Atherosclerosis 288 (2019) 194–202

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Lipoprotein(a) reductions from PCSK9 inhibition and major adverse cardiovascular events: Pooled analysis of alirocumab phase 3 trials

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HIGHLIGHTS

- Analysis of 10 phase 3 ODYSSEY trials, alirocumab (ALI) *vs.* placebo or ezetimibe.
- Median lipoprotein(a) [Lp(a)] reductions: ALI (21.4–25.6%) *vs.* control (0.0–2.5%).
- Adjusted by baseline characteristics, 12% RRR in MACE per 25% reduction in Lp(a); $p = 0.0254$.
- Adjusted by LDL-C reductions, RRR was not significant; hazard ratio = 0.89, $p = 0.0780$.
- Fully adjusted RRR significant if baseline Lp(a) ≥ *vs.* < 50 mg/dL; *p*-interaction 0.0549.

ARTICLE INFO

Keywords:
PCSK9
Alirocumab
lipoprotein(a)
Low-density lipoprotein cholesterol
Cardiovascular risk
Cholesterol-lowering drugs

ABSTRACT

Background and aims: Elevated lipoprotein(a) [Lp(a)] levels are considered a causal factor for cardiovascular disease. In phase 3 ODYSSEY trials, alirocumab reduced levels of low-density lipoprotein cholesterol (LDL-C) and Lp(a), with concomitant reductions in the risk of major adverse cardiovascular events (MACE). We assessed whether lower on-study and greater percentage reductions in Lp(a) are associated with a lower risk of MACE.
Methods: Post-hoc analysis of data pooled from 10 phase 3 ODYSSEY trials comparing alirocumab with control (placebo or ezetimibe) in patients (n = 4983) with cardiovascular disease and/or risk factors, and hypercholesterolemia despite statin/other lipid-lowering therapies.
Results: Median (Q1, Q3) baseline Lp(a) levels were 23.5 (8.0, 67.0) mg/dL. Median Lp(a) changes from baseline with alirocumab were −25.6% *vs.* −2.5% with placebo (absolute reductions 6.8 *vs.* 0.5 mg/dL) in placebo-controlled trials, and −21.4% *vs.* 0.0% with ezetimibe (4.5 *vs.* 0.0 mg/dL) in ezetimibe-controlled trials. During follow-up (6699 patient-years), 104 patients experienced MACE. A 12% relative risk reduction in MACE per 25% reduction in Lp(a) ($p = 0.0254$) was no longer significant after adjustment for LDL-C changes: hazard ratio per 25% reduction: 0.89 (95% confidence interval, 0.79–1.01; $p = 0.0780$). In subgroup analysis, the association between Lp(a) reduction and MACE remained significant in a fully adjusted model among participants with baseline Lp(a) ≥50 mg/dL (*p*-interaction *vs.* Lp(a) < 50 mg/dL: 0.0549).
Conclusions: In this population, Lp(a) reductions were not significantly associated with MACE independently of LDL-C reductions. Reducing the risk of MACE by targeting Lp(a) may require greater reductions in Lp(a) with more potent therapies and/or higher initial Lp(a) levels.

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https://doi.org/10.1016/j.atherosclerosis.2019.06.896
Received 28 September 2018; Received in revised form 24 May 2019; Accepted 6 June 2019
Available online 08 June 2019

1. Introduction

Epidemiological studies have suggested that there is an association between increasing levels of lipoprotein(a) [Lp(a)] and risk of cardiovascular disease (CVD), particularly with Lp(a) levels > 50 mg/dL [1,2]. In addition, several Mendelian randomization and genome-wide association studies have shown that Lp(a) is a likely causal factor for the development of CVD [1,3,4]. However, there are limited treatment options for reducing Lp(a) levels as they are mainly genetically determined; the only previously available treatment, niacin, is no longer available in Europe following reports of an increase in serious adverse events [5]. Despite significantly reducing apolipoprotein (apo) B100 and low-density lipoprotein cholesterol (LDL-C) levels, statins have not been shown to significantly lower Lp(a) levels [1,6].

By contrast, in a pooled analysis of phase 3 ODYSSEY studies, alirocumab, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9), reduced levels of both LDL-C (by 46–60%) and Lp(a) (by 23–29%); notably, whilst the correlation between greater percentage reductions in Lp(a) and greater percentage reductions in LDL-C was significant (Spearman's correlation coefficient, 0.307; $p < 0.0001$), only 9.4% of the variation in the reduction in Lp(a) would be explained by reductions in LDL-C [6]. Presently, it is not clear whether there is any additional cardiovascular benefit associated with the therapeutic lowering of Lp(a) [1]. However, a recent Mendelian randomization analysis [4] showed that the risk of coronary heart disease is proportionally associated with the absolute change in plasma Lp(a) concentration and that a 101.5 mg/dL reduction in Lp(a) concentration was associated with the same risk as a 38.7 mg/dL (1 mmol/L) reduction in LDL-C. Hence, a similar clinically meaningful reduction in risk as that seen with LDL-C lowering would only be seen in those with higher baseline Lp(a) who would achieve greater percentage reductions in Lp(a).

