatal myocardial infarction and/or coronary heart disease death, respectively. These relationships were numerically stronger after adjustment for baseline LDL-C_{corr}. There were no significant relationships between baseline lipoprotein(a) quartile and ischemic stroke, cardiovascular death, or all-cause death. Spline analysis of continuous baseline lipoprotein(a) and the HR for MACE (**Figure 2**) indicated a relatively linear relationship between baseline lipoprotein(a) and the risk of MACE.

Effect of alirocumab on MACE stratified by baseline lipoprotein(a) quartile. Relative and absolute treatment effects on MACE stratified by baseline lipoprotein(a) quartile are shown in **Figure 3**. Overall, the HR for MACE (alirocumab and/or placebo) was 0.85 (95% confidence interval [CI]: 0.78 to 0.93; $p < 0.001$) with an absolute risk reduction of 1.6%. There was no statistically significant interaction between treatment and baseline lipoprotein(a) quartile on the relative risk of MACE ($p_{interaction} = 0.55$) (**Figure 3**, left). In contrast, absolute risk reduction in MACE with alirocumab was several-fold higher in the upper quartiles (2.3% and 2.1%) than in the lower quartiles of baseline lipoprotein(a) (0.4% and 1.4%, respectively), but there was evidence that all were positive ($p_{interaction} = 0.0011$) (**Figure 3**, right). The numbers of patients needed to treat with alirocumab for a median of 2.8 years to prevent 1 event were 238, 69, 43, and 49 in quartiles 1, 2, 3, and 4 of baseline lipoprotein(a), respectively.

Effect of alirocumab on lipoprotein(a) levels. Online Figure 2 shows the medians and IQRs of lipoprotein(a) concentrations by baseline quartile of lipoprotein(a) and treatment group. Baseline distributions of lipoprotein(a) were similar in both treatment groups. At month 4, lipoprotein(a) concentrations were significantly lower in the alirocumab group than in the placebo group, with levels remaining stable at month 12. **Figure 4** shows the absolute change from baseline to month 4 in lipoprotein(a), LDL-C, and LDL-C_{corr} in the alirocumab (**Figure 4A**) and placebo groups (**Figure 4B**). Overall,

FIGURE 2 Spline Analysis of Continuous Baseline Lipoprotein(a) and the Primary Endpoint Hazard Ratio (MACE) in the Placebo Group

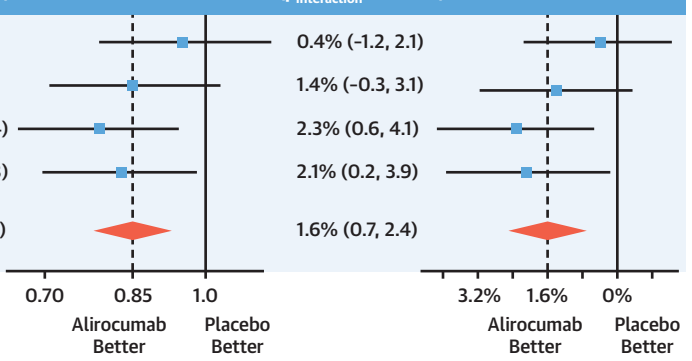


Hazard ratio (HR) set to 1.00 at the overall baseline median (21.2 mg/dl) concentration of lipoprotein(a). $p < 0.0001$ for spline effect. This reflects spline of degree 3 (piecewise cubic curve) with natural cubic basis and 3 knots, located at overall 25th percentile (6.7 mg/dl), median (21.2 mg/dl), and 75th percentile (59.6 mg/dl). The p value for spline effect is based on the score test. The **blue dotted line** indicates the upper bound of 95% confidence intervals (CIs) and the **red dotted line** indicates the lower bound of 95% CIs. Lp(a) = lipoprotein(a); other abbreviation as in Figure 1.

