



Apolipoprotein B, Residual Cardiovascular Risk After Acute Coronary Syndrome, and Effects of Alirocumab

Emil Hagström¹, MD, PhD; P. Gabriel Steg², MD; Michael Szarek³, PhD; Deepak L. Bhatt⁴, MD, MPH; Vera A. Bittner⁵, MD, MSPH; Nicolas Danchin⁶, MD; Rafael Diaz⁷, MD; Shaun G. Goodman⁸, MD, MSc; Robert A. Harrington⁹, MD; J. Wouter Jukema¹⁰, MD, PhD; Evangelos Liberopoulos¹¹, MD; Nikolaus Marx¹², MD; Jennifer McGinniss, PhD; Garen Manvelian, MD; Robert Pordy¹³, MD; Michel Scemama, MD; Harvey D. White¹⁴, DSc; Andreas M. Zeiher¹⁵, MD; Gregory G. Schwartz¹⁶, MD, PhD; for the ODYSSEY OUTCOMES Investigators*

BACKGROUND: Apolipoprotein B (apoB) provides an integrated measure of atherogenic risk. Whether apoB levels and apoB lowering hold incremental predictive information on residual risk after acute coronary syndrome beyond that provided by low-density lipoprotein cholesterol is uncertain.

METHODS: The ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) compared the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab with placebo in 18924 patients with recent acute coronary syndrome and elevated atherogenic lipoproteins despite optimized statin therapy. Primary outcome was major adverse cardiovascular events (MACE; coronary heart disease death, nonfatal myocardial infarction, fatal/nonfatal ischemic stroke, hospitalization for unstable angina). Associations between baseline apoB or apoB at 4 months and MACE were assessed in adjusted Cox proportional hazards and propensity score–matched models.

RESULTS: Median follow-up was 2.8 years. In proportional hazards analysis in the placebo group, MACE incidence increased across increasing baseline apoB strata (3.2 [95% CI, 2.9–3.6], 4.0 [95% CI, 3.6–4.5], and 5.5 [95% CI, 5.0–6.1] events per 100 patient-years in strata <75, 75–<90, ≥90 mg/dL, respectively; $P_{\text{trend}} < 0.0001$) and after adjustment for low-density lipoprotein cholesterol ($P_{\text{trend}} = 0.035$). Higher baseline apoB stratum was associated with greater relative ($P_{\text{trend}} < 0.0001$) and absolute reduction in MACE with alirocumab versus placebo. In the alirocumab group, the incidence of MACE after month 4 decreased monotonically across decreasing achieved apoB strata (4.26 [95% CI, 3.78–4.79], 3.09 [95% CI, 2.69–3.54], and 2.41 [95% CI, 2.11–2.76] events per 100 patient-years in strata ≥50, >35–<50, and ≤35 mg/dL, respectively). Compared with propensity score–matched patients from the placebo group, treatment hazard ratios for alirocumab also decreased monotonically across achieved apoB strata. Achieved apoB was predictive of MACE after adjustment for achieved low-density lipoprotein cholesterol or non–high-density lipoprotein cholesterol but not vice versa.

CONCLUSIONS: In patients with recent acute coronary syndrome and elevated atherogenic lipoproteins, MACE increased across baseline apoB strata. Alirocumab reduced MACE across all strata of baseline apoB, with larger absolute reductions in patients with higher baseline levels. Lower achieved apoB was associated with lower risk of MACE, even after accounting for achieved low-density lipoprotein cholesterol or non–high-density lipoprotein cholesterol, indicating that apoB provides incremental information. Achievement of apoB levels as low as ≤35 mg/dL may reduce lipoprotein-attributable residual risk after acute coronary syndrome.

Correspondence to: Emil Hagström, MD, PhD, Department of Medical Sciences, Cardiology and Uppsala Clinical Research Centre, Uppsala University, 751 85 Uppsala, Sweden. Email emil.hagstrom@ucr.uu.se

This manuscript was sent to Erin Michos, Guest Editor, for review by expert referees, editorial decision, and final disposition.

*The ODYSSEY OUTCOMES committee members, investigators, and contributors are listed in the [Supplemental Material](#).

Supplemental Material is available at <https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.121.057807>.

Continuing medical education (CME) credit is available for this article. Go to <http://cme.ahajournals.org> to take the quiz.

For Sources of Funding and Disclosures, see page 670.

© 2022 The Authors. *Circulation* is published on behalf of the American Heart Association, Inc., by Wolters Kluwer Health, Inc. This is an open access article under the terms of the [Creative Commons Attribution Non-Commercial-NoDerivs](#) License, which permits use, distribution, and reproduction in any medium, provided that the original work is properly cited, the use is noncommercial, and no modifications or adaptations are made.

Circulation is available at www.ahajournals.org/journal/circ

REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT01663402.

Key Words: acute coronary syndrome ■ apolipoproteins B ■ cholesterol, LDL ■ heart disease risk factors ■ PCSK9 inhibitors

Editorial, see p 673

Clinical Perspective

What Is New?

- In patients with recent acute coronary syndrome and elevated atherogenic lipoproteins despite high-intensity or maximum-tolerated statin treatment, the risk of major adverse cardiovascular events increased with the baseline level of apolipoprotein B.
- Under treatment with the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab, larger relative and absolute reductions in major adverse cardiovascular events were observed with higher baseline and lower achieved levels of apolipoprotein B.
- Achieved levels of apolipoprotein B with alirocumab treatment predicted major adverse cardiovascular events after accounting for achieved low-density lipoprotein cholesterol or non-high-density lipoprotein cholesterol, but not vice versa.

What Are the Clinical Implications?

- In patients with recent acute coronary syndrome receiving optimized statin therapy, a decision to treat with a proprotein convertase subtilisin/kexin type 9 inhibitor may be informed by the level of apolipoprotein B.
- On treatment with the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab, achieved levels of apolipoprotein B convey information on the risk of major adverse cardiovascular events beyond that provided by achieved levels of low-density lipoprotein cholesterol or non-high-density lipoprotein cholesterol.
- Treatment based on apolipoprotein B goals may further reduce lipoprotein-attributable residual risk after acute coronary syndrome.

Apolipoprotein B (apoB) is a key structural element of atherogenic lipoprotein particles, including low-density lipoprotein (LDL), lipoprotein(a), and triglyceride-rich lipoproteins. Although LDL cholesterol (LDL-C) is the most commonly used clinical lipid marker to stratify lipid-associated risk, all apoB-containing lipoproteins may affect the risk of major adverse cardiovascular events (MACE).¹⁻³ Each apoB-containing lipoprotein particle contains 1 apoB molecule, so apoB concentration provides a measure of total concentration of circulating atherogenic lipoprotein particles. In

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
apoB	apolipoprotein B
ARR	absolute risk reduction
HDL-C	high-density lipoprotein cholesterol
HR	hazard ratio
IQR	interquartile range
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
MACE	major adverse cardiovascular events
ODYSSEY OUTCOMES	Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab
PCSK9	proprotein convertase subtilisin/kexin type 9
TWMA	time-weighted moving average

patients with cardiovascular risk factors or stable cardiovascular disease, apoB levels provide incremental prognostic information on risk of incident atherosclerotic cardiovascular disease, MACE, and death, beyond that provided by LDL-C alone.³⁻⁶ Furthermore, in patients with a proatherogenic shift in lipoprotein composition not reflected by levels of LDL-C such as in type 2 diabetes mellitus or obesity, apoB concentration may reflect excess atherosclerotic risk more accurately than LDL-C.⁷

In patients with acute coronary syndrome (ACS), the risk of cardiovascular events is mitigated by lipid-lowering therapy with statins, ezetimibe, and inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9).⁸⁻¹² Statins and ezetimibe lower the circulating concentration of LDL-C; statins additionally lower the concentration of triglyceride-rich lipoproteins; and PCSK9 inhibitors lower the concentration of all 3 types of apoB-containing lipoproteins, including lipoprotein(a), an effect integrated by apoB levels. Although apoB levels contribute beyond LDL-C levels to predict MACE in patients with

established coronary heart disease,^{13,14} a similar association is less well established in patients with ACS.^{15,16} The relationship between apoB levels and MACE in ACS is important because lipoprotein(a) and triglyceride-rich lipoproteins also influence risk after ACS.^{17–20} Moreover, lipid-lowering drugs reduce apoB to a lesser extent than LDL-C.¹⁴ Therefore, a related question is whether on-treatment apoB or on-treatment LDL-C is a more informative indicator of lipoprotein-attributable residual risk.

In this analysis, we used data from the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), which compared the PCSK9 inhibitor alirocumab with placebo in patients with recent ACS, to determine the relationships between baseline or achieved levels of apoB and risk of MACE and to assess whether apoB holds incremental information on risk beyond LDL-C.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request. Qualified researchers may also request access to study documents, including the clinical study report, study protocol with amendments, case report forms, statistical analysis plan, and data set specifications.

Study Population

The ODYSSEY OUTCOMES trial design and primary results have been published.^{12,21} In brief, the trial included 18924 patients ≥ 40 years of age with a recent (1–12 months before randomization) ACS and elevated atherogenic lipoprotein levels (LDL-C ≥ 70 mg/dL [1.81 mmol/L], non-high-density lipoprotein cholesterol [HDL-C] ≥ 100 mg/dL [2.59 mmol/L], or apoB ≥ 80 mg/dL) despite high-intensity statin therapy (atorvastatin 40–80 mg daily, rosuvastatin 20–40 mg daily) or the maximum-tolerated dose of 1 of these statins. The patients were randomly assigned to receive either 75 mg alirocumab or matching placebo subcutaneously every 2 weeks. In patients treated with alirocumab, the dose was blindly increased to 150 mg if the achieved LDL-C level was ≥ 50 mg/dL (1.29 mmol/L). In patients who had 2 consecutive LDL-C measurements < 15 mg/dL (0.39 mmol/L), placebo was blindly substituted for alirocumab. The trial was approved by the institutional review board at each site. All patients provided informed consent.

Outcomes

The primary end point of MACE, comprising death resulting from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, and unstable angina requiring hospitalization, was adjudicated by an independent committee blinded to treatment assignment and lipid levels.

