Relation of lipoprotein(a) levels to incident type 2 diabetes and modification by alirocumab treatment

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Relation of Lipoprotein(a) Levels to Incident Type 2 Diabetes and Modification by Alirocumab Treatment

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OBJECTIVE

In observational data, lower levels of lipoprotein(a) have been associated with greater prevalence of type 2 diabetes. Whether pharmacologic lowering of lipoprotein(a) influences incident type 2 diabetes is unknown. We determined the relationship of lipoprotein(a) concentration with incident type 2 diabetes and effects of treatment with alirocumab, a PCSK9 inhibitor.

RESEARCH DESIGN AND METHODS

In the ODYSSEY OUTCOMES trial alirocumab was compared with placebo in patients with acute coronary syndrome. Incident diabetes was determined from laboratory, medication, and adverse event data.

RESULTS

Among 13,480 patients without diabetes at baseline, 1,324 developed type 2 diabetes over a median 2.7 years. Median baseline lipoprotein(a) was 21.9 mg/dL. With placebo, 10 mg/dL lower baseline lipoprotein(a) was associated with hazard ratio 1.04 (95% CI 1.02−1.06, $P < 0.001$) for incident type 2 diabetes. Alirocumab reduced lipoprotein(a) by a median 23.2% with greater absolute reductions from higher baseline levels and no overall effect on incident type 2 diabetes (hazard ratio 0.95, 95% CI 0.85–1.05). At low baseline lipoprotein(a) levels, alirocumab tended to reduce incident type 2 diabetes, while at high baseline lipoprotein(a) alirocumab tended to increase incident type 2 diabetes compared with placebo (treatment–baseline lipoprotein(a) interaction $P = 0.006$). In the alirocumab group, a 10 mg/dL decrease in lipoprotein(a) from baseline was associated with hazard ratio 1.07 (95% CI 1.03−1.12; $P = 0.0002$) for incident type 2 diabetes.

CONCLUSIONS

In patients with acute coronary syndrome, baseline lipoprotein(a) concentration associated inversely with incident type 2 diabetes. Alirocumab had neutral overall effect on incident type 2 diabetes. However, treatment-related reductions in lipoprotein(a), more pronounced from high baseline levels, were associated with increased risk of incident type 2 diabetes. Whether these findings pertain to other therapies that reduce lipoprotein(a) is undetermined.

Lipoprotein(a) is an LDL particle whose concentration is primarily under genetic control and is believed to have atherogenic, proinflammatory, and prothrombotic properties (1). Epidemiologic and genetic studies show an association of elevated

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lipoprotein(a) concentration with the risk of coronary, peripheral artery, and cerebrovascular disease events (2–4).

For many years, no pharmacologic therapy was identified that both lowered lipoprotein(a) concentration and reduced the risk of major adverse cardiovascular events (MACE). This changed with the advent of inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9). These agents reduce the concentration of LDL cholesterol (LDL-C) substantially (by 50–60%), reduce the concentration of lipoprotein(a) modestly (by 20–25%), and reduce MACE (5,6). In large placebo-controlled trials that evaluated PCSK9 inhibitors, the risk of MACE among patients assigned to placebo was associated with lipoprotein(a) concentration (7–10) and reduction in the risk of MACE with the PCSK9 inhibitor alirocumab was associated with the magnitude of lipoprotein(a) reduction (7,10). Pharmacologic agents under development that inhibit the synthesis of apolipoprotein(a) may reduce lipoprotein(a) concentration by >70% and are being evaluated for effects on MACE (11,12).

An unexplained observation in cohort studies and clinical trials has been an association of lower lipoprotein(a) levels with greater prevalence of type 2 diabetes (13–15). Some genetic and observational cohort studies in populations without evident cardiovascular disease have also shown an association of lower levels of lipoprotein(a) with greater incidence of diabetes (13,16–18). To date, an association between lower levels of lipoprotein(a) and incident diabetes has not been demonstrated in patients with established cardiovascular disease. Importantly, to date there has been no evidence to indicate whether the incidence of diabetes is modulated by pharmacologic therapy that lowers lipoprotein(a).

In this analysis, we determined whether the incidence of diabetes was related to lipoprotein(a) concentration in patients with recent acute coronary syndrome and whether that risk was modulated by treatment with alirocumab.