In a pooled analysis of phase 3 ODYSSEY trials of alirocumab, we have previously demonstrated that there is a continuous relationship between lower on-study levels of LDL-C (including levels < 50 mg/dL) and lower rates of major adverse cardiovascular events (MACE) — hazard ratio (HR [95% confidence interval (CI)] 0.76 [0.63–0.91] per 39 mg/dL decrease; $p = 0.0025$) [7]. Comparable results were obtained when studying the percentage reductions in LDL-C and MACE (0.71 [90.57–0.89] per additional 50% reduction; $p = 0.003$) and for lower on-study levels and percentage reductions in apoB and non-high-density lipoprotein cholesterol (non-HDL-C) [7]. In this *post-hoc* analysis, similar methodology within the same pooled dataset was used to assess the impact of reductions in Lp(a) levels on the incidence of MACE and the extent to which any potential benefit is independent of reductions in LDL-C.

2. Patients and methods

2.1. Study population

For the present analysis, data were pooled from 10 phase 3 ODYSSEY randomized trials of alirocumab *vs.* control (placebo or ezetimibe). The design of these trials has been described in detail previously (Supplementary Fig. 1) [8–16]. Briefly, patients (aged ≥18 years, n = 4983) had a history of established atherosclerotic CVD, presence of cardiovascular risk factors without established atherosclerotic CVD, or heterozygous familial hypercholesterolemia, with LDL-C inadequately controlled by their existing treatment (statin/other lipid-lowering therapy/diet). Entry criteria included baseline LDL-C ≥70 mg/dL for those with prior CVD or ≥100 mg/dL for those without established CVD but with other risk factors. Exceptions were the LONG TERM study [15] (LDL-C ≥70 mg/dL for all patients), MONO [16] (LDL-C ≥100 mg/dL for all patients), and HIGH FH [11] (LDL-C ≥160 mg/dL for all patients). Patients with triglyceride (TG) levels > 400 mg/dL were excluded. Patients were randomized to receive alirocumab or control (placebo or ezetimibe). Most patients were receiving background statin therapy (except for two trials where patients were not receiving concomitant statin therapy [MONO [16] and ALTERNATIVE [14]]). The double-blind treatment periods ranged from 24 to 104 weeks; six of the 10 studies, representing approximately 80% of the population, had a minimum study duration of 52 weeks. In eight studies, patients received an initial dosage of alirocumab 75 mg every 2 weeks (Q2W) with a potential adjustment to 150 mg Q2W at Week 12 depending upon achievement of pre-specified LDL-C levels at Week 8 (≥70 mg/dL, or ≥70 or ≥100 mg/dL according to cardiovascular risk), and two studies used alirocumab 150 mg Q2W only.

2.2. LDL-C and Lp(a) measurements

Calculated LDL-C levels were determined using the Friedewald equation [17] if TGs were < 400 mg/dL (total cholesterol – high-density lipoprotein cholesterol [HDL-C] – TGs/5); in cases with TGs above this threshold, LDL-C was determined using the beta quantification method; however, such data are not included in this analysis.

Calculated LDL-C levels were corrected for the cholesterol content of Lp(a) (Lp(a)-corrected LDL-C), which may be 30–45% of the mass of Lp(a) depending on the individual [18]; hence, Lp(a)-corrected LDL-C was determined as either calculated LDL-C − 0.45 x Lp(a) or calculated LDL-C − 0.30 x Lp(a), which assumes that 45% or 30% of the mass of Lp(a) is cholesterol, respectively [19–21]. Unless otherwise specified, we used 45% as the correction factor for the cholesterol content of Lp(a) in the main analyses: nevertheless, for means of comparison, sensitivity analyses were performed using 30% as the correction factor and results are also briefly reported.

Serum Lp(a) levels were determined by centralized laboratories (Medpace Reference Laboratories [MRL] and for LONG TERM only, Covance Central Laboratory Services Inc. [CCLS]) using an internally standardized assay (for which a possible isoform-dependency has neither been demonstrated nor excluded) on a Siemens BNII nephelometer (Siemens, Erlangen, Germany) that measures in mg/dL. The assay employed by MRL was calibrated using N Diluent, N Lp(a) Standard SY, and the International Federation of Clinical Chemistry and World Health Organization standards [6,22], and that of CCLS was calibrated using the manufacturer's N Lp(a) Standard. MRL reported results lower than 3 mg/dL as < 3 mg/dL and CCLS reported Lp(a) concentrations below 4 mg/dL as < 4.0 mg/dL (methods are further described in the Supplementary Material). Serum samples were submitted on the day of collection from sites and analysis was performed on the day of receipt (Mon–Fri); if this was a Saturday, samples were refrigerated and analyzed the following Monday. The reported intra-assay reliability in coefficients of variation was 1.8–4.0% and inter-assay precision was 3.1–4.4%.