Measurement of Lipoproteins

ApoB concentration was measured in serum after an overnight fast, at randomization, at 4 months and at specified times thereafter. The samples were shipped at ambient temperature

and measured at COVANCE Central Laboratories on the day of receipt with an immunonephelometry assay on the Siemens BNII Nephelometer (Siemens, Erlangen, Germany). Accuracy was validated by comparison with the American Pathologists Chemistry Survey. The interassay coefficient of variation was 2.4%, with a lower limit of detection of 35 mg/dL. LDL-C was estimated with the Friedewald formula 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 β quantification. Furthermore, in select analyses, we used the Martin-Hopkins formula instead of the Friedewald formula to estimate LDL-C concentrations.²² Non-HDL-C was calculated by total cholesterol minus HDL-C. Baseline apoB was considered as a continuous variable and also as a categorical variable in 3 pre-specified strata, < 75 , 75 – < 90 , and ≥ 90 mg/dL. Achieved apoB at month 4 of alirocumab treatment was considered a categorical variable in 3 post hoc strata: ≤ 35 mg, > 35 – < 50 , and ≥ 50 mg/dL. These strata were defined by the lower limit of detection of apoB (35 mg/dL) and a boundary level of 50 mg/dL that was approximately the median of samples with apoB concentration above the lower limit of detection. Strata of achieved LDL-C with alirocumab were prespecified (< 25 , 25–50, and > 50 mg/dL).²³

Statistical Analysis

Continuous variables are described by median (interquartile range [IQR]). Categorical variables are presented as counts and percentages. Distributions of apoB are described by treatment group at baseline, along with the absolute change from baseline to month 4 (122 ± 28 days) after randomization. The last value was analyzed if a patient had multiple values within the time window. For the purposes of calculating these distributions, apoB values below the lower limit of detection were set to 35 mg/dL. At baseline, there were no missing values for apoB, and 3 patients were missing LDL-C. At 4 months, apoB was missing in 4.7% in the alirocumab group and 5.2% in the placebo group. At 12 months, apoB was missing in 8.8% of patients without a first MACE event before 12 months in the alirocumab group.

Missing postrandomization lipoprotein values were imputed by a prespecified pattern-mixture model following intention-to-treat principles.¹² In brief, a missing value for a given patient within 21 days after a dose of study treatment was assumed to be influenced by the last dose of study treatment and therefore imputed from their other nonmissing values measured within 21 days after a dose, whereas missing values > 21 days after a dose were imputed from their baseline value. For comparative purposes, similar assessments were made for the baseline and achieved LDL-C and non-HDL-C levels. Relative effects on first MACE are summarized by hazard ratios (HRs) with corresponding 95% CIs and *P* values from proportional hazards models. Event rates are expressed as the number of events per 100 patient-years of follow-up. The underlying proportional hazards assumptions of the proportional hazard models were verified by visual inspection of Kaplan-Meier graphs and plots of cumulative sums of Martingale residuals (Kolmogorov-type supremum test $P > 0.05$ in all cases; data not shown).

Relationships between baseline apoB and first MACE in the placebo group were determined by 3 models using prespecified baseline apoB strata as the predictor variable: model A,

unadjusted; model B, adjusted for demographic and nonlipid clinical variables (age, sex, race, geographic region, body mass index, smoking history, diabetes mellitus, time from index ACS to randomization); and model C, model B with the addition of baseline LDL-C. An additional analysis used LDL-C estimated by the Martin-Hopkins formula in model C. Thus, a comparison of models B and C determines whether baseline apoB provides incremental predictive information after baseline LDL-C has been taken into account. A *P* value was computed for linear trend in the estimated log HR across the ordered baseline apoB strata. A spline analysis of degree 2 (piecewise quadratic curve) of the relationship between continuous baseline apoB and MACE in the placebo group was performed, setting the HR to 1.00 at the overall baseline median concentration of apoB and 3 knots, located at the overall 25th percentile, median, and 75th percentile. For comparison, a spline analysis was also performed assessing the relationship between baseline non-HDL-C and MACE, with the HR set to 1.00 at the overall baseline median concentration of non-HDL-C and 3 knots located at the overall 25th percentile, median, and 75th percentile. The *P* value for the spline effect was based on the score test.

Heterogeneity in the relative and absolute effects of alirocumab treatment on first MACE was assessed according to baseline apoB strata. To assess heterogeneity in relative treatment effects, we constructed a proportional hazards model with baseline apoB stratum, treatment, and their interaction as predictors and computed a *P* value for linear trend across the estimated log HR (ie, the 3 interaction terms). To assess heterogeneity in absolute treatment effects, we constructed absolute risk reductions (ARRs) with alirocumab treatment, quantified as differences in the event rates per 100 patient-years of follow-up, along with associated 95% CIs. The cumulative incidence of first MACE by apoB strata and treatment group was estimated with Kaplan-Meier curves.

The propensity score-matched analysis included 9246 patients randomly assigned to alirocumab (including 437 [4.7%] with imputed month 4 apoB) and 9243 patients assigned to placebo (including 487 [5.2%] with imputed month 4 apoB) without a first MACE before their month 4 apoB assessment and made up 97.7% of the overall intention-to-treat population.

Month 4 values of apoB were selected because they reflect levels after several doses of alirocumab treatment and because relatively few MACE occurred before this time point.¹² In relating achieved month 4 apoB levels to risk of MACE, we considered the potential for confounding attributable to differences in baseline characteristics or study medication adherence across apoB strata that were expected to be prognostic for MACE. To account for such differences, a propensity score was used to match each patient in the alirocumab group with a patient in the placebo group with similar baseline characteristics and adherence. To improve the quality of the match, the analysis used matching with replacement that allowed a given patient receiving placebo to be matched to patients receiving alirocumab in different achieved apoB stratum but not to multiple alirocumab patients within an achieved apoB stratum.²⁴ A threshold of *P*<0.1 with forward selection in a logistic regression model was used to determine which

characteristic differed between patients in each achieved apoB stratum of the alirocumab group and eligible patients receiving placebo. Baseline characteristics considered for matching were age, sex, and geographic region; history of diabetes mellitus, current smoking, previous coronary artery bypass grafting, previous percutaneous coronary intervention, peripheral artery disease, cerebrovascular disease, heart failure, chronic obstructive pulmonary disease, and malignancy; type of index ACS (non-ST-segment-elevation myocardial infarction, ST-segment-elevation myocardial infarction, or unstable angina), revascularization for the index ACS, and intensity of statin therapy at randomization (high intensity versus other); body mass index, systolic blood pressure, and estimated glomerular filtration rate dichotomized at 60 mL·min⁻¹·1.73 m⁻²; and baseline concentrations of apoB, LDL-C, and lipoprotein(a). Adherence was assessed by the number of doses of study medication injected during the 61 days preceding the month 4 apoB measurement, as reported in patient diaries. There was no imputation of missing adherence data. Greedy matching on propensity scores was performed with caliper 0.25.

A series of spline analyses of degree 2 (piecewise quadratic curve) were performed in the alirocumab group. The estimated HR was set to 1.00 at the median month 4 concentration for the lipoprotein parameter that was related to the risk of MACE, with knots at the 25th percentile, median, and 75th percentile. The first set described the relationship between continuous apoB at month 4 and subsequent risk of MACE after adjustment for month 4 LDL-C; similar analyses adjusted for month 4 LDL-C estimated by the Martin-Hopkins formula and for month 4 non-HDL-C. A second set described the relationship between continuous month 4 LDL-C or month 4 LDL-C estimated by the Martin-Hopkins formula and subsequent risk of MACE after adjustment for month 4 apoB. Last, the relationship between continuous achieved non-HDL-C at month 4 and subsequent risk of MACE was described after adjustment for month 4 LDL-C.

To account for all apoB and LDL-C assessments in the study and for cumulative effects of changes in these lipid parameters over time, the relationship between continuous time-weighted moving average (TWMA) apoB, LDL-C, and MACE was analyzed within the alirocumab group. TWMA apoB and LDL-C were calculated from all available baseline and postrandomization values before a MACE event or right censoring for MACE at the last follow-up and specified as time-varying covariates in a Cox proportional hazards regression model. Separate analyses were performed with LDL-C estimated from the Friedewald and Martin-Hopkins formulas. Imputed values were excluded. This analysis therefore accounts for the potential effects of discontinuation of study medication, changes in background statin treatment, and protocol-specified blinded adjustment of alirocumab dose over the entire observation period.

Values of *P*<0.05 from 2-sided tests were considered statistically significant. All analyses were conducted according to intention to treat, including all patients and events from randomization to the common study end date (November 11, 2017). All analyses were conducted (by M.S.) with SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Median apoB at baseline was 79 mg/dL (IQR, 69–93 mg/dL). The distribution of baseline apoB in the placebo group is shown in Figure 1. Baseline apoB strata of <75, 75–<90, and ≥90 mg/dL comprised 7330, 5874, and 5720 patients, respectively (Table). Patients in the highest apoB strata were more likely to be women; to have diabetes mellitus, hypertension, and previous atherosclerotic events such as myocardial infarction, percutaneous coronary intervention, and coronary artery bypass grafting; and less likely to be treated with a high-intensity statin regimen (Table). Patients in the lowest apoB stratum at baseline were more likely to have subsequent blinded substitution of placebo for alirocumab. In each stratum, patient characteristics were well balanced in the alirocumab and placebo groups (Table). Patients were followed up for a median of 2.8 years (IQR, 2.3–3.4 years).

Effect of Alirocumab on ApoB Levels

At month 4 of treatment, the median apoB level was 39 mg/dL (IQR, 35–53 mg/dL) in the alirocumab group and 80 mg/dL (IQR, 68–95 mg/dL) in the placebo group. The median absolute change from baseline in apoB was –36 mg/dL (IQR, –47 to –24 mg/dL) in the alirocumab group versus 0 mg/dL (IQR, –9 to 10 mg/dL) in the placebo group. Patients in the highest baseline apoB stratum had the largest absolute change in apoB, –56 mg/dL (IQR, –66 to –41 mg/dL) compared with –41 mg/dL (IQR, –46 to –31 mg/dL) in the middle baseline stratum and –27 mg/dL (IQR, –33 to –18 mg/dL) in the lowest baseline stratum. The correlation between achieved apoB and achieved LDL-C is shown in Figure S1.

Among patients in the alirocumab group who achieved current US²⁵ or European²⁶ guideline-specified goals for LDL-C (calculated with the Martin-Hopkins formula) or non-HDL-C, we assessed the correspondence with achieved apoB quantile (Table S1). Among patients with achieved LDL-C levels <70, <55, or <40 mg/dL, 54.4%, 50.7%, and 40.7% failed to achieve an apoB level ≤35 mg/dL. We also determined the correspondence between achievement of Martin-Hopkins LDL-C or non-HDL-C in the lowest quartile (<22.0 or <40.9 mg/dL, respectively) and achieved quantiles of apoB. Of patients who achieved LDL-C in the lowest quartile, 18.2% did not achieve apoB ≤35 mg/dL. Furthermore, of those with non-HDL-C in the lowest quartile, 3.9% did not reach apoB ≤35 mg/dL.