RESEARCH DESIGN AND METHODS

Patients and Treatments

This report is a post hoc analysis of the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) (clinicaltrials.gov, NCT01663402) (6,19), which compared the effects of alirocumab or placebo in 18,924 patients with recent acute coronary syndrome and persistent dyslipidemia despite intensive or maximum tolerated statin treatment. The protocol was approved by the institutional review board at each site, and all patients provided informed consent. Qualifying patients were hospitalized for acute myocardial infarction or unstable angina 1–12 months prior to randomization and had LDL-C ≥70 mg/dL, non-HDL cholesterol ≥100 mg/dL, or apolipoprotein B ≥80 mg/dL despite treatment with atorvastatin 40–80 mg daily, rosuvastatin 20–40 mg daily, or the highest tolerated dose of one of these statins. Lipoprotein(a) concentration was not considered in qualification. Qualifying patients were randomized in a 1:1 ratio to receive alirocumab 75 mg or matching placebo, administered subcutaneously every 2 weeks. As previously described (19), the alirocumab dose was blindly titrated between 75 and 150 mg for maximization of the number of patients who achieved an LDL-C level of 25–50 mg/dL or blindly replaced by placebo in cases of sustained LDL-C levels <15 mg/dL. Participants and physicians were blinded to the treatment allocation. For protection of the blind, all treatment kit boxes had the same look and feel and were labeled with a double-blind label. Details on randomization procedures are described in supplementary material. The primary outcome of MACE comprised death from coronary heart disease, nonfatal myocardial infarction, ischemic stroke, or hospitalization for unstable angina.

Definition of Baseline and Incident Diabetes

Classification of patients according to presence of diabetes at baseline and criteria for incident diabetes after randomization have previously been published (20). In brief, diabetes was considered present at baseline if there was a medical history of type 1 or type 2 diabetes, treatment with an antihyperglycemic medication, hemoglobin A_{1c} at least 6.5% (48 mmol/mol), or fasting plasma glucose at least 126 mg/dL. The primary end point in this analysis was incident diabetes in those without diabetes at baseline. Incident diabetes was adjudicated by a blinded panel of expert physicians based on adverse events indicating new type 1 or type 2 diabetes, initiation of antihyperglycemic medication, two measurements of hemoglobin A_{1c} at least 6.5% (unless only one measurement was available or only the last value was at least 6.5%), or two measurements of fasting plasma glucose at least 126 mg/dL.

Measurement of Lipoproteins

Plasma lipids, including LDL-C and lipoprotein(a), were measured at baseline and at specified time points thereafter. LDL-C was calculated by the Friedewald formula unless levels were <15 mg/dL or the accompanying triglyceride concentration was >400 mg/dL; in those cases, LDL-C was measured by β quantification. Lipoprotein(a) mass was measured per protocol at baseline, month 4, and month 12 with an automated immunoturbidimetric assay on a Siemens BNII nephelometric analyzer (Siemens Healthcare Diagnostics, Malvern, PA) with a lower limit of detection of 2 mg/dL and an interassay coefficient of variation of 3.1–4.8% depending on the lipoprotein(a) concentration. Heterogeneity in apolipoprotein(a) size has only a moderate effect on lipoprotein(a) recovery with this assay (21). Calculated or measured LDL-C includes the concentration of cholesterol contained in lipoprotein(a). To account for this, we calculated LDL-C corrected for lipoprotein(a) cholesterol as LDL-C$_{corrected}$ = LDL-C − [lipoprotein(a) × 0.3] (22,23).

Statistical Analysis

Median (quartile 1–3) baseline lipoprotein(a) was compared in patients with or without diabetes at baseline and by baseline quartile among patients without diabetes at baseline. Levels below the lower limit of detection were assigned a value of 2 mg/dL.

The probability of new-onset (incident) type 2 diabetes during follow-up as a function of baseline lipoprotein(a) as a spline effect of degree 3 (piecewise cubic curve) was estimated for each treatment group by logistic regression with a logit link function and the logarithm of follow-up time as an offset variable in the models. Additionally, the relative treatment effects on incident type 2 diabetes overall and as a

function of baseline lipoprotein(a) were estimated in competing risks proportional hazards models, where death was treated as a competing terminal event. These relative relationships were also determined after adjustment for variables associated with lipoprotein(a) concentration including sex, race, geographical region, and plasma triglycerides. To determine whether assigned treatment (alirocumab or placebo) modified the relationship of baseline lipoprotein(a) with the relative risk of type 2 diabetes, P values for interaction were calculated.

Incident type 2 diabetes (cases per 100 patient-years of observation) was also determined in each treatment group according to baseline quartile of lipoprotein(a). Treatment hazard ratios (alirocumab/placebo) for incident type 2 diabetes were calculated in each baseline lipoprotein(a) quartile in competing risks models, and P_{trend} was calculated.

The change in lipoprotein(a) concentration from baseline to month 4 and month 12 of assigned treatment with alirocumab was calculated. Within the alirocumab group, that change was related to the subsequent risk of incident type 2 diabetes as a time-varying covariate in Cox regression models [hazard ratio per 10 mg/dL decrease in lipoprotein(a)] with death as a competing terminal event. The following models were developed: model 1, without covariates; model 2, adjusted for baseline lipoprotein(a); and model 3, additionally adjusted for demographic and clinical variables (sex, race, and geographic region; baseline statin treatment intensity, BMI, triglycerides, hemoglobin A_{1c}, and LDL-C$_{corrected}$; and time-varying change in LDL-C$_{corrected}$ from baseline to month 4 and month 12).

In patients with diabetes at baseline, we determined whether changes from baseline to month 12 in hemoglobin A_{1c} and fasting serum glucose were influenced by baseline lipoprotein(a) concentration. There was no imputation for missing hemoglobin A_{1c} or glucose values.