the median relative and absolute changes in lipoprotein(a) from baseline to month 4 in the alirocumab group were −23% (IQR: −47% to 0%) and −5.0 mg/dl (IQR −13.5 to 0 mg/dl), respectively. Although the relative change in lipoprotein(a) with alirocumab treatment was similar across baseline lipoprotein(a) quartiles, there was a substantial gradient of median absolute change that ranged from 0 mg/dl in quartile 1 to −20.2 mg/dl in quartile 4. Most patients in quartile 1 had no change in lipoprotein(a) from baseline to month 4, whereas >80% of patients in each of the other quartiles had decreases. Changes

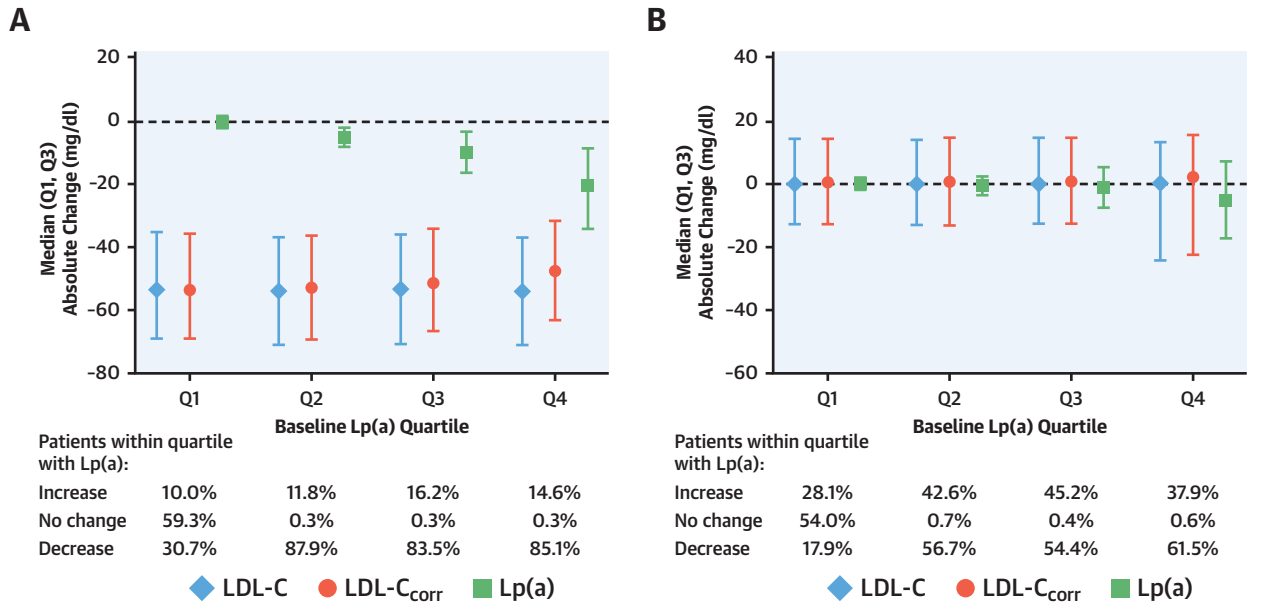
FIGURE 3 Relative and Absolute Treatment Effect on MACE by Baseline Lipoprotein(a) Quartile

Subgroup	MACE Incidence: Alirocumab n/N (%)	MACE Incidence: Placebo n/N (%)	HR (95% CI) ($p_{interaction}$ = 0.55)	Absolute Risk Reduction (95% CI) ($p_{interaction}$ = 0.0011)
Quartile 1	211/2,327 (9.1)	228/2,403 (9.5)	0.95 (0.79, 1.15)	0.4% (-1.2, 2.1)
Quartile 2	219/2,438 (9.0)	239/2,293 (10.4)	0.85 (0.71, 1.03)	1.4% (-0.3, 3.1)
Quartile 3	212/2,356 (9.0)	269/2,373 (11.3)	0.79 (0.66, 0.94)	2.3% (0.6, 4.1)
Quartile 4	261/2,341 (11.2)	316/2,393 (13.2)	0.83 (0.70, 0.98)	2.1% (0.2, 3.9)
Overall	903/9,462 (9.5)	1,052/9,462 (11.1)	0.85 (0.78, 0.93)	1.6% (0.7, 2.4)