Baseline ApoB and Incidence of MACE in the Placebo Group

In the placebo group, the incidence of MACE increased across baseline apoB strata (Figure 1). In the unadjusted model (model A), relative to the lowest baseline apoB

stratum, patients in the middle and highest strata were at 24% (HR, 1.24 [95% CI, 1.06–1.45]) and 71% (HR, 1.71 [95% CI, 1.48–1.97]) higher risk for MACE, respectively ($P_{\text{trend}} < 0.0001$). With adjustment for demographic and nonlipid clinical variables (model B), these increased risks were 19% (HR, 1.19 [95% CI, 1.02–1.40]) and 64% (HR, 1.64 [95% CI, 1.41–1.90]), respectively ($P_{\text{trend}} < 0.0001$). Baseline apoB stratum predicted the risk of MACE even after further adjustment for baseline LDL-C (model C). In this model, the increased risks in the middle and highest strata were 9% (HR, 1.09 [95% CI, 0.93–1.28]) and 23% (HR, 1.23 [95% CI, 1.02–1.48]), respectively ($P_{\text{trend}} = 0.035$). When model C was adjusted for LDL-C estimated with the Martin-Hopkins formula, the results were attenuated compared with the analysis with adjustment for LDL-C estimated with the Friedewald formula, with HRs in the middle and highest apoB strata of 1.10 (95% CI, 0.92–1.30) and 1.17 (95% CI, 0.96–1.42), respectively ($P_{\text{trend}} = 0.13$). In an unadjusted model assessing the relationship between continuous baseline apoB level and MACE, there was a fairly linear association ($P < 0.0001$ for spline effect; Figure 1). For every 10 mg/dL increment in baseline apoB, there was an 11% higher risk of MACE (HR, 1.11 [95% CI, 1.09–1.14]; $P < 0.0001$). Spline analysis of the continuous relationship between baseline non-HDL-C and MACE (Figure S2) provided results nearly identical to those for the relationship between baseline apoB and MACE, with a 7% higher risk of MACE (HR, 1.07 [95% CI, 1.05–1.08]; $P < 0.0001$) per 10 mg/dL increment in non-HDL-C.

Effects of Alirocumab on MACE by Baseline ApoB Stratum

Overall, alirocumab reduced the risk of MACE compared with placebo, with an HR of 0.85 (95% CI, 0.78–0.93; $P < 0.001$) and an ARR of 0.6 events per 100 patient-years of follow-up. There was a significant linear trend in the treatment HR for incident MACE across baseline apoB strata ($P < 0.0001$; Figure 2), decreasing from 0.90 for <75 mg/dL to 0.80 for ≥90 mg/dL. Together with the ascending relationship between baseline apoB and absolute risk of MACE in the placebo group, the absolute reduction in risk of MACE with alirocumab increased from 0.3 events per 100 patient-years for patients with baseline apoB <75 mg/dL to 1.1 per 100 patient-years for patients with baseline apoB ≥90 mg/dL. In Figure 3, Kaplan-Meier curves show the cumulative incidence of MACE by apoB stratum and treatment allocation. Early and consistent curve separation is evident in the highest baseline apoB stratum.

Effects of Alirocumab on MACE by Achieved ApoB Stratum

Baseline characteristics, adherence, and month 4 lipoprotein levels of patients who achieved month 4 apoB

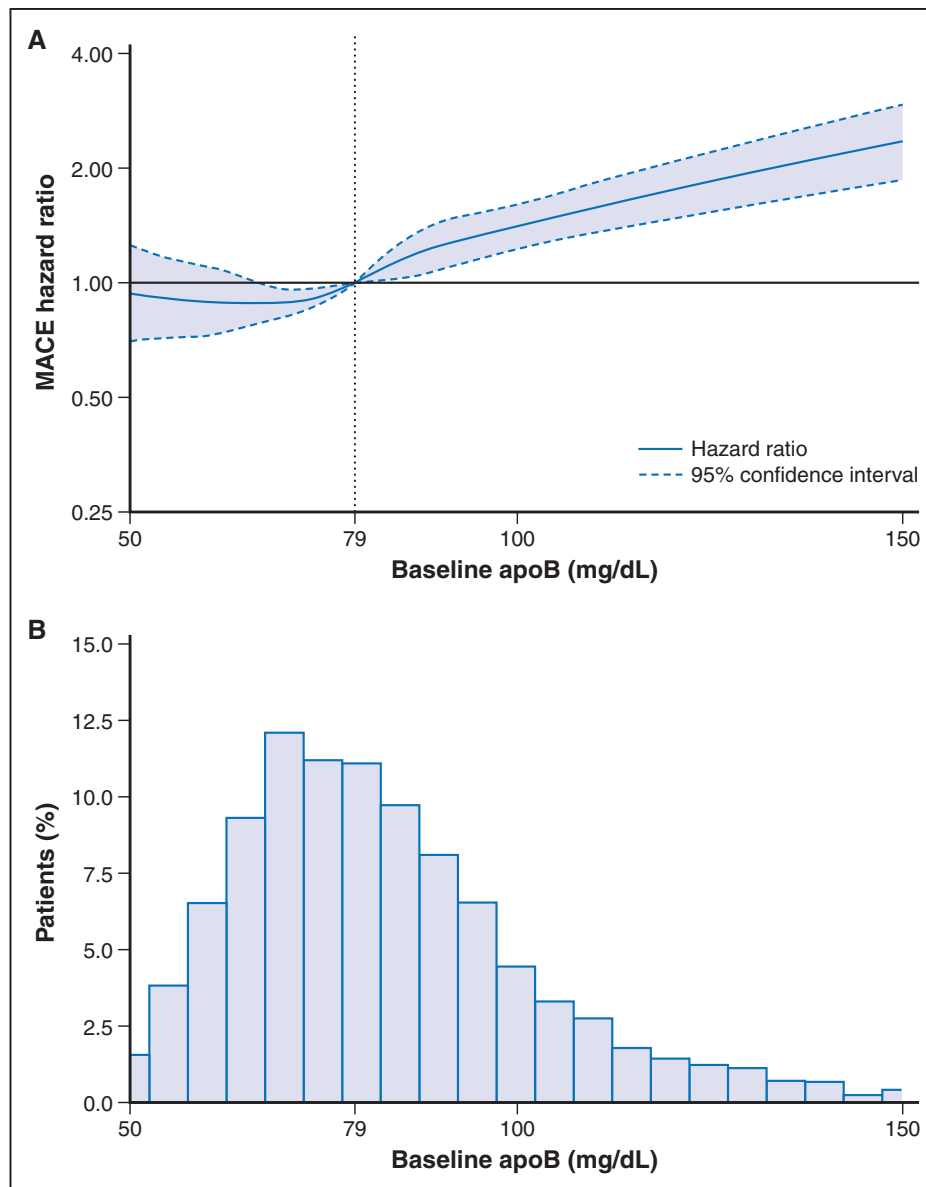


Figure 1. Spline analysis of continuous baseline apoB and incident MACE in the placebo group.

A, Hazard ratio set to 1.00 at the overall baseline median (79 mg/dL) concentration of apoB. Score test $P < 0.0001$ for spline effect. This reflects spline of degree 2 (piecewise quadratic curve) with 3 knots, located at the 25th (69 mg/dL), 50th (79 mg/dL), and 75th (93 mg/dL) percentiles and spanning the approximate 1st (50 mg/dL) to 99th (150 mg/dL) percentiles overall. Dotted lines indicate the lower and upper bounds of the 95% CI. **B**, Histogram of baseline apoB in the placebo group. ApoB indicates apolipoprotein B; and MACE, major adverse cardiovascular events.

≥ 50 , >35 – <50 , or ≤ 35 mg/dL are shown in Table S2, along with the characteristics of corresponding propensity score–matched patients from the placebo group.

The incidence rates for MACE after month 4 in all eligible patients, in each achieved apoB stratum of the alirocumab group, and in corresponding propensity score–matched patients from the placebo group are displayed in Figure 4; the cumulative incidence of MACE is depicted in Figure S3. The analysis includes 1576 events, representing 80.6% of the events from randomization. Overall, MACE after month 4 occurred at rates of 3.16 (95% CI, 2.94–3.41) and 3.91 (95% CI, 3.66–4.18) per 100 patient-years of observa-

tion in the alirocumab and placebo groups, respectively (HR, 0.81 [95% CI, 0.73–0.89]; ARR, 0.75 events per 100 patient-years). In the alirocumab group, the incidence of MACE after month 4 decreased monotonically across apoB strata of ≥ 50 , >35 – <50 , and ≤ 35 mg/dL, with rates of 4.26 (95% CI, 3.78–4.79), 3.09 (95% CI, 2.69–3.54), and 2.41 (95% CI, 2.11–2.76) per 100 patient-years, respectively. In the corresponding propensity score–matched patients from the placebo group, incidence rates for MACE after month 4 also decreased monotonically from 4.30 (95% CI, 3.81–4.83) to 3.90 (95% CI, 3.44–4.40) and 3.31 (95% CI, 2.94–3.71) per 100 patient-years, respectively.

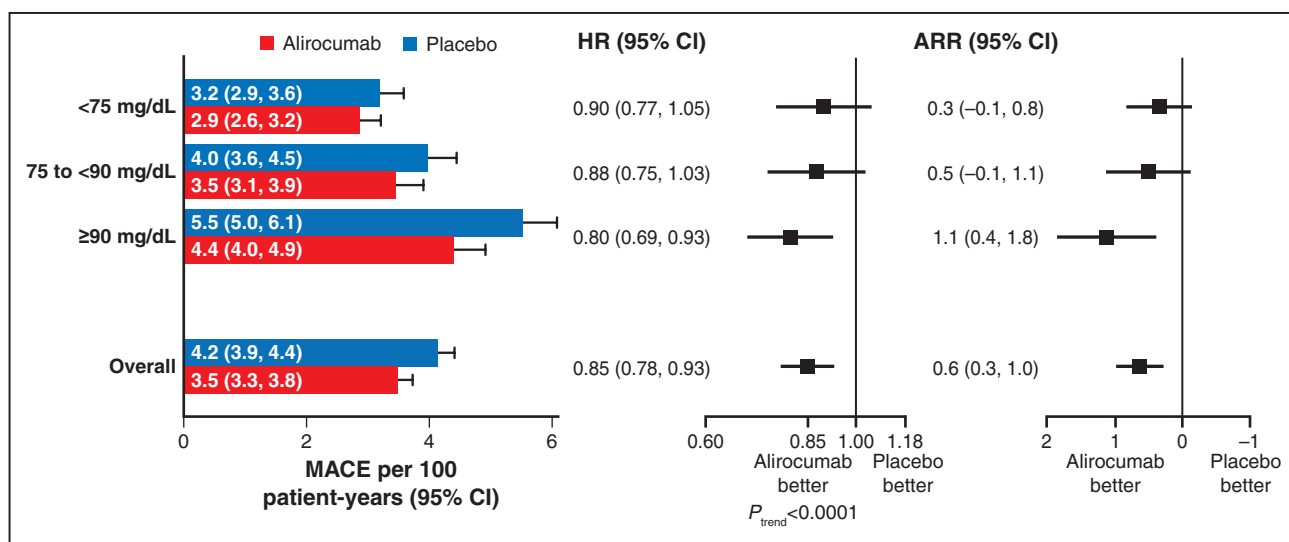


Figure 2. Relative and absolute treatment effects on the incidence rate for MACE, overall and by stratum of baseline apoB.

Relative and absolute treatment effects on the incidence rate of MACE, overall and by stratum of baseline apoB. Forest plots depict relative and absolute risk reduction (ARR) with alirocumab compared with placebo. For relative risk reduction, there was a significant linear trend in the log hazard ratio (HR) across baseline strata, with point estimates progressively further <1.00 for higher strata. ApoB indicates apolipoprotein B; and MACE, major adverse cardiovascular events.