2.3. Major adverse cardiovascular events

MACE were defined as per the ODYSSEY cardiovascular outcomes trial (ODYSSEY OUTCOMES [(Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab]): coronary heart disease death, non-fatal myocardial infarction (MI), ischemic stroke, or unstable angina requiring hospitalization [23]. Cardiovascular events were adjudicated by a central Clinical Events Committee [8] (the same committee that is involved in the aforementioned ODYSSEY Outcomes trial). Unstable angina cases considered here were limited to those with definite evidence of the ischemic condition, i.e. a small proportion of unstable angina events qualified.

2.4. Statistical analysis

Baseline and safety data, and LDL-C and Lp(a) levels during the studies, were analyzed in two pools according to whether they were

placebo- or ezetimibe-controlled. Additionally, an exploratory analysis of safety was performed among those who achieved Lp(a) percentage reductions greater than the median *vs.* those who did not. Average LDL-C and Lp(a) levels during the study period were determined from the area under the curve (using trapezoidal method), taking into account all LDL-C and Lp(a) values up to the end of the treatment period or occurrence of MACE, whichever came first. Average absolute change in Lp(a)-corrected LDL-C and Lp(a) during the study period were determined from the area under the curve (using trapezoidal method), taking into account all values up to the end of the study period or occurrence of MACE, whichever came first. For patients with no post-baseline lipid value, the lipid value at baseline was used. Baseline data were analyzed from all randomized patients; all other analyses used the safety population (all patients who were randomized and received at least one dose of study treatment). Potential differences in percentage change from baseline in Lp(a) between patients with baseline Lp(a) < 50 and ≥ 50 mg/dL were assessed by comparing adjusted mean percentage differences (alirocumab *vs.* control) in four pools according to alirocumab dose, control, and whether background statin was used, using a mixed-effect model with repeated measures as previously described [15], and deriving nominal interaction *p*-values.

For analysis of the relationship between Lp(a) and MACE, patients were pooled into one overall cohort, regardless of treatment group. In multivariate models, achieved Lp(a) values were assessed following log transformation per one standard deviation (SD; 1.06 Log_e or 2.9-fold) difference in on-study levels or per 25% reduction from baseline (with adjustment for baseline characteristics and with or without adjustment for either average achieved LDL-C or percentage reduction in LDL-C, respectively). A log transformation was used to normalize the distribution of Lp(a) values. To enable comparison with earlier analyses of LDL-C per 39 mg/dL decrease, equivalent to 0.76 x population SD [7], the same ratio of 0.76 x SD was maintained in the present study for analyses of log-transformed achieved Lp(a) values.

3. Results

3.1. Baseline patient characteristics

Baseline characteristics of the pooled cohort are shown in Table 1. Patients were generally well matched between randomized groups, with an average age of 59 years in the placebo-controlled trials and 62 years in the ezetimibe-controlled trials. Overall, 63% were male and 90% were White, mean body mass index was 30 kg/m^2, and around 31% of patients had diabetes mellitus; 36% of patients in the placebo-controlled trials and 5.6% in the ezetimibe-controlled trials had heterozygous familial hypercholesterolemia (Table 1). Mean (± SD) on-study LDL-C levels were 56.9 ± 38.8 and 126.5 ± 43.9 mg/dL for alirocumab and placebo, respectively, in placebo-controlled studies, and 64.0 ± 42.4 and 100.9 ± 50.8 mg/dL for alirocumab and ezetimibe, respectively, in ezetimibe-controlled studies [7].

3.2. Baseline and on-study Lp(a) levels

The distribution of Lp(a) levels at baseline was generally similar across the treatment groups (Fig. 1A and Table 1). Overall, median (Q1, Q3) baseline Lp(a) levels were 23.5 (8.0, 67.0) mg/dL (Supplementary Fig. 2A).

Median (Q1, Q3) on-study Lp(a) values were 16.3 (4.8, 52.4) mg/dL with alirocumab *vs.* 22.6 (6.9, 64.2) mg/dL with placebo in the placebo-controlled pool, and 17.0 (5.3, 54.5) mg/dL with alirocumab *vs.* 21.9

Table 1
Baseline characteristics of patients pooled from 10 phase 3 ODYSSEY trials.