Comparisons of independent groups were by Wilcoxon rank-sum tests for continuous variables and χ^2 tests for categorical variables. For all analyses, two-tailed P values <0.05 were considered statistically significant, with no adjustment for multiple testing. All analyses were conducted according to intention to treat, including all patients

and events from randomization to the common study end date (11 November 2017). Analyses were performed in SAS, version 9.4 (IBM, Armonk, NY).

RESULTS

Patient Characteristics and Association With Baseline Lipoprotein(a) Concentration
A total of 18,924 patients underwent randomization at 1,315 sites in 57 countries (Supplementary Table 1). Of these, 9,462 were assigned to alirocumab and 9,462 to placebo. In consideration of all trial participants, quartile boundaries for baseline lipoprotein(a) were 6.7, 21.2, and 59.6 mg/dL. The prevalence of diabetes decreased across increasing baseline lipoprotein(a) quartiles (30.7%, 29.0%, 29.0%, and 26.5%; P_{trend} = 0.0001).

At baseline, diabetes was present in 5,444 (28.8%) patients (n = 37 with type 1 diabetes) and not present in 13,480 patients (71.2%). Table 1 shows the characteristics of those with diabetes at baseline and by quartile of baseline lipoprotein(a) for those without diabetes at baseline. LDL-C and LDL-C$_{corrected}$ did not differ in patients with or without diabetes at baseline, and neither did the use of intensive statin therapy. However, baseline lipoprotein(a) concentration was lower among those with diabetes (median 19.5 mg/dL [quartile 1–3 6.2–55.0]) in comparison with those without diabetes at baseline (21.9 mg/dL [6.9–61.1]; P < 0.0001). Among patients without diabetes at baseline, higher baseline quartile of lipoprotein(a) was associated with characteristics including female sex, black race, enrollment in North America, absence of current smoking, higher LDL-C, lower LDL-C$_{corrected}$, and lower triglycerides.

Incident Type 2 Diabetes, According to Baseline Lipoprotein(a) Concentration, and Effect of Alirocumab Treatment
Median follow-up for incident diabetes was 2.7 years (quartile 1–3 2.2–3.4). Overall, 1,324 patients developed diabetes during the trial (all type 2), of whom 648 were assigned to alirocumab and 676 to placebo, corresponding to a treatment hazard ratio of 0.95 (95% CI 0.85–1.05) with death as a competing event. Supplementary Table 2 shows the criteria that were fulfilled for the

diagnosis of incident type 2 diabetes in each treatment group.

Figure 1 shows incident type 2 diabetes by treatment group according to splines of continuous baseline lipoprotein(a) among those without diabetes at baseline. In the placebo group, decreasing baseline lipoprotein(a) was associated with increasing risk of incident type 2 diabetes. In proportional hazards models, each 10 mg/dL decrease in baseline lipoprotein(a) concentration was associated with a hazard ratio of 1.04 (95% CI 1.02–1.06; P < 0.0001) in unadjusted analysis and a hazard ratio of 1.03 (95% CI 1.01–1.05; P = 0.0024) in adjusted analysis. In contrast, in the alirocumab group the incidence rate for type 2 diabetes was essentially constant across the range of baseline lipoprotein(a), with a hazard ratio of 1.00 (95% CI 0.98–1.02; P = 0.96) per 10 mg/dL decrease in baseline lipoprotein(a) in unadjusted and 1.00 (95% CI 0.98–1.01; P = 0.56) in adjusted analysis. Treatment assignment significantly modified the relationship between baseline lipoprotein(a) and incident type 2 diabetes with $P_{interaction}$ = 0.003 in unadjusted analysis and $P_{interaction}$ = 0.006 with adjustment for baseline characteristics. As shown in Fig. 1, the crossover point of the spline curves was at a baseline lipoprotein(a) level of 50 mg/dL. Thus, in patients with baseline lipoprotein(a) <50 mg/dL the estimated incidence of type 2 diabetes was lower with alirocumab than placebo. In contrast, in patients with baseline lipoprotein(a) ≥50 mg/dL the estimated incidence of type 2 diabetes was higher with alirocumab than placebo.

Similar findings were derived from analysis by baseline quartile of lipoprotein(a) (Fig. 2). In the placebo group, the incidence rate of type 2 diabetes (cases per 100 patient-years) decreased monotonically from 4.6 (95% CI 4.0–5.2) in quartile 1 to 3.6 (95% CI 3.1–4.2) in quartile 2, 3.5 (95% CI 3.0–4.1) in quartile 3, and 3.1 (95% CI 2.6–3.6) in quartile 4 (P_{trend} = 0.0003) (Fig. 2, left panel). In contrast, in the alirocumab group there was no apparent relationship between baseline lipoprotein(a) quartile and incident type 2 diabetes, with incidences of 3.6 (95% CI 3.1–4.2), 3.3 (95% CI 2.8–3.9), 3.7 (95% CI 3.1–4.3), and 3.4 (95% CI 2.9–3.9) in quartiles 1–4, respectively (P_{trend} =