From these incidence rates, relative and absolute treatment benefit of alirocumab increased monotonically across decreasing strata of achieved apoB. Treatment HR was 0.99 (95% CI, 0.84–1.17; ARR, 0.03 events per 100 patient-years) with achieved apoB ≥ 50 mg/dL, 0.79 (95% CI, 0.66–0.95; ARR, 0.81 events per 100 patient-years) with achieved apoB >35 – <50 mg/dL, and 0.73 (95% CI, 0.61–0.87; ARR, 0.90 events per 100 patient-years) with achieved apoB ≤ 35 mg/dL.

Effects of Alirocumab on MACE According to Achieved ApoB in Relation to Achieved LDL-C or Non-HDL-C

When we modeled continuous achieved apoB in spline analysis, with the HR set to 1.00 at the median apoB level (39 mg/dL) and with adjustment for achieved LDL-C, the risk of MACE increased monotonically with apoB level above the median and decreased with apoB below the median (Figure 5). Results were similar when the relationship between achieved apoB and MACE was adjusted for achieved LDL-C estimated with the Martin-Hopkins formula (Figure S4). Conversely, there was no association between continuous achieved LDL-C (calculated with either the Friedewald or Martin-Hopkins formula) and risk of MACE with adjustment for achieved apoB (Figure S5A [top] and Figure S6). Analogous findings were obtained when achieved apoB and LDL-C were considered as categorical variables. Figure S7 shows the number of patients in the alirocumab group classified into each of the 3 post hoc achieved apoB strata (≥ 50 mg/dL, $n=2706$; >35 – <50 mg/dL, $n=2829$; and ≤ 35 mg/dL, $n=3711$) and the 3 prespecified achieved LDL-C strata (>50 , 25–50, and <25 mg/dL). Overall, 6437 of the 9245 patients (69.6%)

are categorized into the same ordered stratum (ie, concordance for achieved apoB and LDL-C). A total of 2808 patients (30.4%) had discordant apoB and LDL-C ordered strata. The pattern of treatment benefit across achieved LDL-C strata differed from that observed across achieved apoB strata. In each achieved LDL-C stratum, treatment benefit increased in progressively lower achieved apoB strata. In each achieved apoB stratum, treatment benefit was similar in middle and lowest quantiles of achieved LDL-C (25–50 and <25 mg/dL; Figure S7).

Figure S5B (top) shows spline analysis of MACE after month 4 according to continuous achieved non-HDL-C at month 4 adjusted for achieved LDL-C. In contrast to the monotonic relationship for achieved apoB adjusted for achieved non-HDL-C (Figure S5C), the association between non-HDL-C adjusted for achieved apoB and MACE was not monotonic for values above the median, with confidence boundaries for the HR crossing 1.0 over most of the non-HDL-C range. In addition, the relationship between achieved apoB and MACE was monotonic throughout the evaluated range of apoB, whereas the relationship between achieved non-HDL-C and MACE was relatively flat over most of its range.

In a model within the alirocumab group consisting of TWMA apoB (constructed from 40947 values) and LDL estimated with the Friedewald formula (constructed from 87161 values), the MACE HR was 0.91 (95% CI, 0.87–0.96; $P<0.001$) per 10 mg/dL decrement in apoB and 0.96 (95% CI, 0.93–1.00; $P=0.029$) per 10 mg/dL decrement in LDL-C. Overall, the median last TWMA value per patient was 50.3 (IQR, 41.8–64.7) for apoB and 42.3 (IQR, 31.6–60.6) for LDL-C. Findings were similar when LDL-C was calculated by the Martin-Hopkins formula. The MACE HR per 10 mg/dL decrement was 0.93 (95%

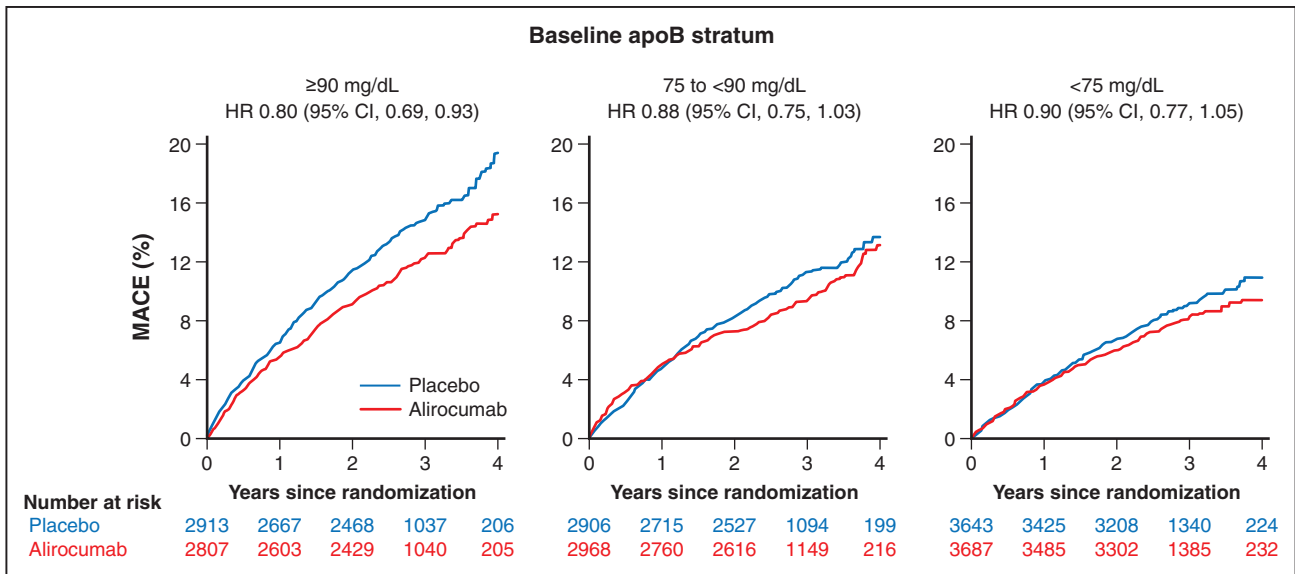


Figure 3. Unadjusted cumulative incidence of the primary composite outcome across baseline apoB strata.

ApoB indicates apolipoprotein B; HR, hazard ratio; and MACE, major adverse cardiovascular events.

CI, 0.88–0.98; $P=0.010$) for apoB and 0.95 (95% CI, 0.91–0.98; $P=0.004$) for LDL-C. Overall, the median last TWMA value was 50.3 mg/dL (IQR, 41.8–64.7) for apoB and 42.3 mg/dL (IQR, 31.6–60.6) for LDL-C, reflecting modest increases over time after month 4 as shown by baseline apoB stratum in the Table.

Sensitivity Analysis

Patients in the lowest achieved apoB stratum at month 4 were more likely to have blinded, protocol-specified

substitution of placebo for alirocumab after month 4 (567 of 724 patients). The association between achieved apoB strata and outcomes was assessed in a sensitivity analysis that excluded these 724 patients (Figure S8). Findings were similar to those of the main analyses. In the alirocumab group, the risk of MACE decreased across decreasing achieved apoB strata. The risk of MACE also decreased in corresponding matched patients from the placebo group. Treatment HR declined monotonically from highest to lowest achieved apoB stratum in the alirocumab group; the

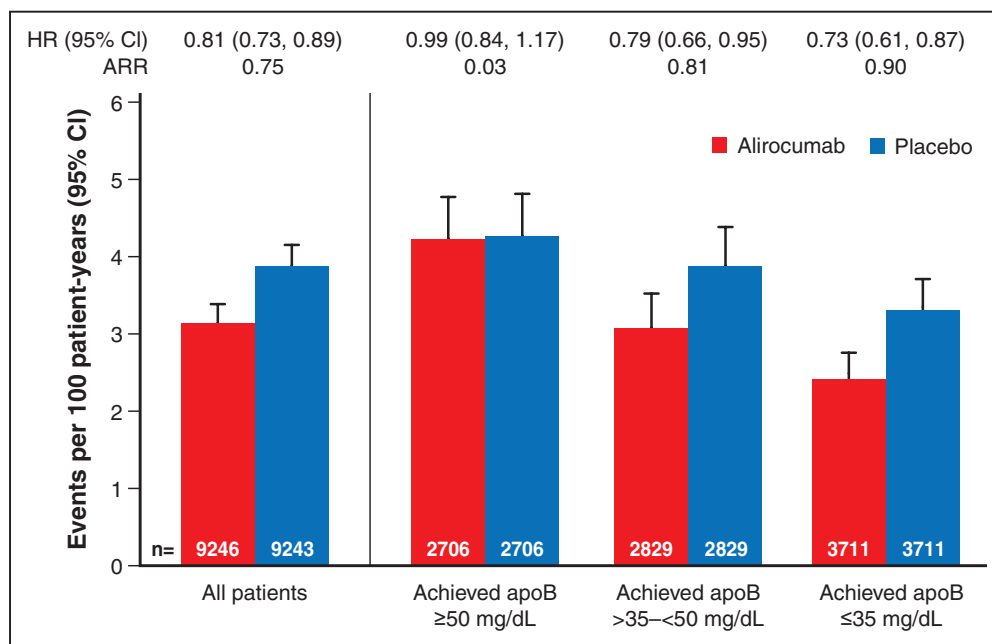


Figure 4. Incidence rate for first major adverse cardiovascular events after month 4 according to achieved apoB stratum at month 4 in the alirocumab group and in propensity score-matched patients from the placebo group.

ApoB indicates apolipoprotein B; ARR, absolute risk reduction; and HR, hazard ratio.