	Placebo-controlled trials		Ezetimibe-controlled trials	
	Alirocumab (n = 2324)	Placebo (n = 1175)	Alirocumab (n = 864)	Ezetimibe (n = 620)
Age, mean ± SD, years	58.7 ± 11.6	58.8 ± 11.4	61.9 ± 9.4	62.1 ± 9.5
Sex, male, n (%)	1415 (60.9)	712 (60.6)	581 (67.2)	388 (62.6)
Race, White, n (%)	2139 (92.0)	1072 (91.2)	745 (86.2)	548 (88.4)
BMI, mean ± SD, kg/m^2	30.1 ± 5.6	30.3 ± 5.6	30.2 ± 6.0	30.0 ± 5.7
HeFH, n (%)	838 (36.1)	419 (35.7)	40 (4.6)	43 (6.9)
Diabetes, n (%)	699 (30.1)	355 (30.2)	283 (32.8)	192 (31.0)
ASCVD, n (%)[a]	1615 (69.5)	834 (71.0)	651 (75.3)	411 (66.3)
CHD	1454 (62.6)	766 (65.2)	611 (70.7)	390 (62.9)
Ischemic stroke/TIA	199 (8.6)	86 (7.3)	67 (7.8)	42 (6.8)
PAD	97 (4.2)	56 (4.8)	33 (3.8)	19 (3.1)
Current smoker, n (%)	453 (19.5)	231 (19.7)	146 (16.9)	118 (19.0)
High-intensity statin, n (%)[b]	1327 (57.1)	682 (58.0)	430 (49.8)	265 (42.7)
Non-statin LLT, n (%)[c]	882 (38.0)	461 (39.2)	125 (14.5)	111 (17.9)
LDL-C, mean ± SD, mg/dL				
Calculated LDL-C[d]	126.8 ± 46.3	126.8 ± 44.8	123.2 ± 51.5	125.5 ± 56.9
Lp(a)-corrected LDL-C	106.8 ± 49.8	106.9 ± 48.4	103.7 ± 54.9	106.4 ± 51.6
Lp(a), mg/dL, median (Q1, Q3)	25.0 (8.1, 69.5)	23.0 (7.0, 68.7)	24.0 (8.0, 67.0)	22.0 (8.0, 55.5)
Lp(a) < 50 mg/dL, n (%)	1517 (66.9)	766 (66.4)	556 (65.8)	433 (72.2)
Lp(a) ≥ 50 mg/dL, n (%)	750 (33.1)	388 (33.6)	289 (34.2)	167 (27.8)
Lp(a) < 30 mg/dL, n (%)	1236 (54.5)	642 (55.6)	465 (55.0)	344 (57.3)
Lp(a) ≥ 30 mg/dL, n (%)	1031 (45.5)	512 (44.4)	380 (45.0)	256 (42.7)

Pooled data from 10 phase 3 trials (randomized population). Placebo-controlled trials: LONG TERM, NCT01507831; HIGH FH, NCT01617655; FH I, NCT01623115; FH II, NCT01709500; COMBO I, NCT01644175; ezetimibe-controlled trials: COMBO II, NCT01644188; OPTIONS I, NCT01730040; OPTIONS II, NCT01730053; MONO, NCT01644474; ALTERNATIVE, NCT01709513.
ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CHD, coronary heart disease; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Lp(a), lipoprotein(a); PAD, peripheral artery disease; Q, quarter; SD, standard deviation; TIA, transient ischemic attack.
[a] Patients may be in more than one sub-category within ASCVD.
[b] Atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg.
[c] In combination with statins or not.
[d] Calculated LDL-C, determined by the Friedewald equation.