Incidence of MACE is shown for the alirocumab and placebo groups stratified by baseline quartile of lipoprotein(a) and for the overall population. The Forest plots depict relative and absolute risk reduction with alirocumab compared with placebo. For relative risk reduction, there was no significant interaction by baseline lipoprotein(a) quartile, but absolute treatment effect was significantly greater in the 2 highest lipoprotein(a) quartiles. Abbreviations as in Figures 1 and 2.

FIGURE 4 Absolute Change From Baseline to Month 4 in LDL-C, LDL-C_{corr}, and Lipoprotein(a) Levels



Absolute change from baseline to month 4 in low-density lipoprotein cholesterol (LDL-C), low-density lipoprotein cholesterol corrected for cholesterol content in lipoprotein(a) (LDL-C_{corr}), and lipoprotein(a) levels by baseline lipoprotein(a) quartile in **(A)** alirocumab group and **(B)** placebo group. Medians and interquartile ranges of absolute changes from baseline to month 4 are shown stratified by baseline lipoprotein(a) quartile for 3 lipid parameters: LDL-C **(blue)**, LDL-C_{corr} **(red)**, and lipoprotein(a) **(green)**. The percentages below the x-axis summarize the percent of patients within each baseline lipoprotein(a) quartile with an increase, no change, or decrease in lipoprotein(a) from baseline to month 4. Q = quartile.

in LDL-C were similar in all lipoprotein(a) quartiles; however, accounting for the cholesterol content in lipoprotein(a), the change in LDL-C_{corr} diminished slightly in the upper lipoprotein(a) quartiles, with an overall median change of −51.1 mg/dl (IQR: −67.2 to −33.7 mg/dl) (Figure 4A). Baseline lipoprotein(a) was strongly correlated with the change from baseline to month 4 in lipoprotein(a) and was weakly correlated with the change in LDL-C_{corr} and non−HDL-C_{corr} (Online Figure 3). There were no systematic changes in lipoprotein(a) levels over time in the placebo group (Figure 4B).

TABLE 1 Relationship of Changes in Lipoprotein(a) and LDL-C From Baseline to Month 4 to MACE After Month 4 in the Alirocumab Group

Model	Model Adjustments	Change Parameter	HR (95% CI) per 1-mg/dl Decrease	HR (95% CI) for Observed Median Decrease	p Value
1	None	Lp(a)	0.998 (0.993–1.002)	0.988 (0.967–1.009)	0.2730
2	Baseline Lp(a)	Lp(a)	0.993 (0.989–0.998)	0.968 (0.948–0.989)	0.0027
3A	Baseline Lp(a), baseline LDL-C_{corr}, change from baseline to month 4 in LDL-C_{corr}	Lp(a)	0.994 (0.990–0.999)	0.972 (0.951–0.992)	0.0081
		LDL-C_{corr}	0.996 (0.994–0.998)	0.807 (0.720–0.904)	0.0002
3B	Baseline Lp(a), baseline non−HDL-C_{corr}, change from baseline to month 4 in non−HDL-C_{corr}	Lp(a)	0.994 (0.990–0.998)	0.972 (0.951–0.992)	0.0078
		Non−HDL-C_{corr}	0.997 (0.995–0.998)	0.819 (0.734–0.914)	0.0004
4A	Baseline Lp(a), baseline LDL-C_{corr}, change from baseline to month 4 in LDL-C_{corr}, demographic and clinical characteristics	Lp(a)	0.994 (0.990–0.998)	0.973 (0.953–0.992)	0.0071
		LDL-C_{corr}	0.995 (0.993–0.997)	0.780 (0.696–0.874)	<0.0001
4B	Baseline Lp(a), baseline non−HDL-C_{corr}, change from baseline to month 4 in non−HDL-C_{corr}, demographic and clinical characteristics	Lp(a)	0.994 (0.990–0.998)	0.973 (0.953–0.992)	0.0064
		Non−HDL-C_{corr}	0.996 (0.994–0.998)	0.802 (0.717–0.897)	0.0001