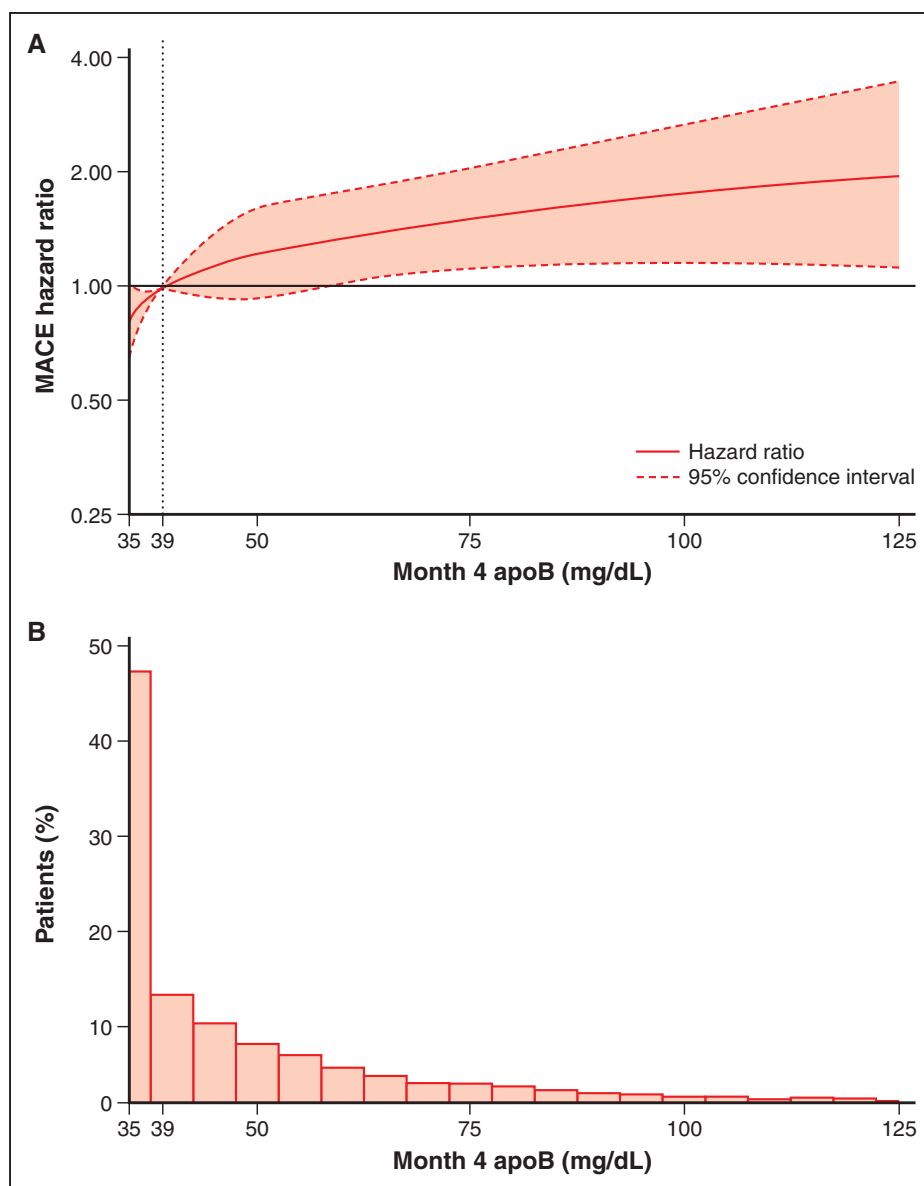


Figure 5. Spline analyses of continuous achieved apoB adjusted for achieved low-density lipoprotein cholesterol, and incidence of MACE in patients treated with alirocumab.

A, Hazard ratio set to 1.00 at the median concentration of apoB (39 mg/dL) achieved within the alirocumab group at month 4. Score test $P=0.0009$ for apoB spline effect. This reflects spline of degree 2 (piecewise quadratic curve) with 3 knots, located at the 25th percentile (35 mg/dL), median (39 mg/dL), and 75th percentile (53 mg/dL) and spanning the minimum (35 mg/dL) to ≈ 99 th (125 mg/dL) percentiles within the alirocumab group. Dotted lines indicate the lower and upper bounds of the 95% CI. **B**, Histogram of month 4 apoB levels within the alirocumab group. The lower limit of detection for apoB was 35 mg/dL. ApoB indicates apolipoprotein B; and MACE, major adverse cardiovascular events.

ARR was least in the highest stratum of achieved apoB and similar in the 2 lower strata.

DISCUSSION

In this study of >18 000 patients on high-intensity or maximum-tolerated statin therapy and assigned to treatment with alirocumab or placebo, there were 4 key findings concerning the relationship of baseline or achieved levels of apoB with the risk of MACE after ACS. First, in the placebo group, higher baseline apoB was associated

with greater risk of MACE. Second, in patients treated with alirocumab, lower achieved apoB at 4 months was associated with greater relative and absolute reductions in MACE after 4 months, with the greatest reductions observed in patients who achieved an apoB level ≤ 35 mg/dL. Third, the relationship between achieved apoB and MACE retained significance after adjustment for achieved levels of LDL-C or achieved levels of non-HDL-C; conversely, achieved levels of LDL-C or non-HDL-C were not predictive of MACE after taking achieved apoB into account. Fourth, among patients in the alirocumab group

Table. Patient Characteristics by Baseline ApoB Strata and Treatment

Characteristic	ApoB strata		
	<75 mg/dL (n=7330)	75–<90 mg/dL (n=5874)	≥90 mg/dL (n=5720)
Baseline characteristics			
Age, y	59 (52 to 66)	58 (51 to 65)	58 (51–64)
Female sex	1740 (23.7)	1431 (24.4)	1591 (27.8)
Body mass index, kg/m ²	27.6 (24.9 to 30.6)	28.1 (25.5 to 31.3)	28.2 (25.5 to 31.5)
Systolic blood pressure, mmHg	125 (116 to 137)	127 (118 to 138)	128 (118 to 138)
Current tobacco smoker	1595 (21.8)	1467 (25.0)	1498 (26.2)
Revascularization for index ACS	5368 (73.2)	4302 (73.2)	4007 (70.1)
Time from index ACS to randomization, mo	2.5 (1.7 to 4.1)	2.7 (1.7 to 4.3)	2.8 (1.8 to 4.8)
Race/ethnicity			
White	5802 (79.2)	4652 (79.2)	4570 (79.9)
Asian	1011 (13.8)	801 (13.6)	686 (12.0)
Black	176 (2.4)	143 (2.4)	154 (2.7)
Other*	341 (4.7)	278 (4.7)	310 (5.4)
Region of enrollment			
Central and Eastern Europe	2105 (38.7)	1578 (29.0)	1754 (32.3)
Western Europe	1818 (24.8)	1372 (23.4)	985 (17.2)
Canada or United States	941 (12.8)	872 (14.8)	1058 (18.5)
Latin America	933 (2.7)	827 (13.9)	838 (14.7)
Asia	939 (12.8)	732 (12.5)	622 (10.9)
Rest of world	594 (8.1)	503 (8.6)	463 (8.1)
Baseline laboratory data			
ApoB, mg/dL	66.0 (61.0 to 71.0)	81.0 (78.0 to 85.0)	102.0 (95.0 to 116.0)
LDL-C, mg/dL	73.0 (64.5 to 81.5)	88.4 (78.8 to 98.0)	116.0 (99.2 to 137.8)
Non-HDL-C, mg/dL	96.0 (87.0 to 104.0)	117.4 (110.0 to 125.9)	152.0 (137.0 to 175.3)
HDL-C, mg/dL	43.6 (37.1 to 51.0)	42.0 (36.0 to 49.8)	41.7 (35.9 to 49.4)
Lipoprotein(a), mg/dL	19.5 (6.6 to 52.9)	22.1 (6.9 to 62.4)	22.6 (6.6 to 65.6)
Triglycerides, mg/dL	101.8 (77.0 to 135.4)	134.5 (101.8 to 180.5)	172.6 (127.0 to 232.0)
eGFR <60 mL·min ⁻¹ ·1.73 m ⁻²	896 (12.2)	797 (13.6)	846 (14.8)
Medical history before index ACS, n (%)			
Hypertension	4517 (61.6)	3772 (64.2)	3960 (69.2)
Diabetes mellitus	1815 (24.8)	1699 (28.9)	1930 (33.7)
Myocardial infarction	1109 (15.1)	1170 (19.9)	1360 (23.8)
Percutaneous coronary intervention	929 (12.7)	1039 (17.7)	1273 (22.3)
Coronary artery bypass grafting	261 (3.6)	329 (5.6)	457 (8.0)
Stroke	189 (2.6)	202 (3.4)	220 (3.8)
Peripheral artery disease	227 (3.1)	261 (4.4)	271 (4.7)
Congestive heart failure	1037 (14.1)	831 (14.1)	947 (16.6)
Chronic obstructive pulmonary disease	254 (3.5)	221 (3.8)	271 (4.7)
Malignancy	194 (2.6)	158 (2.7)	180 (3.1)
Background lipid-lowering therapy at randomization			
High-dose atorvastatin/rosuvastatin	6727 (91.8)	5263 (89.6)	4821 (84.3)
Low- or moderate-dose atorvastatin/rosuvastatin	573 (7.8)	541 (9.2)	493 (8.6)
No statin or other lipid-lowering therapy	8 (0.1)	17 (0.3)	153 (2.7)
Only lipid-lowering therapy other than statin	12 (0.2)	38 (0.6)	232 (4.1)

(Continued)

Table. Continued

Characteristic	ApoB strata		
	<75 mg/dL (n=7330)	75–<90 mg/dL (n=5874)	≥90 mg/dL (n=5720)
Other statin	10 (0.1)	15 (0.3)	21 (0.4)
Postrandomization data, n (%)			
≥4 doses of study medication during the 61 d preceding month 4 assessments	6682 (91.2)	5372 (91.5)	5180 (90.6)
Blinded substitution of placebo for alirocumab	376/3687 (10.2)	222/2968 (7.5)	132/2807 (4.7)
Laboratory data, change from baseline to month 4			
ApoB			
Alirocumab, absolute change, mg/dL	−27.0 (−33.0 to −18.0)	−41.0 (−46.0 to −30.0)	−56.0 (−66.0 to −41.0)
Alirocumab, relative change, %	−42.2 (−47.8 to −30.5)	−52.6 (−56.1 to −37.4)	−54.0 (−62.4 to −39.1)
Placebo, absolute change, mg/dL	4.0 (−3.0 to 12.0)	0 (−8.0 to 9.0)	−6.0 (−19.0 to 6.0)
Placebo, relative change, %	5.7 (−5.1 to 19.2)	0 (−9.9 to 11.7)	−6.3 (−18.2 to 6.3)
LDL-C			
Alirocumab, absolute change, mg/dL	−44.4 (−55.0 to −29.7)	−56.8 (−68.0 to −40.0)	−76.1 (−94.2 to −53.3)
Alirocumab, relative change, %	−62.3 (−73.6 to −44.7)	−65.8 (−76.0 to −49.0)	−66.6 (−78.1 to −49.5)
Placebo, absolute change, mg/dL	3.9 (−6.9 to 15.1)	0.8 (−11.2 to 14.0)	−6.9 (−25.9 to 11.0)
Placebo, relative change, %	5.6 (−9.0 to 22.4)	0.9 (−12.1 to 17.1)	−5.8 (−21.8 to 10.0)
Non-HDL-C			
Alirocumab, absolute change, mg/dL	−48.0 (−60.0 to −32.0)	−63.3 (−75.7 to −44.4)	−85.0 (−105.8 to −59.5)
Alirocumab, relative change, %	−51.5 (−61.4 to −35.9)	−54.6 (−64.1 to −38.6)	−56.2 (−66.5 to −39.9)
Placebo, absolute change, mg/dL	4.6 (−6.6 to 18.1)	0.8 (−12.0 to 15.8)	−8.5 (−29.0 to 12.0)
Placebo, relative change, %	4.8 (−6.6 to 19.9)	0.6 (−10.0 to 13.6)	−5.5 (−18.5 to 7.8)
Lipoprotein(a)			
Alirocumab, absolute change, mg/dL	−4.6 (−12.3 to 0)	−5.3 (−14.0 to 0)	−5.1 (−15.4 to 0)
Alirocumab, relative change, %	−22.6 (−46.7 to 0)	−24.3 (−47.3 to 0)	−23.5 (−47.5 to 0)
Placebo, absolute change, mg/dL	0 (−4.3 to 2.6)	0 (−5.2 to 2.6)	0 (−5.3 to 3.0)
Placebo, relative change, %	0 (−17.0 to 12.0)	0 (−18.1 to 11.2)	0 (−17.6 to 13.0)
Triglycerides			
Alirocumab, absolute change, mg/dL	−9.7 (−33.6 to 14.2)	−18.6 (−49.0 to 11.5)	−30.1 (−74.3 to 9.0)
Alirocumab, relative change, %	−10.5 (−31.1 to 16.1)	−14.8 (−34.0 to 9.6)	−19.6 (−39.3 to 6.0)
Placebo, absolute change, mg/dL	4.4 (−19.5 to 30.1)	−0.9 (−32.0 to 33.0)	−8.8 (−51.0 to 32.7)
Placebo, relative change, %	4.3 (−18.2 to 33.7)	−0.7 (−22.4 to 27.5)	−5.7 (−27.7 to 21.1)
TWMA value in patients treated with alirocumab			
ApoB stratum in the alirocumab group, mg/dL (n)	<75 (3687)	75–<90 (2968)	≥90 (2807)
Month 4 apoB value, mg/dL	35.0 (35.0 to 43.0)	38.0 (35.0 to 51.0)	49.0 (37.0 to 67.0)
Month 4 LDL-C value, mg/dL	27.4 (18.7 to 40.5)	29.7 (20.1 to 45.9)	39.4 (24.3 to 62.2)
Last apoB value, mg/dL	43.6 (38.5 to 54.5)	50.2 (42.7 to 63.2)	61.0 (49.9 to 80.0)
Last LDL-C value, mg/dL	36.7 (28.4 to 51.1)	41.8 (31.4 to 57.6)	52.3 (38.6 to 77.3)