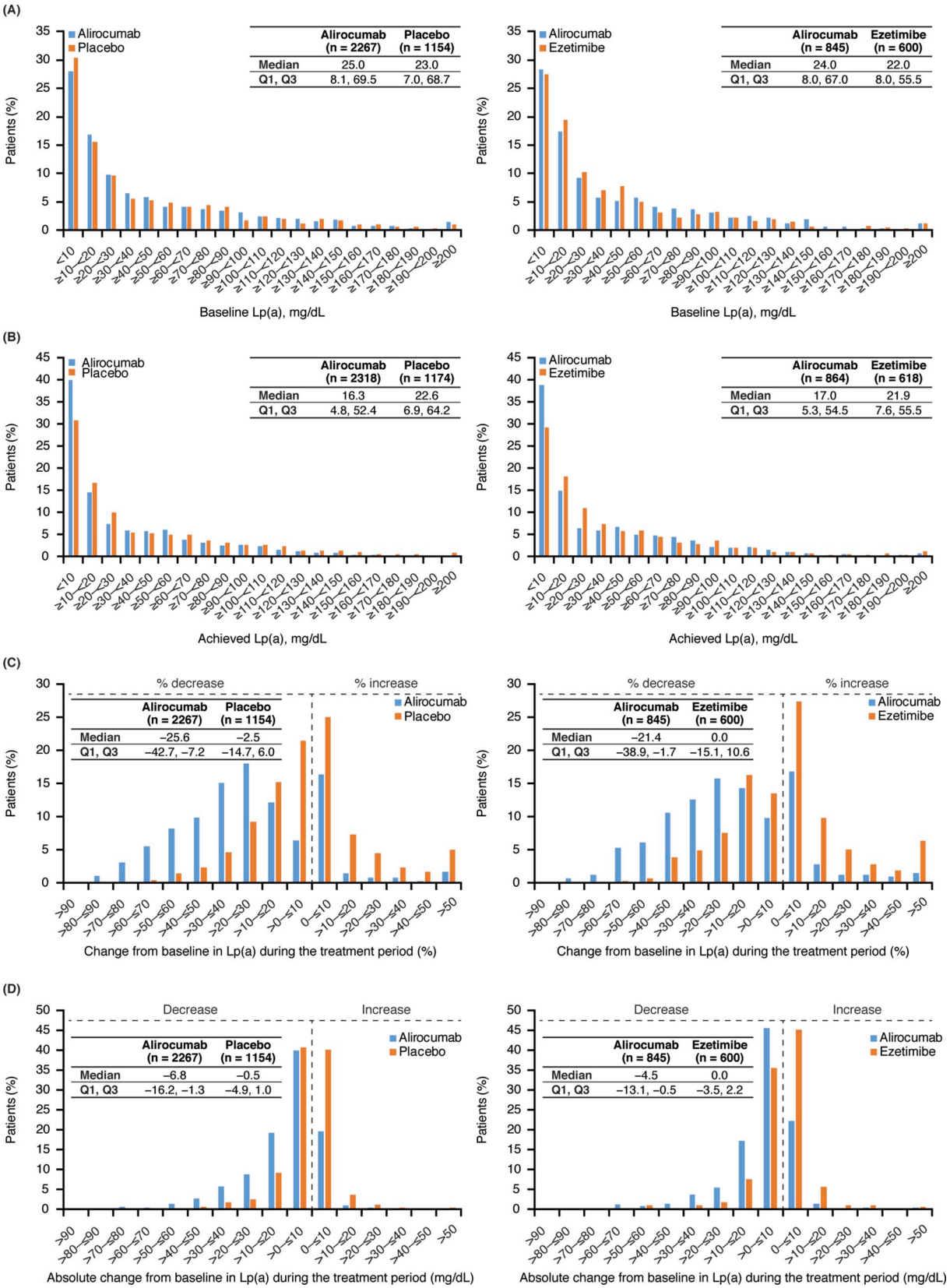

Fig. 1. Distribution of Lp(a) levels (A) at baseline and (B) achieved during the study period, and by (C) percentage and (D) absolute change from baseline (safety population).
Lp(a), lipoprotein(a); Q, quarter.

(7.6, 55.5) mg/dL with ezetimibe in the ezetimibe-controlled pool (Fig. 1B). During the study period, the median (Q1, Q3) percentage change from baseline in Lp(a) was −25.6% (−42.7%, −7.2%) with alirocumab *vs.* −2.5% (−14.7%, 6.0%) with placebo in the placebo-controlled pool, and −21.4% (−38.9%, −1.7%) with alirocumab *vs.* 0.0% (−15.1%, 10.6%) with ezetimibe in the ezetimibe-controlled pool (Fig. 1C); overall, the median percentage reduction was −15.5% (−33.9%, 0.0%) for all patients (Supplementary Fig. 2B). These percentage changes corresponded to median absolute changes in Lp(a) of −6.8 mg/dL with alirocumab *vs.* −0.5 mg/dL with placebo in the placebo-controlled pool, and of −4.5 mg/dL (alirocumab) *vs.* 0.0 mg/dL (ezetimibe) in the ezetimibe-controlled pool (Fig. 1D). Overall reductions in placebo- and ezetimibe-controlled trials stratified by baseline Lp(a), < 50 mg/dL or ≥50 mg/dL, are shown in Supplementary Fig. 3. The percentage changes from baseline in Lp(a) tended to be greater among those with baseline Lp(a) levels < 50 mg/dL than ≥50 mg/dL in placebo-controlled pools (Supplementary Fig. 4): in the alirocumab 150 mg Q2W *vs.* placebo on background statin therapy pool, the adjusted mean difference *vs.* control was −27.7% in those with baseline Lp(a) < 50 mg/dL *vs.* −21.4% among those with baseline Lp(a) ≥50 mg/dL, *p*-interaction = 0.0163; in the alirocumab 75/150 mg Q2W *vs.* placebo on background statin therapy pool, the corresponding values were −21.3% *vs.* −13.4%, respectively, *p*-interaction = 0.028. In the ezetimibe-controlled pools, corresponding results were as follows: alirocumab 75/150 mg Q2W *vs.* ezetimibe on background statin therapy: −25.3% *vs.* −18.6%, *p*-interaction = 0.0976; alirocumab 75/150 mg Q2W *vs.* ezetimibe without background statin therapy: −14.7% *vs.* −10.7%, *p*-interaction = 0.6287.

3.3. Association between Lp(a) levels and MACE

Median (range) follow-up was 84.6 (24–104) weeks (6699 total patient-years). During follow-up, 104 patients reported at least one MACE; median time to event was 36 weeks. Specifically, there were 20 coronary heart disease deaths, 64 non-fatal MIs, 16 ischemic strokes, and four unstable angina episodes (with definite evidence of the ischemic condition).

In analyses adjusted on baseline characteristics only, but unadjusted for change or on-study Lp(a)-corrected LDL-C, there was a 12% relative risk reduction in MACE per 25% reduction in Lp(a) (HR [95% CI] 0.88 [0.78–0.98]; $p = 0.0254$), and a non-significant difference per 1 SD lower on-study Lp(a), 0.89 (0.75–1.05; $p = 0.1562$; Fig. 2).