Table 1—Baseline characteristics in patients with and patients without diabetes at baseline and according to quartile of lipoprotein(a) in patients without diabetes at baseline

		No diabetes at baseline						
Characteristic	Diabetes at baseline (n = 5,444)	All (n = 13,480)	Quartile 1 (<6.9 mg/dL) (n = 3,370)	Quartile 2 (6.9 to <21.9 mg/dL) (n = 3,370)	Quartile 3 (21.9 to <61.1 mg/dL) (n = 3,363)	Quartile 4 (≥61.1 mg/dL) (n = 3,377)	P†	P*
Age, years	59 (53–66)	58 (51–65)	58 (51–65)	58 (52–65)	58 (51–65)	58 (51–64)	0.36	<0.0001
Female sex	31.9	22.4	18.0	21.2	21.9	28.6	<0.0001	<0.0001
Race							<0.0001	<0.0001
White	71.6	82.5	86.4	83.1	79.0	81.6		
Black	3.7	2.0	0.6	0.7	2.6	4.1		
Asian	19.2	10.8	8.2	11.7	13.9	9.4		
Other	5.5	4.7	4.8	4.4	4.5	4.9		
Geographic region							<0.0001	<0.0001
Western Europe	14.9	25.0	24.3	23.8	25.9	25.9		
Eastern Europe	26.0	29.8	37.1	31.5	26.8	24.0		
North America	17.8	14.1	11.2	12.3	14.1	18.8		
South America	15.0	13.1	13.3	13.4	11.5	14.3		
Asia	17.2	10.1	7.8	11.0	12.9	8.5		
Rest of world	9.1	7.9	6.4	8.0	8.7	8.5		
Current smoking	20.1	25.7	27.7	27.1	25.0	23.0	<0.0001	<0.0001
High-intensity statin	87.9	89.2	89.1	87.9	88.6	91.3	0.0006	0.03
ACE inhibitor or ARB	81.9	76.1	77.0	76.4	75.7	75.3	0.35	<0.0001
β-Blocker	85.9	84.0	84.7	83.5	83.3	84.3	0.35	0.0009
BMI, kg/m^2	29 (26–33)	28 (25–30)	28 (25–31)	28 (25–30)	27 (25–30)	27 (25–30)	<0.0001	<0.0001
Fasting blood glucose, mmol/L	7.4 (6.2–9.4)	5.4 (5.0–5.8)	5.5 (5.1–5.9)	5.4 (5.1–5.8)	5.4 (5.0–5.8)	5.4 (5.0–5.8)	<0.0001	<0.0001
Hemoglobin A$_{1c}$							0.72	<0.0001
%	7.0 (6.5–8.2)	5.7 (5.4–5.9)	5.7 (5.4–5.9)	5.7 (5.5–5.9)	5.7 (5.5–5.9)	5.7 (5.4–5.9)		
mmol/mol	53 (48–66)	39 (36–41)	39 (36–41)	39 (37–41)	39 (37–41)	39 (36–41)		
LDL-C, mg/dL	85 (71–103)	87 (74–104)	84 (70–101)	85 (72–102)	87 (74–104)	92 (79–109)	<0.0001	<0.0001
LDL-C$_{corrected}$, mg/dL	74 (59–93)	76 (61–94)	83 (69–100)	81 (68–98)	75 (62–92)	61 (48–78)	<0.0001	0.0006
HDL-C, mg/dL	41 (35–48)	43 (37–51)	43 (37–51)	43 (37–51)	44 (37–51)	44 (37–52)	0.21	<0.0001
Triglycerides, mg/dL	148 (106–204)	124 (90–171)	136 (96–189)	123 (90–172)	119 (88–162)	119 (88–161)	<0.0001	<0.0001
Lipoprotein(a), mg/dL	19.5 (6.2–55.0)	21.9 (6.9–61.1)	2.0 (2.0–4.9)	12.6 (9.6–16.6)	39.0 (29.5–49.6)	93.8 (74.6–121.0)	<0.0001	<0.0001
Estimated glomerular filtration rate, mL/min per 1.73 m^2	77.6 (64.1–91.7)	78.2 (68.3–89.7)	78.5 (68.5–90.4)	78.2 (68.5–89.3)	78.5 (68.3–90.1)	77.9 (68.1–89.7)	0.15	0.0011

Data are percentages or (for continuous variables) median (quartile 1–3). ARB, angiotensin receptor blocker; HDL-C, HDL cholesterol; LDL-C$_{corrected}$, LDL cholesterol corrected for cholesterol content of lipoprotein(a). *P values for comparison of characteristic between patients with diabetes at baseline and all patients without diabetes at baseline. †P values for comparison across lipoprotein(a) quartiles in patients without diabetes at baseline.

0.70). The treatment hazard ratio (alirocumab:placebo) for incident type 2 diabetes increased monotonically across baseline lipoprotein(a) quartiles, from 0.79 (95% CI 0.64–0.96) in quartile 1 to 1.09 (95% CI 0.87–1.38) in quartile 4 (P_{trend} = 0.025) (Fig. 2, right panel).