Observed median decreases for lipoprotein(a) [Lp(a)], low-density lipoprotein cholesterol corrected for lipoprotein(a) cholesterol (LDL-C_{corr}), and non-high density lipoprotein cholesterol corrected for lipoprotein(a) cholesterol (non-HDL-C_{corr}) were 5.0 mg/dl, 5.1 mg/dl, and 57.1 mg/dl, respectively.

CI = confidence interval; HR = hazard ratio.

Effect of alirocumab-induced changes in lipoprotein(a) and LDL-C_{corr} on outcomes. Table 1 shows the results of the sequential Cox proportional hazards models related to the change in lipoprotein(a) on alirocumab treatment to the risk of MACE, with concurrent adjustment for LDL-C_{corr} or non–HDL-C_{corr}. The analysis included 9,245 patients, 710 of whom had a MACE event. Online Table 3 shows the modeling for coronary heart disease death and/or nonfatal myocardial infarction, ischemic stroke, cardiovascular death, or all-cause death. In unadjusted models, no significant relationship was found between the change in lipoprotein(a) and the risk of MACE (model 1). After adjustment for baseline lipoprotein(a), a significant relationship of reduction in lipoprotein(a) with a lower risk of MACE was apparent (model 2). This was because higher baseline lipoprotein(a) was associated with both greater cardiovascular risk and greater reduction in lipoprotein(a) on alirocumab treatment. Therefore, accounting for the former exposed the relationship of the latter to the risk of MACE. Importantly, further adjustment for baseline concentration and change in concentration (baseline to month 4) of either LDL-C_{corr} or non–HDL-C_{corr} did not attenuate the relationship of change in lipoprotein(a) to risk of MACE (comparison of model 2 with models 3A and 3B, respectively). In models adjusted for LDL-C_{corr} or non–HDL-C_{corr} (models 3A and 3B), a 1-mg/dl decrease in lipoprotein(a) was associated with HRs for MACE of 0.994 (95% CI: 0.990 to 0.999) and 0.994 (95% CI: 0.990 to 0.998), respectively. In these models, a 1-mg/dl decrease in LDL-C_{corr} or non–HDL-C_{corr} was associated with HRs for MACE of 0.996 (95% CI: 0.994 to 0.998) and 0.997 (95% CI: 0.995 to 0.998), respectively. This indicated that reductions in lipoprotein(a) and LDL-C_{corr} (or non–HDL-C_{corr}) with alirocumab treatment independently contributed to the reduced risk of MACE. Further adjustment for demographic and clinical variables had minimal effects on the relationships (models 4A and 4B).

