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CLINICAL RESEARCH
Vascular biology and medicine

Lipoprotein(a) lowering by alirocumab reduces the total burden of cardiovascular events independent of low-density lipoprotein cholesterol lowering: ODYSSEY OUTCOMES trial

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Aims

Lipoprotein(a) concentration is associated with first cardiovascular events in clinical trials. It is unknown if this relationship holds for total (first and subsequent) events. In the ODYSSEY OUTCOMES trial in patients with recent

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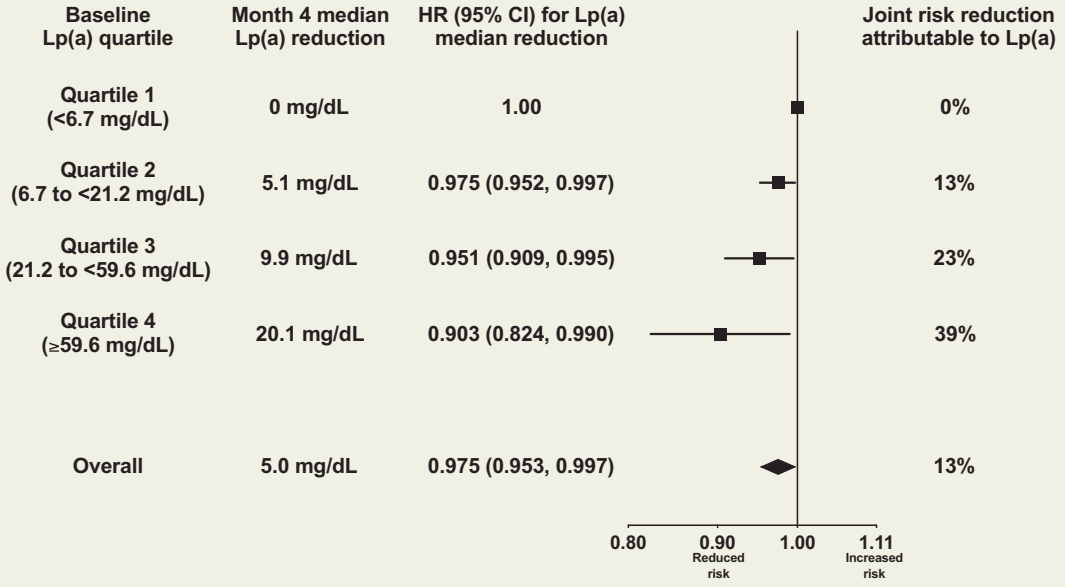
acute coronary syndrome (ACS), the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab reduced lipoprotein(a), low-density lipoprotein cholesterol (LDL-C), and cardiovascular events compared with placebo. This *post hoc* analysis determined whether baseline levels and alirocumab-induced changes in lipoprotein(a) and LDL-C [corrected for lipoprotein(a) cholesterol] independently predicted total cardiovascular events.

Methods and results Cardiovascular events included cardiovascular death, non-fatal myocardial infarction, stroke, hospitalization for unstable angina or heart failure, ischaemia-driven coronary revascularization, peripheral artery disease events, and venous thromboembolism. Proportional hazards models estimated relationships between baseline lipoprotein(a) and total cardiovascular events in the placebo group, effects of alirocumab treatment on total cardiovascular events by baseline lipoprotein(a), and relationships between lipoprotein(a) reduction with alirocumab and subsequent risk of total cardiovascular events. Baseline lipoprotein(a) predicted total cardiovascular events with placebo, while higher baseline lipoprotein(a) levels were associated with greater reduction in total cardiovascular events with alirocumab (hazard ratio P_{trend} = 0.045). Alirocumab-induced reductions in lipoprotein(a) (median -5.0 [-13.6, 0] mg/dL) and corrected LDL-C (median -51.3 [-67.1, -34.0] mg/dL) independently predicted lower risk of total cardiovascular events. Each 5-mg/dL reduction in lipoprotein(a) predicted a 2.5% relative reduction in cardiovascular events.

Conclusion Baseline lipoprotein(a) predicted the risk of total cardiovascular events and risk reduction by alirocumab. Lipoprotein(a) lowering contributed independently to cardiovascular event reduction, supporting the concept of lipoprotein(a) as a treatment target after ACS.

Graphical Abstract



Keywords Lipoprotein • Alirocumab • LDL • Acute coronary syndrome

Introduction

Elevated baseline levels of lipoprotein(a), a genetically determined low-density lipoprotein particle, have been associated with increased risk of cardiovascular events in epidemiological studies[1] and Mendelian randomization analyses.[2,3] In keeping with these observations, recent updates to the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) lipid guidelines[4] have highlighted the role of lipoprotein(a) as a risk enhancer in primary prevention and recommend its measurement at least once in each adult's lifetime and in those at intermediate risk for cardiovascular disease events, with a family history of premature cardiovascular disease, or a family history of elevated lipoprotein(a)[4] to optimize lipid modification therapies for the level of absolute risk.