MACE in Patients Without Diabetes at Baseline According to Baseline Lipoprotein(a) Concentration
Among all trial participants, the primary MACE outcome occurred in 1,052

patients (11.1%) treated with placebo versus 903 patients (9.5%) treated with alirocumab ($P < 0.001$). Among patients without diabetes at baseline assigned to placebo, the 3-year incidence of MACE in baseline lipoprotein(a) quartiles 1–4 was 7.7%, 9.9%, 9.8%, and 12.1%, respectively. Among patients without diabetes at baseline assigned to alirocumab, 3-year incidence of MACE in baseline lipoprotein(a) quartiles 1–4 was 7.5%, 8.2%, 7.6%, and 10.4%. Thus, the risk of MACE was lower with alirocumab than placebo in

each baseline lipoprotein(a) quartile, particularly in quartiles 2–4.

Lipoprotein(a) Lowering by Alirocumab and Its Association With Incident Type 2 Diabetes
Among patients without diabetes at baseline, alirocumab reduced lipoprotein(a) from baseline to month 4 by a median of 23.2% (quartile 1–3 −45.8 to 0), with the absolute decrease from baseline increasing across baseline lipoprotein(a) quartiles (Supplementary Fig.
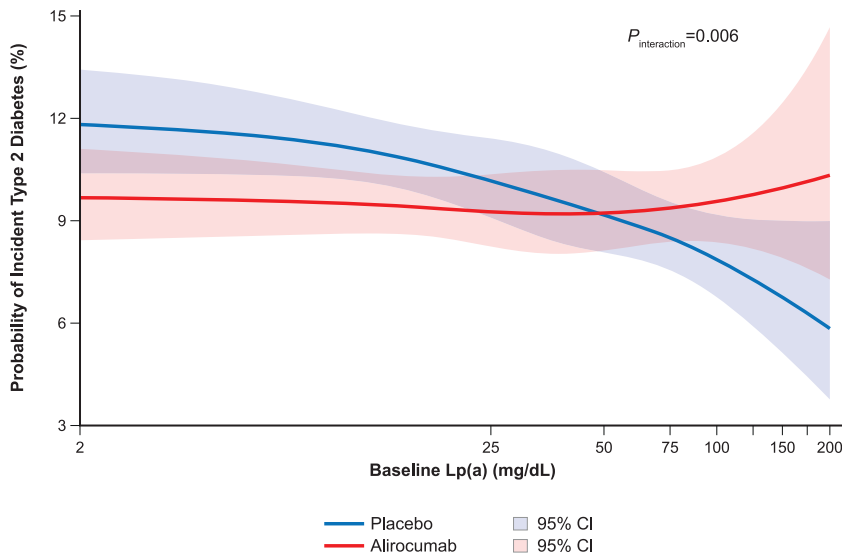
Figure 1—Spline analysis of probability of incident type 2 diabetes by baseline lipoprotein(a) [Lp(a)] and treatment group. The probability of incident type 2 diabetes during follow-up is shown as a function of baseline lipoprotein(a) for each treatment group, estimated from a logistic regression model with a logit link function, the logarithm of follow-up time as an offset variable, and adjustment for race, current smoking, and baseline BMI and triglyceride level. Spline effect is a piecewise cubic curve with degree = 3 with knots at quartiles of baseline lipoprotein(a). Spline effect $P = 0.0002$ for placebo group, $P = 0.82$ for alirocumab group. The interaction P value of treatment and baseline lipoprotein(a) on incident type 2 diabetes ($P_{interaction}$) was 0.003 unadjusted and 0.006 adjusted for the baseline characteristics indicated above.

Fig. 1*B*). Median percent change in lipoprotein(a) from baseline to month 4 in the placebo group was 0% (quartile 1–3 −17 to 13.3), with median changes ranging from nil in quartile 1 to 5.8 mg/dL increase in quartile 4.

As summarized in Table 2, among patients in the alirocumab group without diabetes at baseline, each 10 mg/dL decrease in lipoprotein(a) from baseline was associated with an unadjusted hazard ratio of 1.07 (95% CI 1.03−1.12; $P = 0.0002$) for subsequent incident type 2 diabetes (model 1). This association was similar after adjustment for baseline lipoprotein(a) (model 2) and after additional adjustment for baseline demographic and clinical characteristics (model 3).

Relationship Between Lipoprotein(a) and Glycemic Measures in Patients With Diabetes at Baseline

In patients with diabetes at baseline, Supplementary Table 3 shows absolute change in hemoglobin A_{1c} and fasting glucose from baseline to month 12. There were no differences according to quartile of baseline lipoprotein(a).