In fully adjusted multivariate analyses which adjusted for both baseline characteristics and percentage reductions in Lp(a)-corrected LDL-C or on-study Lp(a)-corrected LDL-C, the risk of MACE was not significantly associated with greater percentage Lp(a) reduction, 0.89 (0.79–1.01 per 25% reduction; $p = 0.0780$; Fig. 3A) or lower on-study Lp(a), 0.91 (0.77–1.07 per 1 SD lower; $p = 0.2387$; Fig. 3B).

When the analysis was stratified by baseline Lp(a) ≥50 *vs.* < 50 mg/dL, the magnitude of the strength of association for reductions in Lp(a) with MACE was greater among those with higher *vs.* lower baseline Lp(a) levels in fully adjusted models; per 25% reduction in Lp (a), 0.60 (0.39–0.92; $p = 0.0201$) for higher baseline Lp(a) *vs.* 0.94 (0.81–1.09; $p = 0.3837$) for lower baseline Lp(a), *p*-interaction between subgroups: 0.0549 (Fig. 4A). When similar analyses were conducted for on-study Lp(a), findings were directionally concordant but the strength of association for a 1 SD lower Lp(a) and risk of MACE for higher *vs.* lower baseline levels of Lp(a) was not significant; for baseline Lp(a) ≥50 mg/dL, 0.49 (0.20–1.16) *vs.* baseline Lp(a) < 50 mg/dL, 0.91 (95% CI 0.71–1.17; *p*-interaction = 0.1737; Fig. 4B).

In analyses adjusted only for baseline characteristics but unadjusted for on-study Lp(a)-corrected LDL-C, with a 5 mg/dL and a 20 mg/dL absolute reduction in Lp(a), there was a statistically significant reduction in MACE, 0.93 (0.87–1.00; $p = 0.0369$) and 0.74 (0.56–0.98; $p = 0.0369$), respectively. However, in fully adjusted multivariate analyses including adjustment for both baseline characteristics and absolute change in Lp(a)-corrected LDL-C, the effects of a 5 mg/dL absolute reduction in Lp(a) and a 20 mg/dL absolute reduction in Lp(a) were no longer statistically significant, 0.94 (0.88–1.01; $p = 0.1101$; Fig. 3C), and 0.79 (0.59–1.06; $p = 0.1101$), respectively.

When similar analyses were conducted considering Lp(a)-derived cholesterol as 30% rather than 45%, in fully adjusted multivariate analyses including adjustment for baseline characteristics and percentage reductions in Lp(a)-corrected LDL-C, again the risk of MACE was not significantly associated with greater percentage Lp(a) reduction, 0.91 (0.80–1.03 per 25% reduction; $p = 0.1257$; Supplementary Fig. 5). However, in an analysis stratified by baseline Lp(a) ≥50 *vs.* < 50 mg/dL, the magnitude of the strength of association for reductions in Lp(a) with MACE was again greater among those with higher *vs.* lower baseline Lp(a) levels in fully adjusted models; per 25% reduction in Lp (a), 0.62 (0.39–0.97; $p = 0.0366$) for higher *vs.* 0.94 (0.81–1.08; $p = 0.3760$) for lower baseline Lp(a), between subgroup *p*-interaction = 0.0870 (Supplementary Fig. 5).

3.4. Safety

The incidence of treatment-emergent adverse events, serious adverse events, and treatment-emergent adverse events leading to discontinuation were similar between the alirocumab and control groups, regardless of the magnitude of percentage reduction in Lp(a) (Supplementary Table 1). There was a higher frequency of injection-site reactions with alirocumab, although these were mostly mild and transient.

4. Discussion

PCSK9 inhibition reduces several atherogenic apoB-related lipid fractions, such as LDL-C, non-HDL-C, and Lp(a). While previous research has shown a significant relationship between lower achieved levels and greater percentage reductions in LDL-C, apoB, and non-HDL-C with the risk of MACE [7] among patients enrolled in alirocumab phase 3 trials, it has remained unclear whether any benefits would be derived from the Lp(a) reductions observed with PCSK9 inhibition. The current study is the first to directly evaluate the impact of Lp(a) reduction on MACE. We did not find a significant association in the overall cohort between reductions in Lp(a), whether that be percentage,

Population	n	HR (95% CI)	*p*–value
(A) All	4738	0.88 (0.78–0.98) per 25% reduction	0.0254
(B) All	4738	0.89 (0.75–1.05) per 1 SD lower	0.1562