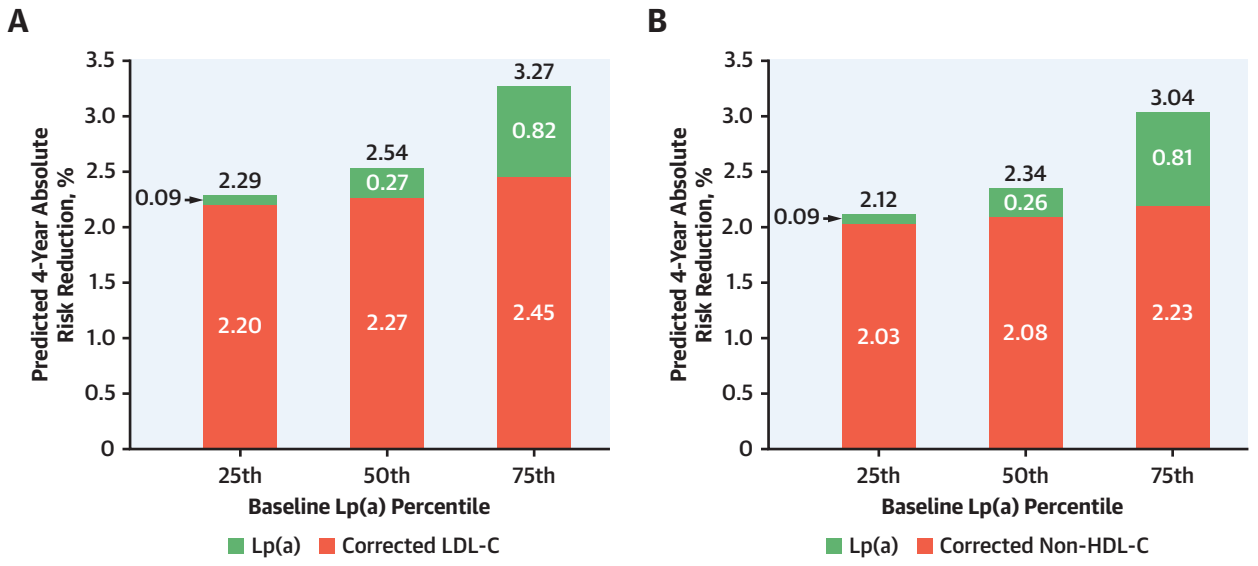
The magnitude of lipoprotein(a) change with alirocumab treatment increased with baseline lipoprotein(a) concentrations. For example, patients at the 25th, 50th, and 75th percentiles of the baseline lipoprotein(a) distribution had expected changes in lipoprotein(a) with alirocumab treatment of −1.6, −4.8, and −13.4 mg/dl, respectively. In turn, greater lipoprotein(a) reduction with alirocumab treatment was associated with greater contribution to the reduction in risk of MACE. The Central Illustration shows the contributions to the predicted MACE absolute risk reduction with alirocumab attributable to changes in lipoprotein(a) and to changes in LDL-C_{corr} (Central Illustration A) or non–HDL-C_{corr} (Central Illustration B) for patients in the 25th, 50th, and 75th percentiles of baseline lipoprotein(a). Consistent with Figure 3 (right), the predicted 4-year absolute risk reduction was greater for higher percentiles of baseline lipoprotein(a). At the 25th percentile, lipoprotein(a) reduction accounted for a small fraction of the predicted 2.29% absolute reduction in MACE with alirocumab, whereas at the 75th percentile of baseline lipoprotein(a), lipoprotein(a) reduction accounted for 25% of the predicted 3.27% absolute reduction in risk of MACE with alirocumab (Central Illustration A). Findings were similar when changes in non–HDL-C_{corr} were considered (Central Illustration B). Thus, among patients with low baseline lipoprotein(a), reduction of lipoprotein(a) with alirocumab contributed minimally to the reduction in MACE. In contrast, among patients with high baseline lipoprotein(a), reduction of lipoprotein(a) with alirocumab contributed substantially to the reduction of MACE, although the effect of reducing LDL-C_{corr} (or non–HDL-C_{corr}) remained primary. The randomized treatment predicted 4-year absolute risk reduction after month 4, based on 18,487 patients and 1,576 events, was 2.34%, and the treatment HR was 0.81 (95% CI: 0.73 to 0.89).

DISCUSSION

Among patients with recent ACS who received intensive or maximum-tolerated statin treatment, baseline lipoprotein(a) levels were predictive of MACE, nonfatal myocardial infarction or coronary heart disease death, and cardiovascular death, independent of baseline LDL-C_{corr}. Baseline lipoprotein(a) level did not predict ischemic stroke or all-cause death. For patients in the upper 2 quartiles of baseline lipoprotein(a), alirocumab was a particularly efficient intervention that required treatment of 43 to 49 patients for a median of 2.8 years to prevent 1 MACE.