1*A*). The median decrease in lipoprotein(a) with alirocumab was nil in quartile 1, increasing to 20.2 mg/dL in quartile 4. In contrast, alirocumab produced similar reductions in LDL-C$_{corrected}$ across baseline lipoprotein (a) quartiles. Similar results were observed for absolute decreases to month 12 (Supplementary
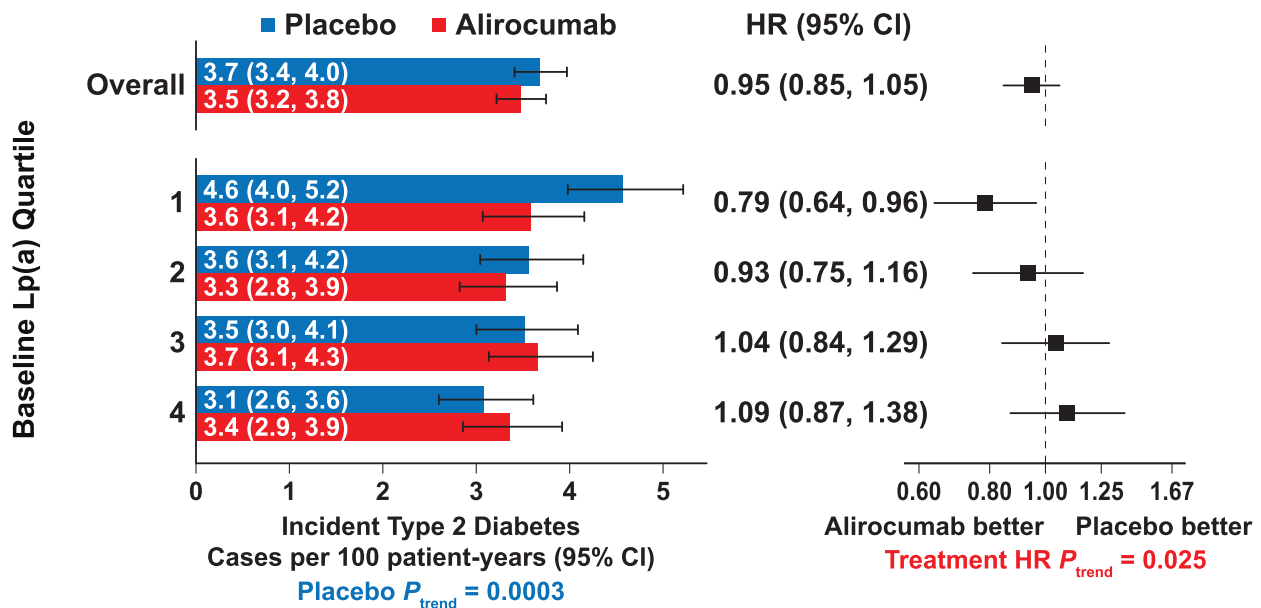
Figure 2—Incidence rate for type 2 diabetes by baseline lipoprotein(a) [Lp(a)] quartile and treatment with placebo or alirocumab. Left panel: incidence rates for type 2 diabetes by treatment group and quartile of baseline lipoprotein(a) for patients without diabetes at baseline (total $n = 13,480$). Baseline lipoprotein(a) quartile ranges are: quartile 1, <6.9 mg/dL; quartile 2, 6.9 to <21.9 mg/dL; quartile 3, 21.9 to <61.1 mg/dL; and quartile 4, ≥61.1 mg/dL. In the placebo group, increasing quartile of baseline lipoprotein(a) was associated with decreasing incidence rate for type 2 diabetes ($P_{trend} = 0.0003$). Right panel: Forest plot depicting treatment hazard ratio (HR) (95% CI) for incident type 2 diabetes by quartile of baseline lipoprotein(a). The point estimate for the treatment hazard ratio increased monotonically from baseline lipoprotein(a) quartile 1 to quartile 4 ($P_{trend} = 0.025$).

Table 2—Relationship of time-varying change in lipoprotein(a) with subsequent incident type 2 diabetes in the alirocumab group

Model	Model adjustments	HR (95% CI) per 10 mg/dL decrease in lipoprotein(a) from baseline	P
1	None	1.07 (1.03–1.12)	0.0002
2	Baseline lipoprotein(a)	1.10 (1.05–1.15)	<0.0001
3	Baseline lipoprotein(a), baseline LDL-C$_{corrected}$, time-varying change in LDL-C$_{corrected}$, demographic and clinical characteristics*	1.08 (1.04–1.13)	0.0001

HR, hazard ratio for incident type 2 diabetes; LDL-C$_{corrected}$, LDL cholesterol corrected for cholesterol content of lipoprotein(a). *Sex, race, geographic region, statin treatment intensity (none, low to moderate, or high), baseline BMI, baseline triglycerides, baseline hemoglobin A$_{1c}$.

CONCLUSIONS

This analysis, comprising 13,480 patients in the ODYSSEY OUTCOMES trial without diabetes at baseline, provides three key insights into the relationship between lipoprotein(a) concentration and risk of type 2 diabetes. First, incident type 2 diabetes in the placebo group increased with decreasing baseline lipoprotein(a) concentration, corroborating prior observations in healthy populations (13,15,17,18), and demonstrating this for the first time in a cohort with established atherosclerotic cardiovascular disease receiving intensive or maximum tolerated statin treatment.