Values are medians (interquartile range) and number (percent) or number/total (percent) for categorical variables. ACS indicates acute coronary syndrome; apoB, apolipoprotein B; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and TWMA, time-weighted moving average.

*Other includes American Indian or native Alaskan, native Hawaiian or Pacific Islander, self-identified mixed race, and self-identified other race.

who achieved current US or European guideline-directed LDL-C or non-HDL-C goals for secondary prevention in very high-risk patients (ie, LDL-C <70 or <55 mg/dL, non-HDL-C <100 or <85 mg/dL),^{25,26} approximately half failed to achieve a simultaneous apoB level ≤35 mg/dL (Table S1). Even among those who achieved the most

stringent goal of LDL-C <40 mg/dL,²⁶ 40.7% did not achieve an apoB level ≤35 mg/dL; furthermore, in patients reaching the lowest LDL-C quartile (<22 mg/dL), 18.2% did not achieve apoB levels ≤35 mg/dL. Despite correlation among categories of achieved LDL-C, non-HDL-C, and apoB, of 6510 patients who achieved

a non-HDL-C level <70 mg/dL, 2849 (43.8%) failed to achieve an apoB level \leq 35 mg/dL. These findings suggest that achievement of even the most stringent current LDL-C or non-HDL-C goals may not ensure that lipoprotein-attributable residual risk has been minimized. However, among those reaching the lowest non-HDL-C quartile (<40.9 mg/dL), only 4% did not achieve apoB levels \leq 35 mg/dL, indicating that treating patients according to non-HDL-C levels may reduce the apoB-associated residual risk.

Although LDL-C is the principal lipid parameter used to estimate lipoprotein-attributable cardiovascular risk, all apoB-containing lipoproteins, including LDL, lipoprotein(a), and triglyceride-rich lipoproteins, may contribute to that risk in the general population and in patients with stable, established coronary heart disease.^{13,27} In contrast, data on the association between apoB and outcomes after ACS are limited.^{15,16} We show that, in analogy with non-ACS populations, a higher apoB concentration was associated with an increased risk of MACE in a fairly linear relationship, despite high-intensity or maximum-tolerated statin therapy.

Non-HDL-C, similar to apoB, includes estimates of atherogenic lipids such as LDL-C, lipoprotein(a), and triglyceride-rich lipoproteins, and both are secondary targets to LDL-C in prevention guidelines.¹³ In this study, the relationships between baseline (on statin) apoB or non-HDL-C and risk of MACE were similar. In contrast, on both statin and alirocumab treatment achieved apoB appeared to be more predictive of future MACE than achieved non-HDL-C, with the former displaying a positive monotonic relationship with MACE but the latter not. The reasons for this incongruity are uncertain. Although plasma levels of apoB and non-HDL-C have high correlation on a population basis, individual discordance is common, related primarily to variance in the cholesterol content of LDL particles.^{5,28–31} The predictive value of apoB versus non-HDL-C under treatment with both statin and PCSK9 inhibitor has not been examined previously. It is possible that under conditions of marked LDL-C reduction, a larger proportion of non-HDL-C resides in the pool of triglyceride-rich lipoproteins, which in turn may be less strongly associated with cardiovascular risk than LDL particles.³²

Pharmacological lowering of atherogenic lipids with high-intensity statin therapy reduces the risk of MACE after an ACS.^{8,9,11,12,33} Despite achievement of a conventional LDL-C goal with statins, there is substantial residual risk for recurrent MACE after ACS that may be reduced with intensified lipid lowering with ezetimibe or a PCSK9 inhibitor.^{10,12,34} Ezetimibe produces an additional lowering of LDL-C but has minimal effects on lipoprotein(a) or triglyceride-rich lipoproteins. In contrast, the addition of a PCSK9 inhibitor to statin produces further reductions in LDL-C, lipoprotein(a), and triglycerides, an effect integrated by levels of apoB. In a previous analysis, we

showed that reduction in the risk of MACE with alirocumab was similar when achieved LDL-C levels were <25 mg/dL compared with 25 to 50 mg/dL.²³ The results of the present analysis suggest that the residual risk of MACE in patients receiving high-intensity statin treatment and alirocumab after ACS may be better gauged by levels of apoB than levels of LDL-C. Achievement of progressively lower strata of apoB, to \leq 35 mg/dL, is associated with progressively lower risk of MACE even after adjustment for achieved LDL-C or non-HDL-C levels. There was also a robust association between continuous achieved apoB and the subsequent risk of MACE, even with adjustment for achieved LDL-C or non-HDL-C. Conversely, achieved LDL-C or non-HDL-C held no prognostic information if adjusted for achieved apoB.

To account for changes in apoB and LDL-C after month 4 due to factors such as discontinuation of study medication, changes in background statin treatment, and protocol-specified changes in alirocumab dose, we performed an analysis in the alirocumab group that related continuous, time-weighted apoB and continuous, time-weighted LDL-C to the risk of MACE. The interpretation of this analysis, similar to the categorical apoB analyses, is that a lower apoB level on treatment with statin and PCSK9 inhibitor predicts the risk of MACE more faithfully than a lower LDL-C level. This was true regardless of whether LDL-C was estimated with the Friedewald or the Martin-Hopkins formula.³⁵ In sum, these findings reinforce previous data suggesting that the number of atherogenic particles (as reflected by apoB levels) predicts risk more accurately than the cholesterol content of those particles.^{36–39} Thus, although apoB, LDL-C, and especially non-HDL-C are correlated, apoB may be a superior predictor of lipoprotein-attributable residual risk after ACS on maximum-intensity lipid-lowering therapy.

There are several explanations for the incomplete estimation of risk with LDL-C observed in this study and in the literature, especially in statin-treated patients.^{3–5,26,40} First, we have shown that lipoprotein(a) is a major predictor of risk and risk reduction with alirocumab and is not taken into account by LDL-C alone.¹⁹ Other apoB-containing lipids such as triglyceride-rich lipoproteins may also contribute to risk after ACS.^{1,18} This is especially important in patients in whom there is a discordance between circulating cholesterol concentration and the number of apoB-containing particles. This may be the case in individuals who have relatively more triglyceride and less cholesterol in apoB-containing particles such as those with type 2 diabetes mellitus, metabolic syndrome, or obesity,^{7,41} with a high concentration of small, dense LDL particles, elevated apoB, but normal LDL-C.^{7,41} ApoB-containing particles other than LDL may assume greater importance in the determination of residual risk when LDL-C levels are low. This may explain why the relationship of baseline apoB to risk of MACE in the pla-

cebo group was attenuated by adjustment for baseline LDL-C with a mean level of ≈ 90 mg/dL, but the relationship of achieved apoB to risk of MACE in the alirocumab group was minimally affected by adjustment for achieved LDL-C with a mean level of ≈ 40 mg/dL. Assessing apoB rather than LDL-C in such patients may more accurately reflect their residual atherogenic lipoprotein burden and hence their residual cardiovascular risk.^{1,7,40}

Strengths and Limitations

Strengths of the present analyses include the use of data from a large multinational study with detailed description of patient phenotype and with adjudicated outcomes. Furthermore, almost 90% of the patients were treated with high-intensity statin therapy. Propensity score-matched analyses to determine the relationship between achieved apoB and risk were included to overcome some potential bias related to baseline differences in patient characteristics.

However, there are some limitations. The analyses of achieved apoB levels use postrandomization data. Even adjusted Cox proportional hazards and propensity score-matched analyses may be subject to residual confounding. The quantile boundaries for baseline apoB were prespecified, but the quantile boundaries for both baseline and achieved apoB were arbitrary. For this reason, the analyses of continuous apoB are useful and corroborate the quantile analyses. Achieved apoB in the trial was influenced by protocol-specified blinded substitution of placebo for alirocumab in patients who had consecutive LDL-C levels < 15 mg/dL. However, despite the fact that patients in the lowest quantile of apoB at month 4 were the most likely to undergo this substitution, they nonetheless had the lowest risk of MACE after month 4. Moreover, the findings were not substantially affected by excluding these patients from the analysis. Results from patients with recent ACS on optimal statin therapy might not be generalizable to other populations. Although ODYSSEY OUTCOMES was an international trial, 79% of the participants were White and 75% were male. Therefore, caution must be applied in generalizing the findings to non-White and female patients with ACS. Relatively few patients in this trial were treated with ezetimibe. It is uncertain whether relationships between baseline or achieved apoB and MACE would have been influenced by greater use of this drug.

A persistent limitation to the use of apoB as a risk predictor or as a therapeutic target has been the lack of a formal, universal standard for its measurement.³⁵ The present findings reinforce the imperative to seek such standardization so that apoB measurements can be applied to guide everyday clinical practice. Estimation of LDL-C levels was performed with the Friedewald

formula, which has known performance issues at high triglyceride levels and low LDL-C levels. To take this into account in a secondary analysis, apoB was adjusted by LDL-C estimated with the Martin-Hopkins formula, which has been shown to perform better than the Friedewald formula.³⁵ The relationship between baseline apoB and risk of MACE was attenuated when LDL-C was estimated by the Martin-Hopkins rather than the Friedewald formula, but the relationship of achieved apoB to risk of MACE in the alirocumab group was minimally affected by such adjustment. These findings indicate that the contribution of LDL particles to residual risk diminishes when their concentration is low. Under those conditions, other apoB-containing particles including lipoprotein(a) or triglyceride-rich lipoproteins whose concentrations are less affected by PCSK9 inhibition, may assume greater importance in determining residual risk.