Until recently, no intervention had demonstrated that modification in lipoprotein(a) levels would translate to a predicted risk reduction

Table 1 Categories of total events

Event	Alirocumab (n = 9462)	Placebo (n = 9462)	Total (n = 18 924)
Cardiovascular	2658	3111	5769
Coronary heart disease death	205	222	427
Non-fatal myocardial infarction[a]	877	1008	1885
Ischaemia-driven coronary revascularization	875	1003	1878
Non-fatal heart failure requiring hospitalization	287	277	564
Unstable angina requiring hospitalization	39	64	103
Death related to underlying coronary heart disease[b]	6	14	20
Death related to peripheral disease	10	11	21
Ischaemic stroke	130	185	315
Fatal	10	16	26
Non-fatal	120	169	289
Haemorrhagic stroke	23	25	48
Fatal	9	8	17
Non-fatal	14	17	31
Peripheral artery disease[c]	157	240	397
Limb revascularization[c]	109	165	274
Critical limb ischaemia[c]	48	75	123
Venous thromboembolism event[c]	49	62	111
Deep venous thrombosis[c]	29	33	62
Pulmonary embolism[c]	20	29	49
Non-cardiovascular death	94	121	215

Values are *n*.
[a]Twenty-six events in the alirocumab group and 43 events in the placebo group subsequently led to coronary heart disease death.
[b]Heart failure, cardiogenic shock, cardiovascular procedure, cardiovascular haemorrhage.
[c]Investigator reported; not subject to adjudication by independent committee.

in subsequent cardiovascular events. However, two large placebo-controlled trials of inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9) have provided such evidence. Reductions in lipoprotein(a) by alirocumab were associated with subsequent reduced risk of first major cardiovascular events[5] and, separately, first major peripheral artery disease (PAD) events or venous thromboembolism (VTE).[6] Importantly, these relationships were independent of the simultaneous alirocumab-induced reduction in low-density lipoprotein cholesterol (LDL-C) corrected for lipoprotein(a) cholesterol ($LDL\text{-}C_{corr}$). In addition, greater reduction in lipoprotein(a) concentration with the PCSK9 inhibitor evolocumab was associated with greater reduction in the risk of first major coronary events.[7]

From the perspective of patients and of healthcare delivery systems, the total burden of cardiovascular disease is more closely tied to total rather than first events. Accordingly, this *post hoc* analysis of the ODYSSEY OUTCOMES trial tested the hypothesis that baseline lipoprotein(a) predicts event burden and modification of this burden by alirocumab, quantified by total cardiovascular events following an index acute coronary syndrome in patients receiving intensive statin therapy. In addition, to expand on previous observations from the study that reductions in lipoprotein(a) are associated with reduced risk of first cardiovascular event,[5,6] we evaluated whether the decrease in lipoprotein(a) concentration under treatment with alirocumab is associated with decreased risk of subsequent total cardiovascular events, independent of the concurrent reduction in LDL-C.

Methods

Patients and treatments

The design,[8] primary results,[9] and total events results[10] of the ODYSSEY OUTCOMES trial have been published. The trial was performed at 1315 sites in 57 countries; the institutional review board at each site approved the protocol. All participants provided informed consent. Randomization in a 1:1 ratio to treatment with alirocumab 75 mg or matching placebo, stratified by country, was performed in 18 924 patients meeting study entry criteria that included age ≥40 years, hospitalization with an acute coronary syndrome (myocardial infarction or unstable angina) 1–12 months before randomization, and LDL-C ≥70 mg/dL (1.81 mmol/l), non-high-density lipoprotein cholesterol ≥100 mg/dL (2.59 mmol/l), or apolipoprotein B ≥80 mg/dL assessed during stable treatment with atorvastatin 40–80 mg daily, rosuvastatin 20–40 mg daily, or the maximum-tolerated dose of either statin. All doses of study medication were given by subcutaneous injection every 2 weeks.

Outcomes

The primary efficacy outcome was time to first occurrence of death from coronary heart disease, non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, or unstable angina requiring hospitalization. The trial continued until 1613 patients experienced a primary outcome event or all surviving patients (other than those enrolled in China) were eligible to be followed for at least 2 years. Ultimately, the latter condition determined the end date of the trial. For the present analysis, we examined all cardiovascular outcomes collected in the trial including cardiovascular death and total (first and subsequent) non-fatal cardiovascular events.

The latter category included non-fatal primary outcome events, haemorrhagic stroke, hospitalization for heart failure, ischaemia-driven coronary revascularization, major PAD events (critical limb ischaemia, lower extremity revascularization procedures, and amputation for ischaemia), and VTE (deep vein thrombosis and pulmonary embolism). Non-cardiovascular deaths were also recorded during follow-up; subcategories of fatal and non-fatal events are listed in *Table 1*. All events included in the analyses except PAD events and VTE were adjudicated by an independent committee blinded to treatment assignment. PAD events and VTE were reported by investigators blinded to treatment assignment on a specific case-report form.