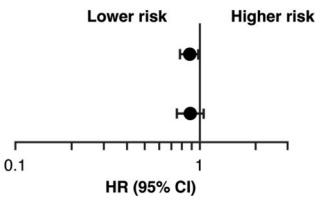

Fig. 2. Relationship between MACE and (A) percentage change in Lp(a) and (B) achieved Lp(a) during the study period: analysis adjusted on baseline characteristics but unadjusted for (A) percentage change in Lp(a)-corrected LDL-C or (B) on-study Lp(a)-corrected LDL-C (safety population).
HR, 95% CI, and *p*-value determined from a multivariate Cox model. Average Lp(a)-corrected LDL-C and Lp(a) during the study period were determined from the area under the curve (using trapezoidal method), taking into account all values up to the end of the study period or occurrence of a MACE, whichever came first. For patients with no post-baseline lipid value, the lipid value at baseline was used. For patients with percentage change in Lp(a) or Lp(a)-corrected LDL-C > 200% (i.e. > 3-fold increase from baseline), percentage change was right-censored to 200. CI, confidence interval; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MACE, major adverse cardiovascular events; 1 SD, standard deviation = 1.06 Log_e or 2.9-fold.

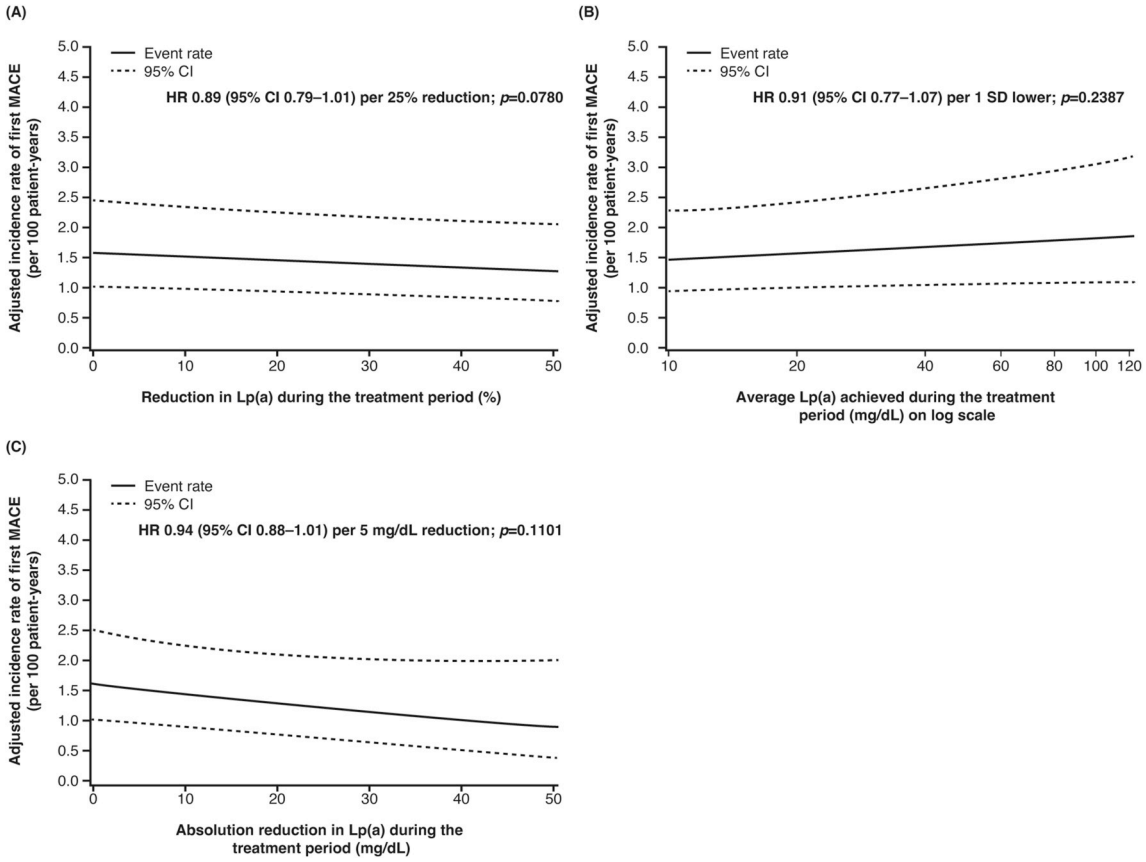

Fig. 3. Adjusted incidence rate of first MACE by (A) percentage change in Lp(a), (B) achieved Lp(a), and (C) absolute change in Lp(a) during the study period. Multivariate analysis adjusted for baseline characteristics and on-study Lp(a)-corrected LDL-C. Event rate and 95% CI determined from a multivariate Poisson model, with adjustment for age, gender, diabetes, prior history of myocardial infarction or stroke, smoking class, baseline Lp(a)-corrected LDL-C, and on-study change in Lp (a)-corrected LDL-C. CI, confidence interval; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MACE, major adverse cardiovascular events; SD, standard deviation.