Last, the lower limit of quantification for apoB was 35 mg/dL; therefore, the association between continuous apoB and MACE could not be ascertained below 35 mg/dL. It is important to note that quantile analyses of achieved apoB levels were not affected by this limitation because the lowest quantile was defined as a level ≤ 35 mg/dL. In fact, the MACE incidence among patients receiving alirocumab with achieved apoB ≤ 35 mg/dL was 22% lower than that in patients with achieved apoB of > 35 – < 50 mg/dL.

Conclusions

In patients with recent ACS receiving high-intensity or maximum-tolerated statin treatment, a higher baseline level of apoB was associated with a higher risk of MACE. Among those treated with the PCSK9 inhibitor alirocumab, lower achieved apoB levels (to ≤ 35 mg/dL) were associated with a lower risk of MACE. Furthermore, lower achieved levels of apoB remained predictive of MACE even after adjustment for achieved LDL-C or non-HDL-C. Conversely, achieved levels of LDL-C or non-HDL-C held no information after adjustment for achieved apoB, indicating that apoB holds incremental predictive information on residual risk beyond either LDL-C or non-HDL-C when the latter 2 levels are low. An achieved apoB concentration ≤ 35 mg/dL was associated with more favorable cardiovascular outcomes than higher achieved apoB levels. However, despite meeting guideline-directed secondary prevention goals for LDL-C or non-HDL-C with statin and alirocumab, a substantial proportion of patients remained at apoB levels > 35 mg/dL, suggesting a potential therapeutic benefit from even more intensive lowering of atherogenic lipoproteins.

ARTICLE INFORMATION

Received October 14, 2021; accepted June 7, 2022.

Affiliations

Uppsala University, Department of Medical Sciences, and Uppsala Clinical Research Center, Sweden (E.H.). Department of Cardiology, Université de Paris, Assistance Publique-Hôpitaux de Paris, Hôpital Bichat, FACT (French Alliance for Cardiovascular Trials), and INSERM U1148, France (P.G.S.). Imperial College, Royal Brompton Hospital, London, UK (P.G.S.). CPC Clinical Research (M. Szarek) and Division of Cardiology (M. Szarek, G.G.S.), University of Colorado School of Medicine, Aurora. State University of New York, Downstate Health Sciences University, Brooklyn (M. Szarek). Department of Medicine, Brigham and Women's Hospital Heart & Vascular Center and Harvard Medical School, Boston, MA (D.L.B.). Division of Cardiovascular Disease, University of Alabama at Birmingham (V.A.B.). Department of Cardiology, Hôpital Européen Georges Pompidou, AP-HP, Paris, France (N.D.). Université Paris Descartes, France (N.D.). Estudios Cardiológicos Latino América, Instituto Cardiovascular de Rosario, Argentina (R.D.). Canadian VIGOUR Centre, University of Alberta, Edmonton, Canada (S.G.G.). St. Michael's Hospital, University of Toronto, Ontario, Canada (S.G.G.). Stanford Center for Clinical Research, Department of Medicine, Stanford University, CA (R.A.H.). Department of Cardiology, Leiden University Medical Center, the Netherlands (J.W.J.). Netherlands Heart Institute, Utrecht (J.W.J.). School of Medicine, National and Kapodistrian University of Athens, Greece (E.L.). University Hospital, RWTH Aachen University, Germany (N.M.). Regeneron Pharmaceuticals Inc, Tarrytown, NY (J.M., G.M., R.P.). Sanofi, Paris, France (M. Scemama). Green Lane Cardiovascular Services, Auckland City Hospital and Auckland University, New Zealand (H.D.W.). Department of Medicine III, Goethe University, Frankfurt am Main, Germany (A.M.Z.).

Acknowledgments

The authors thank the patients, study coordinators, and investigators who participated in this trial. Sophie Rushton-Smith, PhD (MedLink Healthcare Communications, London), provided editorial assistance in the preparation of the manuscript (limited to editing for style, referencing, and figure and table editing) and was funded by Sanofi.

Sources of Funding

This work was supported by Sanofi and Regeneron Pharmaceuticals, Inc.

Disclosures

Dr Hagström reports research grant funding from Sanofi-Aventis, Pfizer, Amgen, and Swedish Heart and Lung Foundation, as well as consulting or honoraria from Amgen, Sanofi-Aventis, Novartis, and NovoNordisk. Dr Steg reports grants, personal fees, and nonfinancial support from Sanofi; grants and personal fees from Amarin, Servier, and Bayer; and personal fees from Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Idorsia, Pfizer, and Novartis. In addition, Dr Steg has a patent on the use of alirocumab to reduce risk after ACS (royalties to Sanofi) pending. Dr Szarek reports serving as a consultant or on advisory boards (or both) for CiVi, Resverlogix, Baxter, Esperion, Sanofi, and Regeneron Pharmaceuticals, Inc. Dr Bhatt reports the following relationships: Advisory Board: Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Janssen, Level Ex, Medscape Cardiology, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences, and Stasys; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care, and TobeSoft; chair: inaugural chair, American Heart Association Quality Oversight Committee; Data Monitoring committees: Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Boston Scientific (chair, PEITHO trial), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Novartis, and Population Health Research Institute; honoraria: American College of Cardiology (senior associate editor, Clinical Trials and News, ACC.org; chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (editor in chief, *Harvard Heart Letter*), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Duke Clinical Research Institute (clinical trial steering committees, including for the PRO-NOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (editor in chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (guest editor, associate editor), K2P (cochair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Piper Sandler, Population Health Research Institute (for the

COMPASS operations committee, publications committee, steering committee, and US national coleader, funded by Bayer), Slack Publications (chief medical editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (secretary/treasurer), WebMD (CME steering committees); other: *Clinical Cardiology* (deputy editor), NCDR-ACTION Registry Steering Committee (chair), and VA CART Research and Publications Committee (chair); research funding: Abbott, Afimmune, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CSL Behring, Eisai, Ethicon, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Lexicon, Lilly, Medtronic, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Owkin, Pfizer, PhaseBio, PLx Pharma, Regeneron, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, and 89Bio; royalties: Elsevier (editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); site coinvestigator: Abbott, Biotronik, Boston Scientific, CSI, St. Jude Medical (now Abbott), Philips, and Svelte; trustee: American College of Cardiology; and unfunded research: FlowCo, Merck, and Takeda. Dr Bittner reports grant support from Sanofi, Regeneron Pharmaceuticals, AstraZeneca, DalCor, Esperion, and Novartis; consulting fees from Pfizer; honoraria from Medscape; and fees for participating on a Data Safety Monitoring Board or Advisory Board from the National Institutes of Health. Dr Danchin reports speaking and consulting fees or fees for participation in advisory boards, critical events committees, or data safety monitoring boards from Amgen, AstraZeneca, Bayer, BMS, Boehringer-Ingelheim, China National Clinical Research Center for Neurological Diseases Intercept, MSD, Novo-Nordisk, Pfizer, Sanofi, Servier, UCB, and Vifor. Dr Diaz reports research grants from Sanofi, DalCor Pharmaceuticals, Population Health Research Institute, Duke Clinical Research Institute, the TIMI group, Amgen, Ciriuz, Montreal Health Innovations Coordinating Center, and Lepetit, as well as personal fees, as a member of the Executive Steering Committee, from Amgen and Ciriuz. Dr Goodman reports research grant support (eg, Steering Committee or Data and Safety Monitoring Committee) and/or speaker/consulting honoraria (eg, Advisory Board) from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CSL Behring, Daiichi-Sankyo/American Regent, Eli Lilly, Esperion, Ferring Pharmaceuticals, GlaxoSmithKline, HLS Therapeutics, JAMP Pharma, Janssen/Johnson & Johnson, Merck, Novartis, Novo Nordisk A/C, Pendopharm, Pfizer, Regeneron, Sanofi, Servier, and Valeo Pharma, as well as salary support/honoraria from the Heart and Stroke Foundation of Ontario/University of Toronto (Polo) Chair, Canadian Heart Research Centre and MD Primer, Canadian VIGOUR Centre, Cleveland Clinic Coordinating Centre for Clinical Research, Duke Clinical Research Institute, New York University Clinical Coordinating Centre, and PERFUSE Research Institute. Dr Harrington reports receiving research grants (all Data Safety Monitoring Board related) from AstraZeneca, Janssen, and Bristol-Myers Squibb; serving on the Advisory Board for Gilead (uncompensated) and WebMD; and serving on the Board of Directors (unpaid) for the American Heart Association and Stanford HealthCare. Dr Jukema reports research grants from the Netherlands Heart Foundation, the Interuniversity Cardiology Institute of the Netherlands, and the European Commission Seventh Framework Programme, as well as research support from Amgen, Astellas, AstraZeneca, Daiichi-Sankyo, Lilly, Merck-Schering-Plough, Pfizer, Roche, and Sanofi. Dr Liberopoulos reports personal fees from Sanofi, Servier, Boehringer-Ingelheim, MSD, Lilly, Novartis, and Chiesi, as well as personal fees and nonfinancial support from Amgen, AstraZeneca, and Bayer. Dr Marx has served as a consultant and speaker for Amgen and Sanofi-Aventis. All honoraria go the RWTH Aachen University. Drs McGinniss, Manvelian, and Pordy are employees of Regeneron Pharmaceuticals and may hold shares and/or stock options in the company. Dr Scemama is an employee of Sanofi and may hold shares and/or stock options in the company. Dr White reports receiving grant support paid to the institution and fees for serving on a steering committee for the ODYSSEY OUTCOMES trial from Sanofi-Aventis 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 Dalcatrapib 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. Dr White was on the Advisory Board for Acetelion, Sirtex, and Genentech, Inc (an affiliate of F. Hoffmann-La Roche Ltd, "Roche"; Lytics PostPCI Advisory Board at European Society of Cardiology) and received lecture fees from AstraZeneca. Dr Zeiher reports consulting fees from Novo Nordisk, Sanofi, and Boehringer Ingelheim; speaker fees from Bayer, Pfizer, Novartis, and Amgen; and travel costs from Sanofi, Boehringer Ingelheim, and Amgen. Dr Zeiher is president of the German Cardiac Society. Dr Schwartz reports research grants to the University of Colorado from Resverlogix, Sanofi, The Medicines Company, and Roch; and is coinventor of pending US patent 62/806,313 (Methods for Reducing Cardiovascular Risk) assigned in full to the University of Colorado.