Measurement of lipoproteins

Details of lipoprotein measurements have been described.[5] Lipoprotein(a) mass was measured at COVANCE Central Laboratories (Los Angeles, California, USA) on a Siemens BNII nephelometric analyser using an immunoturbidometric assay with rabbit polyclonal anti-lipoprotein(a) detection antibody and interassay coefficient of variation 3.1–4.8% depending on lipoprotein(a) concentration (Siemens, Healthcare Diagnostics, Malvern, PA, USA). To account for the fact that measured LDL-C includes cholesterol contained in lipoprotein(a) particles [~30% of lipoprotein(a) mass is cholesterol], corrected LDL-C was calculated using the formula[11]:

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

Additional analyses varied the percentage from 30% to determine if results were sensitive to the selection of this correction factor.

Statistical analysis

Lipoprotein(a) and LDL-C_{corr} distributions were assessed for the overall population and by the treatment group at baseline and at Month 4 (± 4 weeks) after randomization. If a patient had multiple values within the time window, the first value was included in the analyses. Missing values were imputed by prespecified methods.

We applied a marginal proportional hazards model that allows for the possibility of a given patient having multiple cardiovascular events while treating non-cardiovascular death as a competing event.[12] Relative effects on first and total cardiovascular events are summarized by hazard ratios (HRs), corresponding 95% confidence intervals (CIs), and *P*-values. Rates of events are expressed as the number of events per 100 patient-years of follow-up.

Relationships between baseline lipoprotein(a) and total cardiovascular events in the placebo group were determined by models using baseline lipoprotein(a) quartile as the predictor variable, adjusted for demographic and clinical variables (age, sex, race, geographic region, body mass index, smoking history, diabetes, time from index acute coronary syndrome to randomization), and baseline LDL-C_{corr}. A *P*-value was computed for linear trend in the estimated log HRs across baseline lipoprotein(a) quartiles. Cumulative incidence functions were used to estimate, by baseline lipoprotein(a) quartile, rates of total cardiovascular events through 4 years of follow-up in the placebo group in the presence of competing non-cardiovascular death.

Heterogeneity in the relative and absolute effects of alirocumab treatment on total cardiovascular events was assessed according to baseline lipoprotein(a) quartile. To assess heterogeneity in relative treatment effects, we constructed a Cox proportional hazards model with baseline lipoprotein(a) quartile, treatment, and their interaction as predictors and computed a *P*-value for linear trend across the estimated log HRs. To assess heterogeneity in absolute treatment effects, we constructed absolute risk reductions with alirocumab treatment, quantified as differences in the event rates per 100 person-years of follow-up, along with associated 95% CIs.[13]

To determine the association between modification in lipoprotein(a) levels by alirocumab treatment and total events, the relationships between the change in lipoprotein(a) from baseline to Month 4 and the risk of cardiovascular events after Month 4 were described using models with patients in the alirocumab group. The following models were developed: a model without covariates (Model 1), a model adjusted for baseline lipoprotein(a) (Model 2); a model additionally adjusted for baseline LDL-C_{corr} and change from baseline to Month 4 in LDL-C_{corr} (Model 3); and a model adjusted for all variables in Model 3 as well as the demographic and clinical variables indicated above (Model 4). A comparison of Models 2 and 3 indicates whether the relationship between the change in lipoprotein(a) and total events is modified by adjustment for the simultaneous change in LDL-C_{corr}, while a comparison of Models 3 and 4 indicates if this relationship is confounded by other baseline characteristics of the patients. Sensitivity analyses excluded patients who had protocol-specified blinded substitution of placebo for alirocumab in response to consecutive LDL-C measurements <15 mg/dL. Effects are summarized by the observed median reduction in lipoprotein(a) (all models) and LDL-C_{corr} (Models 3 and 4) at Month 4. The predicted risk reduction attributable to reduction in lipoprotein(a) as a percentage of the joint predicted risk reduction by decreases in lipoprotein(a) and LDL-C_{corr} was determined from the estimated log HRs from Model 3.

Continuous variables are expressed as median (Quartile 1, Quartile 3) whereas categorical variables are expressed as counts and percentages. 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 conducted by an independent academic statistical team at the State University of New York Downstate School of Public Health using SAS version 9.4.

Results

Categories of total vascular events

The median follow-up was 2.8 (2.3, 3.4) years. The types and counts of total cardiovascular events and non-cardiovascular deaths after randomization by treatment assignment are presented in *Table 1*. The absolute reduction in total events by alirocumab was primarily due to effects on non-fatal myocardial infarction, ischaemia-driven coronary revascularization, and major PAD events. Competing non-cardiovascular deaths were relatively infrequent, with fewer in the alirocumab group than in the placebo group.

Table 2 summarizes the distributions of cardiovascular events and non-cardiovascular deaths by event number. The total number of cardiovascular events, 5769, was 1.85 times the number of first events, 3114. As illustrated in Supplementary material online, *Figure S1*, there were 192 fewer first and 453 fewer total cardiovascular events with alirocumab than with placebo (2658 vs. 3111). Although the majority of patients did not experience a cardiovascular event during the study, a meaningful subset—48% of the patients with a non-fatal first cardiovascular event (1382 of 2860), corresponding to 7% of the total study population—experienced more than one cardiovascular event. In addition, cardiovascular death occurred in a relatively small proportion (2.7%) of the study population, and only 1.3% of patients had a cardiovascular death without a preceding non-fatal cardiovascular event, so that nearly all patients were at risk for multiple events.