Second, the relationship between baseline lipoprotein(a) concentration and incident type 2 diabetes was modified by alirocumab treatment. At low baseline lipoprotein(a) concentrations, alirocumab had minimal effect on lipoprotein(a) levels and tended to reduce the estimated risk of incident type 2 diabetes compared with placebo. This was particularly evident in the lowest quartile of baseline lipoprotein(a) (<6.9 mg/dL). Conversely, at high baseline lipoprotein(a) levels, alirocumab produced notable reductions in lipoprotein(a) concentrations and tended to increase the estimated risk of incident type 2 diabetes compared with placebo. Treatment and baseline lipoprotein(a) had significant interaction on the risk of incident type 2 diabetes. The concentration of lipoprotein(a) at which alirocumab had a neutral effect on incident type 2 diabetes was ~50 mg/dL.

Third, within the alirocumab group, each 10 mg/dL decrease in lipoprotein(a) from baseline to month 4 was associated with a significant hazard ratio for incident type 2 diabetes after adjustment for demographic and clinical variables, baseline lipoprotein(a), and the concurrent change from baseline in LDL-C$_{corrected}$. This finding suggests that treatment-induced reduction in lipoprotein(a) concentration may increase the risk of incident type 2 diabetes.

Mechanisms Linking Lipoprotein(a) With Type 2 Diabetes

Potential mechanisms linking lipoprotein(a) and type 2 diabetes remain uncertain. Specifically, it is unknown whether the association is due to an effect of insulin resistance or hyperinsulinemia to suppress levels of lipoprotein(a) or whether low levels of lipoprotein(a) are causally related to the development of insulin resistance and type 2 diabetes. In a study of 607 subjects without diabetes, those with, compared with those without, metabolic syndrome had lower lipoprotein(a) concentrations in conjunction with higher levels of insulin, C-peptide, and HOMA of insulin resistance (HOMA-IR) (24). In another study of 1,685 individuals without diabetes, lipoprotein(a) levels were also inversely associated with HOMA-IR, and lipoprotein(a) levels fell in the period immediately preceding a transition to type 2 diabetes (16). The latter finding led the authors to postulate that autoimmune phenomena might be responsible for an association of low lipoprotein(a) and incident type 2 diabetes.

In some cases, genetic data support a relationship between lipoprotein(a) levels and incident type 2 diabetes. In analyses of Chinese and Danish cohorts, increased risk of type 2 diabetes was found in individuals with genetically determined low lipoprotein(a) plasma concentration due to large lipoprotein(a) isoform size related to the number of kringle IV type 2 repeats (25–27). However, a Mendelian randomization analysis showed that genetic variants associated with fasting insulin levels bore no relation to lipoprotein(a) concentration (28), and in analyses of the European Prospective Investigation into Cancer (EPIC)-Norfolk and DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) cohorts (15) there was no association found of rs10455872, a single nucleotide polymorphism of the *LPA* gene affecting lipoprotein(a) plasma concentration, with incident type 2 diabetes.

Effect of PCSK9 Inhibition With Alirocumab on Incident Type 2 Diabetes

Genetic data have indicated that polymorphisms affecting the *HMGCR*, *PCSK9*, or *NPC1L1* genes that result in lower levels of LDL-C are associated with an increased risk of diabetes (29–31) and, conversely, that elevated LDL-C due to familial hypercholesterolemia is associated with a lower risk of diabetes (32). In the current analysis, despite substantial lowering of LDL-C levels, alirocumab had an overall neutral effect on incident type 2 diabetes. The difference in these findings may reflect a shorter duration of observation in the current study. Alternatively, the contrasting findings might be related to a protective effect of higher lipoprotein(a) concentration. In healthy observational cohorts such as those contributing to the genetic analyses, the median lipoprotein(a) concentration is typically ~10 mg/dL (15–18); at baseline in the ODYSSEY OUTCOMES trial, the median lipoprotein(a) concentration was 21 mg/dL.

A neutral overall effect of alirocumab on incident type 2 diabetes could also be related to circulating PCSK9 levels, which have been positively correlated with levels of glucose, insulin, and HOMA-IR (33–35) and associated with the presence of metabolic syndrome (36). A rise in PCSK9 levels is observed in response to a short-term high-fructose diet in healthy subjects (37). Treatment with a

PCSK9 antibody lowers the circulating concentration of free PCSK9 (38), but limited data do not indicate that treatment affects insulin sensitivity (39).

Relation of Lipoprotein(a) and Alirocumab Treatment to Glycemic Measures in Patients With Diabetes at Baseline

Among patients with established diabetes, we did not observe differential changes in hemoglobin A_{1c} or fasting glucose over time according to baseline lipoprotein(a) quartile. We cannot exclude the possibility that a potential influence of lipoprotein(a) concentration on glycemic measures in these patients was mitigated by changes in patient behaviors (i.e., lifestyle modification) or physician practice (i.e., intensification of antihyperglycemic drug therapy) in response to laboratory values.