Alirocumab produced a median 23% reduction in lipoprotein(a). The absolute reduction in lipoprotein(a) was directly related to the baseline concentration. A novel observation from this analysis was that the reductions of lipoprotein(a) and LDL-C_{corr} (or non–HDL-C_{corr}) by alirocumab were independently associated with the absolute reduction in risk of MACE. The relative contribution of lipoprotein(a) reduction to reduced risk of MACE was negligible when baseline lipoprotein(a) concentration was low but became substantial when baseline lipoprotein(a) concentration was high. Nonetheless,

CENTRAL ILLUSTRATION **Relative Contributions of Changes in Concentrations of Corrected Low-Density Lipoprotein Cholesterol, Corrected Non-High-Density Lipoprotein Cholesterol, and Lipoprotein(a) to the Absolute Reduction in Major Adverse Cardiovascular Events in the Alirocumab Group**



Bittner, V.A. et al. J Am Coll Cardiol. 2020;75(2):133–44.

Based on models with adjustments for baseline levels shown in Table 1 (Models 3A and 3B), **A** shows the absolute contributions of reductions in lipoprotein(a) [Lp(a)] and low-density lipoprotein cholesterol corrected for the cholesterol in Lp(a) (LDL-C_{corr}) to the predicted 4-year absolute reduction in major adverse cardiovascular events (MACE) at the 25th, 50th, and 75th percentile of baseline Lp(a) concentration (Model 3A), while **B** shows the corresponding data for reductions in non-high-density lipoprotein cholesterol corrected for the cholesterol in Lp(a) (non-HDL-C_{corr}) (Model 3B). The absolute contribution of Lp(a) reduction to reduced risk of MACE was minimal when baseline Lp(a) concentration was low but was substantial when baseline Lp(a) concentration was high. The expected baseline levels at the 25th, 50th, and 75th percentiles of baseline Lp(a) are 87.3 mg/dl, 84.3 mg/dl, and 76.4 mg/dl, respectively for LDL-C_{corr} and 118.2 mg/dl, 114.7 mg/dl, and 105.4 mg/dl, respectively, for non-HDL-C_{corr}. The expected reductions at the 25th, 50th, and 75th percentiles of baseline Lp(a) are 1.6 mg/dl, 4.8 mg/dl, and 13.4 mg/dl, respectively, for Lp(a), 51.1 mg/dl, 50.5 mg/dl, and 48.9 mg/dl, respectively, for LDL-C_{corr}, and 57.1 mg/dl, 56.2 mg/dl, and 53.9 mg/dl, respectively, for non-HDL-C_{corr}.

reduction of MACE remained predominantly attributable to reduction of LDL-C_{corr} (or non–HDL-C_{corr}) across the range of baseline lipoprotein(a) concentrations.

These novel observations added to evidence from epidemiological (1,2) and genetic (5,23,24) studies that lipoprotein(a) is an independent and causal contributor to the risk of coronary heart disease and supported the hypothesis that interventions specifically aimed at reducing lipoprotein(a) have the potential to reduce cardiovascular risk through that mechanism.

Our data indicate a greater benefit of lipoprotein(a) reduction than that estimated in a Mendelian randomization analysis relating genetically determined lipoprotein(a) levels in healthy individuals to the risk of incident coronary heart disease (5,24). This might be the case if lipoprotein(a) was a more important risk factor in patients with advanced atherosclerosis (as in ACS) than in healthy populations. Lipoprotein(a) was purported to have a role in thrombosis and atherosclerosis (25). Both processes are involved in the pathogenesis of ACS. Because of the propensity of lipoprotein(a) to bind to fibrin in the injured vascular wall (2), outcomes after ACS may be particularly sensitive to its concentration.

Our finding that lipoprotein(a) was a prognostic marker in a statin-treated coronary heart disease population was consistent with a recent meta-analysis of 7 statin trials (26). In contrast, 2 trials among patients with ACS found no association between baseline lipoprotein(a) and MACE, but enrolled patients with lower baseline lipoprotein(a) levels than those measured in the present study (3,4).