Table 2 Distribution of first and subsequent cardiovascular events and non-cardiovascular death

Event number and type	Alirocumab (*n* = 9462)	Placebo (*n* = 9462)	Total (*n* = 18 924)
First			
Cardiovascular	1461	1653	3114
Fatal	125	129	254
Non-fatal	1336	1524	2860
Non-cardiovascular death	62	84	146
Second			
Cardiovascular	633	749	1382
Fatal	62	61	123
Non-fatal	571	688	1259
Non-cardiovascular death	16	17	33
Third			
Cardiovascular	253	321	574
Fatal	30	35	65
Non-fatal	223	286	509
Non-cardiovascular death	6	10	16
Fourth and subsequent			
Cardiovascular	311	388	699
Fatal	23	46	69
Non-fatal	288	342	630
Non-cardiovascular death	10	10	20
Total			
Cardiovascular	2658	3111	5769
Fatal	240	271	511
Non-fatal	2418	2840	5258
Non-cardiovascular death	94	121	215

Values are *n*.

Baseline lipoprotein(a) and total cardiovascular events in the placebo group

The cumulative incidence functions for total cardiovascular events over time by baseline lipoprotein(a) quartile are shown for the placebo group in *Figure 1*. The relationship between baseline lipoprotein(a) quartile and the number of events per 100 patient-years of follow-up in the placebo group is presented in *Figure 2*. There was a monotonic gradient of risk in relation to baseline lipoprotein(a) quartile, with the largest number of total cardiovascular events in the highest baseline lipoprotein(a) quartile (HR $P_{trend} < 0.0001$). The magnitude of the gradient was substantial: over 4 years, the estimated number of cardiovascular events per 100 patients was 53.7 among patients in the highest quartile (≥59.6 mg/dL) vs. 37.5 among patients in the lowest quartile (<6.7 mg/dL), corresponding to an adjusted 60% higher risk ($P < 0.0001$).

Effect of alirocumab on total cardiovascular events by baseline lipoprotein(a) quartile

Relative and absolute treatment effects on total cardiovascular events stratified by baseline lipoprotein(a) quartile are shown in *Figure 2*. Overall, the alirocumab: placebo HR for first cardiovascular event was 0.88 (95% CI, 0.82–0.94; $P = 0.0002$). For total cardiovascular events, the HR was 0.85 (95% CI, 0.78–0.93; $P = 0.0004$) with an absolute risk reduction of 1.7 events per 100 patient-years of follow-up. There was a significant linear trend in the HR for total cardiovascular events across baseline lipoprotein(a) quartiles ($P = 0.045$), decreasing from 0.95 in Quartile 1 to 0.75 in Quartile 4. Coupled with the relationship between baseline lipoprotein(a) and risk in the placebo group, the absolute risk reduction increased more than seven-fold, from 0.5 events per 100 patient-years of follow-up in Quartile 1 to 3.7 events per 100 patient-years in Quartile 4.

Effect of alirocumab-induced changes in lipoprotein(a) and LDL-C_{corr} on total cardiovascular events

This analysis included 9129 of the 9462 (96.5%) patients randomized to alirocumab with lipoprotein measurements at baseline and Month 4, who experienced a total of 2223 vascular events after their Month 4 assessment. Among these patients, the median absolute changes from baseline to Month 4 were -5.0 (-13.6, 0) mg/dL for lipoprotein(a) and -51.3 (-67.1, -34.0) mg/dL for LDL-C_{corr}. The median changes in lipoprotein(a) by baseline quartile were 0 (-1.4, 0), -5.1 (-7.9, -2.3), -9.9 (-16.3, -3.2), and -20.1 (-34.0, -8.0) mg/dL for Quartiles 1, 2, 3, and 4, respectively. Corresponding median changes

in LDL-C_{corr} by baseline lipoprotein(a) quartile were -53.3 (-68.8, -35.5), -52.7 (-69.2, -36.1), -51.2 (-66.5, -34.0), and -47.2 (-63.5, -31.4) mg/dL. The randomized treatment HR after the Month 4 assessments (HR, 0.85; 95% CI, 0.77–0.93) was nearly identical to the overall treatment HR (0.85; 95% CI, 0.78–0.93).