Strengths and Limitations

Strengths of this analysis include a large, multinational cohort of patients at high risk for diabetes, a high incidence rate for type 2 diabetes, and a systematic, blinded process for the adjudication of incident diabetes. Among the limitations, the effect of alirocumab on incident type 2 diabetes was observed on a background of intensive statin treatment. Whether alirocumab modulated an effect of statin treatment or exerted an independent effect on the risk of incident diabetes cannot be determined. Lipoprotein(a) was measured with a mass assay. The correlation of lipoprotein(a) mass and molar concentration is imperfect. We cannot exclude the possibility that an analysis based on lipoprotein(a) molar concentration or isoform size might have yielded different results. The current findings associate lipoprotein(a) reduction due to PCSK9 inhibition with the risk of incident type 2 diabetes; however, it is unknown whether a similar association exists when lipoprotein(a) is reduced by other mechanisms. For example, niacin lowers lipoprotein(a) and increases incident diabetes (40), but to date no patient-level analysis has investigated whether these effects are associated.

Clinical Implications

LDL is the primary atherogenic lipoprotein. PCSK9 inhibitors, when added to background statin therapy, reduce LDL-C substantially and consistently across a range of concomitant lipoprotein(a) concentrations, with a corresponding reduction in the risk of MACE and without an overall increase in the risk of incident diabetes (5,6). PCSK9 inhibitors also produce a modest relative reduction in lipoprotein(a) levels, the absolute magnitude of which becomes notable in those with high baseline levels. As elevated levels of lipoprotein(a) are associated with an increased risk of MACE, patients with higher baseline lipoprotein(a) levels also achieve larger reductions in MACE with PCSK9 inhibition (7,8,10).

The current analysis indicates that among patients assigned to placebo, those with higher lipoprotein(a) levels have a lower risk of incident type 2 diabetes. Under treatment with alirocumab, patients with higher baseline lipoprotein(a) have larger absolute decreases in its concentration that in turn are associated with greater risk of incident type 2 diabetes. It remains to be determined whether the treatment hazard ratio for incident type 2 diabetes per unit decrease in lipoprotein(a) concentration determined in this analysis will apply to innovative therapies that target the synthesis of apolipoprotein(a) and reduce lipoprotein(a) concentration substantially more than PCSK9 inhibitors (12).

In the current analysis, alirocumab tended to increase incident diabetes at baseline lipoprotein(a) concentrations >50 mg/dL. However, this is also a threshold concentration of lipoprotein(a) that has been used to define significantly elevated cardiovascular risk (41). Accordingly, the current findings should not dissuade practitioners from using PCSK9 inhibitors in patients at very high cardiovascular risk who have elevated levels of LDL-C and lipoprotein(a). In such patients, the cardiovascular benefits of treatment will most likely outweigh a possible increased risk of incident diabetes, and the decision to treat should draw upon a calculus akin to the estimation of cardiovascular benefits and diabetes risk with intensive statin treatment (42). For example, the projected effects of alirocumab treatment may be considered in two hypothetical patients with recent acute coronary syndrome: one with baseline lipoprotein(a) ≤6.7 mg/dL (in quartile 1) and the other with baseline lipoprotein(a) >59.6 mg/dL (in quartile 4).

For the first patient, alirocumab treatment is projected to reduce the 3-year incidence of MACE by 0.2%. Concurrently, alirocumab would have no meaningful effect on absolute lipoprotein(a) concentration and would be projected to reduce the 3-year incidence of type 2 diabetes by 2.9%. These point estimates correspond to numbers needed to treat for 3 years of 500 to prevent one MACE and 34 to prevent one case of type 2 diabetes. In the second patient, alirocumab treatment is estimated to reduce the 3-year incidence of MACE by 1.6%. Concurrently, alirocumab would reduce lipoprotein(a) by a median of 20.2 mg/dL, associated with an increase in the 3-year incidence of type 2 diabetes of 0.9%. These point estimates correspond to a number needed to treat for 3 years of 62 to prevent one MACE and a number needed to harm of 111 to result in an additional case of type 2 diabetes. Thus, the former patient achieves a small reduction in MACE accompanied by a reduction in incident type 2 diabetes, while the latter patient achieves a larger reduction in MACE but with an increase in incident type 2 diabetes.

Conclusion

Among patients with recent acute coronary syndrome and elevated LDL-C levels despite optimized statin therapy, the prevalence and the incidence of type 2 diabetes increased with decreasing levels of baseline lipoprotein(a). Treatment with alirocumab modified the relationship between baseline lipoprotein(a) and incidence of type 2 diabetes. In patients with low baseline lipoprotein(a), alirocumab had minimal effect on lipoprotein(a) and was associated with a lower estimated incidence of type 2 diabetes compared with placebo. In contrast, in patients with high baseline lipoprotein(a), alirocumab decreased lipoprotein(a) levels in association with a higher estimated incidence of type 2 diabetes compared with placebo. An increased incidence of type 2 diabetes may be a consequence of therapeutic lipoprotein(a) reduction through PCSK9 inhibition.

version to publish. G.G.S. and M.S. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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