Niacin and cholesteryl ester transfer protein inhibitors reduced lipoprotein(a) by 20% to 25%; however, trials with these agents did not show reduction in MACE (10,11,27). A potential benefit of

lipoprotein(a) reduction with niacin or cholesteryl ester transfer protein inhibitors was perhaps mitigated by other, undesirable effects of the drugs (27,28). The FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial (29) compared the PCSK9 inhibitor evolocumab with placebo in patients with stable atherosclerotic cardiovascular disease and demonstrated reduction of lipoprotein(a) and reduction in MACE similar in magnitude to the present analysis. A regression analysis of treatment group differences in lipoprotein(a) at week 48 by baseline decile found a correlation between greater differences in lipoprotein(a) and risk of coronary events after adjustment for LDL-C. Our findings extend those of the FOURIER trial by demonstrating, for the first time, that patient-level pharmacological lowering of lipoprotein(a) relatively early after the initiation of therapy was associated with reduced risk of subsequent MACE, independent of concurrent reductions of LDL-C_{corr} or non–HDL-C_{corr}.

The predicted MACE 4-year absolute risk reductions corresponding to joint changes in lipoprotein(a) and LDL-C_{corr} (or non–HDL-C_{corr}) with alirocumab shown in the **Central Illustration** varied around the randomized treatment risk reduction of 2.34%. Although this is >2.0%, the previously reported risk reduction in the ODYSSEY OUTCOMES trial (16), numerical correspondence of these risk reductions were not necessarily expected, because the analysis in **Table 1** and the **Central Illustration** considered MACE beginning after the month 4 assessment for each patient, whereas the overall analysis of the trial considered MACE beginning at randomization. Alirocumab had no apparent effect on MACE through month 4; therefore, effects after month 4 were greater than the overall effects during the trial.

STUDY LIMITATIONS. The cholesterol content in lipoprotein(a) particles is variable. Correction of LDL-C or non–HDL-C by 30% of lipoprotein(a) mass is thus an approximation of the contribution from cholesterol in lipoprotein(a). Lipoprotein(a) mass, as measured in this study, correlates imperfectly with molar concentration of lipoprotein(a) because mass is influenced by apolipoprotein(a) isoform size. At high lipoprotein(a) mass, molar concentration is underestimated, and vice versa (30). However, to the extent such effects were present, they would have biased our study toward the null. Furthermore, the magnitude of lipoprotein(a) lowering by alirocumab is not affected by apolipoprotein(a) size (28,31). Changes in lipoprotein(a) might reflect adherence to study treatment, and possibly, general adherence (i.e., to other evidence-based cardiovascular therapies and lifestyle modifications), which, in turn, might affect prognosis. However, changes in LDL-C or non–HDL-C would be similarly reflective of adherence, and adjustment for those variables should account for any effect of adherence in the present analysis. Finally, results in patients with ACS who received intensive statin therapy might not be generalizable to other populations.

CONCLUSIONS

There is strong evidence that elevated lipoprotein(a) contributes to the incidence of coronary heart disease, but no treatment has yet been proven to reduce coronary risk through a reduction in lipoprotein(a). The ODYSSEY OUTCOMES trial was not designed specifically to enroll and treat patients with high lipoprotein(a). However, our observations suggest that reduction of lipoprotein(a) contributed to the reduction of cardiovascular risk with alirocumab therapy, independent of the concurrent reduction of other atherogenic lipoproteins. Therefore, lipoprotein(a) is both a prognostic factor and a potentially important independent treatment target among patients with recent ACS.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Baseline levels of lipoprotein(a) and LDL-C and reductions by alirocumab are associated with the risk of MACE in patients after recent ACS.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine whether lipoprotein(a) is an important treatment target after recent ACS.

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KEY WORDS acute coronary syndromes, alirocumab, low-density lipoprotein cholesterol, major adverse cardiovascular events, proprotein convertase subtilisin/kexin type 9 inhibition

APPENDIX For a complete list of the ODYSSEY OUTCOMES committee members, investigators, and contributors, an expanded Methods section, and supplemental figures and tables, please see the online version of this paper.