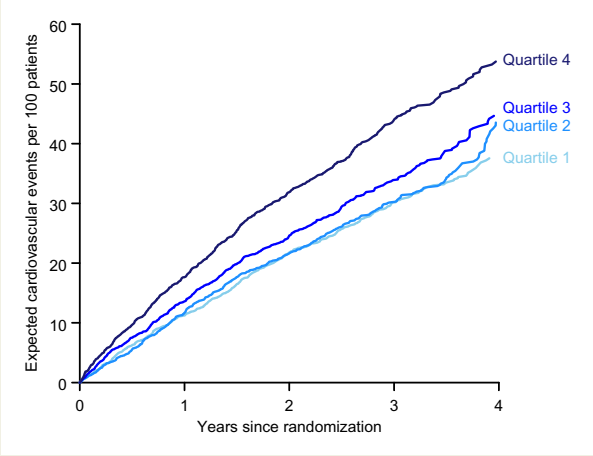


Figure 1 Cumulative incidence functions for total cardiovascular events by quartile of baseline lipoprotein(a) (<6.7, 6.7 to <21.2, 21.2 to <59.6, and ≥59.6 mg/dL) in the placebo group. The estimated number of events per 100 patients at 4 years was 37.5, 43.5, 44.7, and 53.7 for Quartiles 1, 2, 3, and 4, respectively. The hazard ratios (95% confidence intervals) for Quartile 2, Quartile 3, and Quartile 4, relative to Quartile 1, are 1.05 (0.88–1.25), 1.17 (0.99–1.38), and 1.60 (1.34–1.89), respectively (P_{trend} < 0.0001). Hazard ratios and *P*-value reflect adjustment for age, sex, race, geographic region, body mass index, smoking status, diabetes status, time from index acute coronary syndrome to randomization, and baseline low-density lipoprotein cholesterol corrected for lipoprotein(a) cholesterol.

Table 3 summarizes the results of sequential marginal proportional hazards models relating the observed median change in lipoprotein(a) on alirocumab treatment to the risk of total vascular events. In an unadjusted model, a relationship between change in lipoprotein(a) and the risk of vascular events was not evident (Model 1). Larger changes in lipoprotein(a) under alirocumab treatment were associated with higher baseline lipoprotein(a) levels, and therefore higher risk. A significant relationship between reduction in lipoprotein(a) under alirocumab treatment and reduction in risk of total cardiovascular events was therefore revealed after adjustment for baseline lipoprotein(a) (Model 2). Additional adjustment for baseline and change in LDL-C_{corr} (Model 3) and further adjustment for demographic and clinical variables (Model 4) had a minor influence on this relationship. In all cases, reductions in both lipoprotein(a) and LDL-C_{corr} were associated with lower risk of cardiovascular events. In the model with lipoprotein(a) and LDL-C_{corr} (Model 3), the predicted relative risk reductions associated with median changes were 2.5% (HR, 0.975) for lipoprotein(a) and 15.8% (HR, 0.842) for LDL-C_{corr}; 13% of the predicted joint risk reduction was attributable to lipoprotein(a). Results were similar after excluding 715 patients with per-protocol blinded substitution of placebo for alirocumab (Supplementary material online, *Table S1*), and when the lipoprotein(a) correction factor for the calculation was specified to be 15% (Supplementary material online, *Table S2*) or 55% (Supplementary material online, *Table S3*).

Given that as baseline lipoprotein(a) increases, the alirocumab-induced change in lipoprotein(a) also increases while the alirocumab-induced change in LDL-C_{corr} remains relatively constant, the predicted risk reductions associated with reductions in lipoprotein(a) and LDL-C_{corr} were investigated by baseline lipoprotein(a) quartile; the results are summarized in the *Take home figure* with details in *Table 4*. Lipoprotein(a) did not contribute to the joint predicted risk