Supplemental Material

Tables S1 and S2

Figures S1–S8

ODYSSEY OUTCOMES Committees and Investigators

REFERENCES

- Sniderman AD, Thanassoulis G, Glavinovic T, Navar AM, Pencina M, Catapano A, Ference BA. Apolipoprotein B particles and cardiovascular disease: a narrative review. *JAMA Cardiol*. 2019;4:1287–1295. doi: 10.1001/jamacardio.2019.3780
- Nordestgaard BG, Chapman MJ, Ray K, Borén J, Andreotti F, Watts GF, Ginsberg H, Amarencu P, Catapano A, Descamps OS, et al. Lipoprotein(a) as a cardiovascular risk factor: current status. *Eur Heart J*. 2010;31:2844–2853. doi: 10.1093/eurheartj/ehq386
- Borén J, Williams KJ. The central role of arterial retention of cholesterol-rich apolipoprotein-B-containing lipoproteins in the pathogenesis of atherosclerosis: a triumph of simplicity. *Curr Opin Lipidol*. 2016;27:473–483. doi: 10.1097/MOL.0000000000000330
- Sniderman AD, Williams K, Contois JH, Monroe HM, McQueen MJ, de Graaf J, Furberg CD. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. *Circ Cardiovasc Qual Outcomes*. 2011;4:337–345. doi: 10.1161/CIRCOUTCOMES.110.959247
- Johannessen CDL, Mortensen MB, Langsted A, Nordestgaard BG. Apolipoprotein B and non-HDL cholesterol better reflect residual risk than LDL cholesterol in statin-treated patients. *J Am Coll Cardiol*. 2021;77:1439–1450. doi: 10.1016/j.jacc.2021.01.027
- Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet*. 2001;358:2026–2033. doi: 10.1016/S0140-6736(01)07098-2
- Taskinen MR, Borén J. New insights into the pathophysiology of dyslipidemia in type 2 diabetes. *Atherosclerosis*. 2015;239:483–495. doi: 10.1016/j.atherosclerosis.2015.01.039
- Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, Zeiher A, Chaitman BR, Leslie S, Stern T. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA*. 2001;285:1711–1718. doi: 10.1001/jama.285.13.1711
- Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495–1504. doi: 10.1056/NEJMoa040583
- Cannon CP, Blazing M, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387–2397. doi: 10.1056/NEJMoa1410489
- Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713–1722.
- Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittrner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379:2097–2107. doi: 10.1056/NEJMoa1801174
- Kastelein JJ, van der Steeg WA, Holme I, Gaffney M, Cater NB, Barter P, Deedwania P, Olsson AG, Boekholdt SM, Demicco DA, et al. Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. *Circulation*. 2008;117:3002–3009. doi: 10.1161/CIRCULATIONAHA.107.713438
- Sniderman AD. Differential response of cholesterol and particle measures of atherogenic lipoproteins to LDL-lowering therapy: implications for clinical practice. *J Clin Lipidol*. 2008;2:36–42. doi: 10.1016/j.jacl.2007.12.006
- Ray KK, Cannon CP, Cairns R, Morrow DA, Ridker PM, Braunwald E. Prognostic utility of apoB/AI, total cholesterol/HDL, non-HDL cholesterol, or hs-CRP as predictors of clinical risk in patients receiving statin therapy after acute coronary syndromes: results from PROVE IT-TIMI 22. *Arterioscler Thromb Vasc Biol*. 2009;29:424–430. doi: 10.1161/ATVBAHA.108.181735
- Meeusen JW, Donato LJ, Jaffe AS. Lipid biomarkers for risk assessment in acute coronary syndromes. *Curr Cardiol Rep*. 2017;19:48. doi: 10.1007/s11886-017-0863-9
- Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, Braunwald E. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol*. 2008;51:724–730. doi: 10.1016/j.jacc.2007.10.038
- Schwartz GG, Abt M, Bao W, DeMicco D, Kallend D, Miller M, Mundl H, Olsson AG. Fasting triglycerides predict recurrent ischemic events in patients with acute coronary syndrome treated with statins. *J Am Coll Cardiol*. 2015;65:2267–2275. doi: 10.1016/j.jacc.2015.03.544
- Bittrner VA, Szarek M, Aylward PE, Bhatt DL, Diaz R, Edelberg JM, Fras Z, Goodman SG, Halvorsen S, Hanotin C, et al. Effect of alirocumab on lipoprotein(a) and cardiovascular risk after acute coronary syndrome. *J Am Coll Cardiol*. 2020;75:133–144. doi: 10.1016/j.jacc.2019.10.057
- O'Donoghue ML, Fazio S, Giugliano RP, Stroes ESG, Kanevsky E, Gouni-Berthold I, Im K, Lira Pineda A, Wasserman SM, Ceska R, et al. Lipoprotein(a), PCSK9 inhibition, and cardiovascular risk. *Circulation*. 2019;139:1483–1492. doi: 10.1161/CIRCULATIONAHA.118.037184
- Schwartz GG, Bessac L, Berdan RA, Bhatt DL, Bittrner V, Diaz R, Goodman SG, Hanotin C, Harrington RA, Jukema JW, et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY OUTCOMES trial. *Am Heart J*. 2014;168:682–689. doi: 10.1016/j.ahj.2014.07.028
- Martin SS, Giugliano RP, Murphy SA, Wasserman SM, Stein EA, Ceska R, Lopez-Miranda J, Georgiev B, Lorenzatti AJ, Tikkanen MJ, et al. Comparison of low-density lipoprotein cholesterol assessment by Martin/Hopkins estimation, Friedewald estimation, and preparative ultracentrifugation: insights from the FOURIER trial. *JAMA Cardiol*. 2018;3:749–753. doi: 10.1001/jamacardio.2018.1533
- Schwartz GG, Gabriel Steg P, Bhatt DL, Bittrner VA, Diaz R, Goodman SG, Jukema JW, Kim YU, Li QH, Manvelian G, et al. Clinical efficacy and safety of alirocumab after acute coronary syndrome according to achieved level of low-density lipoprotein cholesterol: a propensity score-matched analysis of the ODYSSEY OUTCOMES trial. *Circulation*. 2021;143:1109–1122. doi: 10.1161/CIRCULATIONAHA.120.049447
- Dehejia R, Wahba S. Propensity score-matching methods for nonexperimental causal studies. *Rev Economics Statistics*. 2002;84:151–161.
- Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139:e1082–e1143. doi: 10.1161/CIR.0000000000000625
- Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41:111–188. doi: 10.1093/eurheartj/ehz455
- Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease, 1: evidence from genetic,

- epidemiologic, and clinical studies: a consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 2017;38:2459–2472. doi: 10.1093/eurheartj/ehx144
28. Sniderman A, Williams K, Cobbaert C. ApoB versus non-HDL-C: what to do when they disagree. *Curr Atheroscler Rep*. 2009;11:358–363. doi: 10.1007/s11883-009-0054-2
 29. Clark D 3rd, Nicholls SJ, St John J, Elshazly MB, Kapadia SR, Tuzcu EM, Nissen SE, Puri R. Visit-to-visit cholesterol variability correlates with coronary atheroma progression and clinical outcomes. *Eur Heart J*. 2018;39:2551–2558. doi: 10.1093/eurheartj/ehy209
 30. Mora S, Glynn RJ, Ridker PM. High-density lipoprotein cholesterol, size, particle number, and residual vascular risk after potent statin therapy. *Circulation*. 2013;128:1189–1197. doi: 10.1161/CIRCULATIONAHA.113.002671
 31. Cantey EP, Wilkins JT. Discordance between lipoprotein particle number and cholesterol content: an update. *Curr Opin Endocrinol Diabetes Obes*. 2018;25:130–136. doi: 10.1097/MED.0000000000000389
 32. Heidemann BE, Koopal C, Bots ML, Asselbergs FW, Westerink J, Visseren FLJ. The relation between VLDL-cholesterol and risk of cardiovascular events in patients with manifest cardiovascular disease. *Int J Cardiol*. 2021;322:251–257. doi: 10.1016/j.ijcard.2020.08.030
 33. de Lemos JA, Blazing MA, Wiviott SD, Lewis EF, Fox KA, White HD, Rouleau JL, Pedersen TR, Gardner LH, Mukherjee R, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA*. 2004;292:1307–1316. doi: 10.1001/jama.292.11.1307
 34. Fruchart JC, Davignon J, Hermans MP, Al-Rubeaan K, Amarencu P, Assmann G, Barter P, Betteridge J, Bruckert E, Cuevas A, et al. Residual macrovascular risk in 2013: what have we learned? *Cardiovasc Diabetol*. 2014;13:26. doi: 10.1186/1475-2840-13-26
 35. Wilson PWF, Jacobson TA, Martin SS, Jackson EJ, Le NA, Davidson MH, Vesper HW, Frikke-Schmidt R, Ballantyne CM, Remaley AT. Lipid measurements in the management of cardiovascular diseases: practical recommendations: a scientific statement from the National Lipid Association Writing Group. *J Clin Lipidol*. 2021;15:629–648. doi: 10.1016/j.jacl.2021.09.046
 36. Marston NA, Giugliano RP, Melloni GEM, Park JG, Morrill V, Blazing MA, Ference B, Stein E, Stroes ES, Braunwald E, et al. Association of apolipoprotein B-containing lipoproteins and risk of myocardial infarction in individuals with and without atherosclerosis: distinguishing between particle concentration, type, and content. *JAMA Cardiol*. 2022;7:250–256. doi: 10.1001/jamacardio.2021.5083
 37. Wilkins JT, Li RC, Sniderman A, Chan C, Lloyd-Jones DM. Discordance between apolipoprotein B and LDL-cholesterol in young adults predicts coronary artery calcification: the CARDIA study. *J Am Coll Cardiol*. 2016;67:193–201. doi: 10.1016/j.jacc.2015.10.055
 38. Cao J, Nomura SO, Steffen BT, Guan W, Remaley AT, Karger AB, Ouyang P, Michos ED, Tsai MY. Apolipoprotein B discordance with low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol in relation to coronary artery calcification in the Multi-Ethnic Study of Atherosclerosis (MESA). *J Clin Lipidol*. 2020;14:109–121.e5. doi: 10.1016/j.jacl.2019.11.005
 39. Langlois MR, Sniderman AD. Non-HDL cholesterol or apoB: which to prefer as a target for the prevention of atherosclerotic cardiovascular disease? *Curr Cardiol Rep*. 2020;22:67. doi: 10.1007/s11886-020-01323-z
 40. Thanassoulis G, Williams K, Ye K, Brook R, Couture P, Lawler PR, de Graaf J, Furberg CD, Sniderman A. Relations of change in plasma levels of LDL-C, non-HDL-C and apoB with risk reduction from statin therapy: a meta-analysis of randomized trials. *J Am Heart Assoc*. 2014;3:e000759. doi: 10.1161/JAHA.113.000759
 41. Kathiresan S, Otvos JD, Sullivan LM, Keyes MJ, Schaefer EJ, Wilson PW, D'Agostino RB, Vasan RS, Robins SJ. Increased small low-density lipoprotein particle number: a prominent feature of the metabolic syndrome in the Framingham Heart Study. *Circulation*. 2006;113:20–29. doi: 10.1161/CIRCULATIONAHA.105.567107