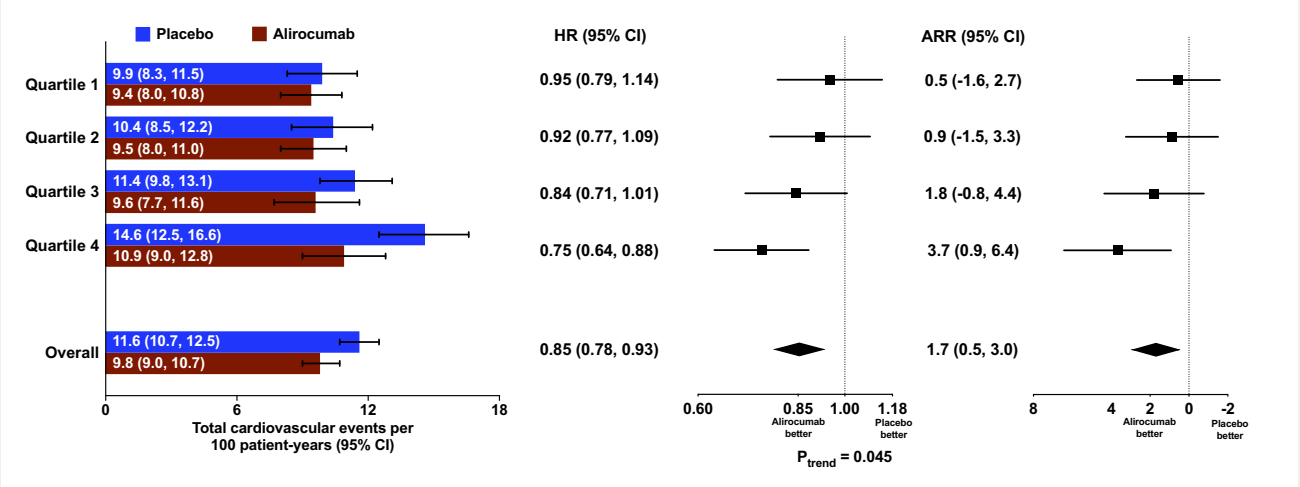
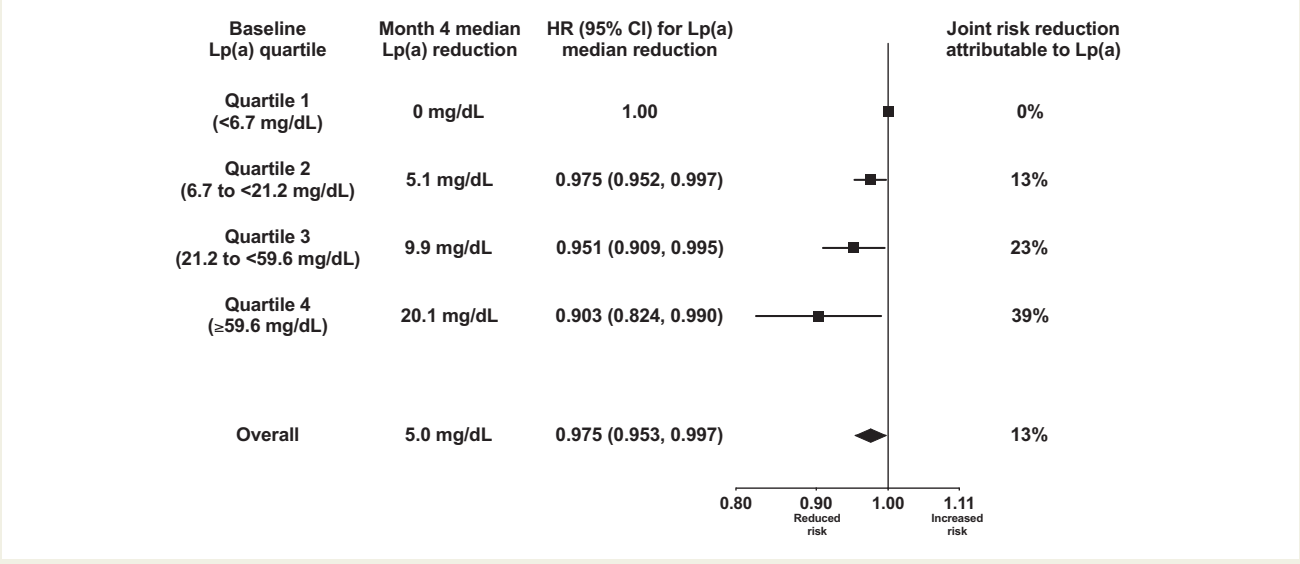


Figure 2 Relative and absolute treatment effects on total cardiovascular events, overall and by quartile of baseline lipoprotein(a). The rates of total vascular events per 100 patient-years of follow-up are shown for the alirocumab and placebo groups stratified by baseline quartile of lipoprotein(a) and for the overall population. The forest plots depict relative and absolute risk reduction with alirocumab compared with placebo. For relative risk reduction, there was a significant linear trend in the log hazard ratios across baseline quartiles, with point estimates progressively further below 1.00 for higher quartiles. CI, confidence interval; HR, hazard ratio.

Table 3 Relationship between reductions in lipoprotein(a) and low-density lipoprotein cholesterol from baseline to Month 4 and total cardiovascular events after Month 4 in the alirocumab group

Model	Model adjustments	Change parameter	HR (95% CI) for observed median reduction	*P*-value
1	None	Lipoprotein(a)	0.990 (0.964–1.017)	0.46
2	Baseline lipoprotein(a)	Lipoprotein(a)	0.972 (0.950–0.995)	0.016
3	Baseline lipoprotein(a), baseline LDL-C_{corr}, change from baseline to Month 4 in LDL-C_{corr}	Lipoprotein(a)	0.975 (0.953–0.997)	0.029
		LDL-C_{corr}	0.842 (0.755–0.940)	0.002
4	Baseline lipoprotein(a), baseline LDL-C_{corr}, change from baseline to Month 4 in LDL-C_{corr}, demographic and clinical characteristics	Lipoprotein(a)	0.978 (0.958–0.999)	0.036
		LDL-C_{corr}	0.820 (0.734–0.916)	0.001

Observed median reductions in lipoprotein(a) and LDL-C_{corr} were 5.0 and 51.3 mg/dL, respectively. The randomized treatment HR after Month 4 lipoprotein(a) and LDL-C measurements was 0.85 (95% CI 0.77–0.93).
CI, confidence interval; HR, hazard ratio; LDL-C_{corr}, low-density lipoprotein cholesterol corrected for lipoprotein(a) cholesterol.



Take home figure Relationship between reduction in lipoprotein(a) (Lp(a)) from baseline to Month 4 and total cardiovascular events after Month 4 in the alirocumab group, overall and by quartile of baseline lipoprotein(a). The percentages represent the predicted risk reduction attributable to the median reduction in lipoprotein(a) within each quartile or overall as a percentage of the joint predicted risk reduction by median decreases in lipoprotein(a) and low-density lipoprotein cholesterol corrected for lipoprotein(a) cholesterol. Lipoprotein(a) did not contribute to the joint predicted risk reduction in Quartile 1 (<6.7 mg/dL) while contributing 39% of the joint reduction in Quartile 4 (≥59.6 mg/dL). CI, confidence interval; HR, hazard ratio.

reduction in Quartile 1, but contributed 39% of the joint reduction in Quartile 4. Consequently, the relative contribution of lipoprotein(a) change to the reduction in the risk of total cardiovascular events becomes greater as baseline lipoprotein(a) level increases.

Discussion

Among patients with recent acute coronary syndrome receiving intensive or maximally tolerated statin treatment, it was previously reported from the ODYSSEY OUTCOMES trial that baseline lipoprotein(a) level predicted risk of a first primary outcome event (death from coronary heart disease, non-fatal myocardial infarction, ischaemic stroke, or hospitalization for unstable angina) among patients treated with placebo. In patients treated with alirocumab, the absolute reduction in lipoprotein(a) predicted the absolute reduction in risk of a first event, independent of the concurrent reduction in LDL-C_{corr}.[5] Similar findings were reported for first major PAD or VTE events.[6]

The present report extends those findings and provides additional clinical context by including a substantially larger number of events (2223) than the previous first primary outcome (710) or first PAD or VTE event (116) analyses, and spanning a broader range of cardiovascular event categories, including ischaemia-driven coronary revascularization and hospitalization for heart failure. The disease burden of cardiovascular events was substantial; among patients who had a

Table 4 Relationship between reductions in lipoprotein(a) and low-density lipoprotein cholesterol corrected for lipoprotein(a) cholesterol from baseline to Month 4 and total cardiovascular events after Month 4 in the alirocumab group by quartile of baseline lipoprotein(a)[a]

Baseline Lp(a) quartile	Change parameter	HR (95% CI) for observed median reduction within quartile	Joint predicted risk reduction attributable to lipoprotein(a) change (%)[b]
Quartile 1 (<6.7 mg/dL)	Lipoprotein(a)	1.000	0
	LDL-C_{corr}	0.836 (0.746–0.937)	
Quartile 2 (6.7 to <21.2 mg/dL)	Lipoprotein(a)	0.975 (0.952–0.997)	13
	LDL-C_{corr}	0.838 (0.749–0.938)	
Quartile 3 (21.2 to <59.6 mg/dL)	Lipoprotein(a)	0.951 (0.909–0.995)	23
	LDL-C_{corr}	0.842 (0.755–0.940)	
Quartile 4 (≥59.6 mg/dL)	Lipoprotein(a)	0.903 (0.824–0.990)	39
	LDL-C_{corr}	0.854 (0.772–0.944)	

CI, confidence interval; HR, hazard ratio; LDL-C_{corr}, low-density lipoprotein cholesterol corrected for lipoprotein(a) cholesterol.
[a]Observed median reductions in lipoprotein(a) by baseline quartile were 0, 5.1, 9.9, and 20.1 mg/dL for Quartiles 1, 2, 3, and 4, respectively. Corresponding median reductions in LDL-C_{corr} by baseline lipoprotein(a) quartile were 53.3, 52.7, 51.2, and 47.2 mg/dL. Models reflect adjustments corresponding to Model 3 in Table 3.
[b]Log(HR) for lipoprotein(a)/[log(HR) for lipoprotein(a) + log(HR) for LDL-C_{corr}].

non-fatal cardiovascular event, 48% experienced multiple events during the study. In the current analysis, baseline lipoprotein(a) predicted the burden of total cardiovascular events. The magnitude of lipoprotein(a) reduction by alirocumab, which was greater for higher levels of baseline lipoprotein(a), was associated with the benefit of treatment on those events, with greater relative and absolute risk reduction across successively higher quartiles of baseline lipoprotein(a). Furthermore, the association of alirocumab-induced reduction in lipoprotein(a) with reduced risk of total cardiovascular events was independent of the concurrent alirocumab-induced reduction in LDL-C_{corr}. Overall, each 5 mg/dL reduction in lipoprotein(a) with alirocumab predicted a 2.5% relative reduction in total cardiovascular events, which was similar in magnitude to that for first primary events.[5] Although most of the reduction was attributable to LDL-C_{corr}, the contribution of lipoprotein(a) change to the reduction in risk of total cardiovascular events was substantial for higher levels of baseline lipoprotein(a).

In a *post hoc* regression-based analysis of the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial, which included patients in both the placebo and evolocumab groups, lipoprotein(a) concentration at week 12 of assigned treatment was associated with the subsequent risk of first major coronary event.[7] Although these results are supportive of the present study, the analysis of FOURIER did not examine the relationship between change in lipoprotein(a) from baseline under evolocumab treatment and the risk of a subsequent event, or the relationship of achieved lipoprotein(a) levels to total event burden.

The findings from the present study are consistent with the 2019 ESC/EAS 2019 guidelines,[4] which have highlighted the emerging importance of lipoprotein(a) in cardiovascular risk assessment and further extend the evidence base for lipoprotein(a) to a contemporary population with recent acute coronary syndrome. ODYSSEY OUTCOMES recruited patients on the basis of an LDL-C >1.8 mmol/L (70 mg/dL), and those in the highest quartile of lipoprotein(a) had as much as a 60% increased risk of total cardiovascular events, corresponding to 16 extra events per 100 patients over 4 years, vs. those in the lowest quartile. Under the alirocumab treatment, this risk was reduced by 3.7 total events per 100 patient-years in the highest quartile, with 39% of the benefit attributable to lipoprotein(a) lowering. Likewise, if a 10% relative reduction in the risk of cardiovascular events is considered to be the minimum clinically meaningful effect, the present results indicate that with alirocumab given over the duration of the trial, patients with lipoprotein(a) ≥60 mg/dL would be expected to have their risk reduced by at least 10% consequent to reduction in lipoprotein(a), independent of any benefits from LDL-C reduction. Therefore, in patients with recent acute coronary syndrome, measurement of lipoprotein(a) levels might be a useful tool to identify patients at particularly high risk of recurrent events and who may derive substantial absolute and relative benefit from alirocumab treatment. It remains to be determined whether the findings from the present analysis are scalable to the larger reductions in lipoprotein(a) expected with antisense oligonucleotide and small-interfering RNA agents targeting the expression of apolipoprotein(a).[14]

A limitation of the analyses is that the majority of events were cardiac, restricting the ability to investigate if relationships with lipoprotein(a) potentially differ by vascular territory (e.g. cerebrovascular, peripheral). In addition, lipoprotein(a) was assessed by a mass concentration assay, and measurement by a molar concentration assay might have affected the observed relationships between alirocumab-induced changes in lipoprotein(a) with subsequent cardiovascular events. Furthermore, the applied LDL-C corrected formula used 30% lipoprotein(a) mass to estimate the cholesterol content of lipoprotein(a), and while results were consistent with higher or lower correction factors, the actual content may vary over a range around these nominal values.[15] Finally, the current analysis does not define the mechanisms by which PCSK9 inhibition lowers lipoprotein(a) concentration. Kinetic studies indicate that in statin-treated patients with elevated lipoprotein(a) levels, alirocumab reduces those levels by increasing clearance.[16]

Conclusions

Recent results from ODYSSEY OUTCOMES have demonstrated that, among patients receiving intensive statin therapy following a recent acute coronary syndrome, patient-level reductions in lipoprotein(a) by alirocumab independently contributed to reduced risk of a first primary outcome event and first PAD or VTE event. The present analyses demonstrate that baseline lipoprotein(a) predicted total cardiovascular event risk in the placebo group and relative and absolute risk reduction in the alirocumab group. This risk modification was partially attributable to changes in lipoprotein(a), where reduction in lipoprotein(a) by alirocumab was associated with fewer total cardiovascular events independent of LDL-C_{corr} reduction. These findings support the concept of lipoprotein(a) as a treatment target among high-risk patients with a recent acute coronary syndrome.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data Sharing

Individual participant data are not available.

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Conflict of interest: M.S. reports serving as a consultant or on advisory boards (or both) for CiVi, Resverlogix, Baxter, Esperion, Sanofi, and Regeneron Pharmaceuticals, Inc. V.A.B reports grant support from Sanofi, Astra Zeneca, DalCor, Esperion, Bayer, The Medicines Company, and Amgen, all paid directly to her institution, and personal fees from Sanofi. P.A. reports research grants from Sanofi, CSL, AstraZeneca, Da Cor, and advisory boards and speaker fees from Sanofi, Amgen, CSL, Astra Zeneca, Bayer, Novartis, and Boehringer Ingelheim. 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Corrigendum

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Corrigendum to: 2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk* [*Eur Heart J* (2019); doi:10.1093/eurheartj/ehz455].

The following post-publication corrections have been made to these Guidelines:

In row 4 of Table 3, 'should' has been corrected to 'may';
in 4.2.1, paragraph 3, 'should' has been corrected to 'may' to read 'Overall, CAC score assessment with CT may be considered in individuals. . .' This has also been corrected in the second row of 'Recommendations for cardiovascular imaging for risk assessment of atherosclerotic cardiovascular disease,' and the Class has been corrected to 'IIb';
in the second paragraph of 7.5.2, '5-10 mg of monacolin K' has been corrected to '2.5-10 mg';
and in the Key messages section, number 4, 'ApoB may be a better measure of an individual's exposure to atherosclerotic lipoproteins' has been corrected to 'ApoB may be a better measure of an individual's exposure to pro atherogenic lipoproteins'.