(A)

Population	n	HR (95% CI) per 25% reduction	*p*–value
All	4738	0.89 (0.79–1.01)	0.0780
Baseline Lp(a) <50 mg/dL	3199	0.94 (0.81–1.09)	0.3837
Baseline Lp(a) ≥50 mg/dL	1539	0.60 (0.39–0.92)	0.0201

(B)

Population	n	HR (95% CI) per 1 SD lower	*p*–value
All	4738	0.91 (0.77–1.07)	0.2387
Baseline Lp(a) <50 mg/dL	3199	0.91(0.71–1.17)	0.4604
Baseline Lp(a) ≥50 mg/dL	1539	0.49 (0.20–1.16)	0.1026

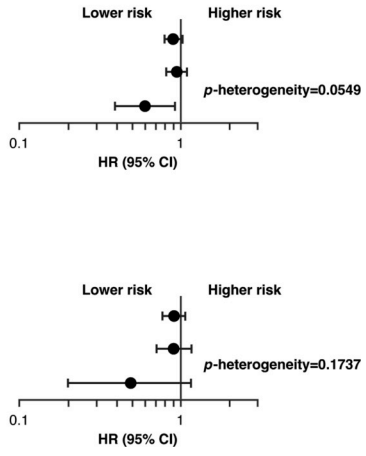

Fig. 4. Risk of MACE associated with (A) percentage reduction in Lp(a) and (B) lower achieved Lp(a) stratified by baseline Lp(a).
HR, 95% CI, and *p*-value determined from a multivariate Cox model. Analysis adjusted for age, gender, diabetes mellitus, prior history of myocardial infarction/stroke, baseline Lp(a)-corrected LDL-C, smoking status, and percentage reduction in Lp(a)-corrected LDL-C. CI, confidence interval; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MACE, major adverse cardiovascular events; 1 SD, standard deviation = 1.06 Log_e or 2.9-fold.

absolute, or on-study levels, and incidence of MACE once changes in LDL-C were controlled in the overall population. However, there was a significant association between reductions in Lp(a) and MACE in the subgroup of patients with baseline Lp(a) ≥50 mg/dL ($p = 0.0201$), as discussed below. Importantly, when we recalculated these results, assuming that the cholesterol content of Lp(a) is 30% rather than 45%, there was no material change in our findings.

Although studies with PCSK9 inhibitors have shown a linear relationship between on-study LDL-C and MACE [7,24], and, whilst evolocumab [25] and alirocumab also reduce Lp(a) [6] by ~25% and 23–29%, respectively, at present it is unclear whether there is an additional benefit from PCSK9 inhibition. A recent analysis by Ference et al. compared the annual and cumulative benefits of statins with PCSK9 monoclonal antibodies when standardized per 39 mg/dL (1 mmol/L) lowering of LDL-C [26]. This analysis suggested that the reduction in CVD per 39 mg/dL (1 mmol/L) lower LDL-C is identical between statins and PCSK9 inhibitors. When cardiovascular outcomes in patients on statins and PCSK9 inhibitors are compared in populations without significantly elevated Lp(a), there is little difference in the CTT meta-analysis MACE end-point per mmol/L lowering in LDL-C per year

of treatment [26,27]. This suggests that for PCSK9 inhibitors and statins, the benefits observed in patients not selected on the basis of elevated Lp(a) may be mainly explained by the reductions in LDL-C levels rather than any anti-inflammatory effects of statins or any Lp(a)-lowering effects of PCSK9 inhibitors. These data are also supported by the observation that statins also reduce C-reactive protein but do not lower Lp(a), while PCSK9 inhibitors do the opposite [25], suggesting that it might be unlikely that there is a meaningful contribution from Lp(a) reduction to the risk of MACE with PCSK9 monoclonal antibodies in the overall population. Notably, PCSK9 inhibitors will generally be given to patients on background statin therapy; hence, this is the context under which PCSK9 inhibitors will lower Lp(a) levels and effects may differ under conditions of monotherapy or combination therapy. Watts et al. reported that evolocumab, as monotherapy, reduced Lp(a) by reducing its production rate, while in combination with statins showed no effect on Lp(a) production, but rather increased the Lp(a) fractional catabolic rate [28].

In the ODYSSEY trials, there was a statistically significant but modest association between changes in LDL-C and Lp(a), whereby 9% of the variation in the reduction in Lp(a) could be accounted for by LDL-C changes [6]. Among patients with higher baseline Lp(a), > 50 mg/dL, the correlation was slightly stronger but was still only responsible for about 16% of the variation in the reduction in Lp(a), suggesting that LDL-C reductions do not explain the vast majority of the reductions in Lp(a). These data are consistent with observations of evolocumab, where slightly stronger correlation coefficients were seen; even then, only about 25% of the variation in the reduction in Lp(a) with evolocumab could be explained by reductions in LDL-C [25].

Alirocumab reduces Lp(a) levels by up to 29%, whereas statins have not been shown to significantly reduce Lp(a) levels [1,6,29], with some studies showing an increase in Lp(a) following statin treatment [30]. The mechanism by which PCSK9 inhibition reduces Lp(a) is unclear; it may involve both the LDL receptor as well as non-LDL receptor pathways [6,25]. Alirocumab reduces LDL-C by preventing PCSK9-mediated LDL receptor degradation, resulting in an increased number of LDL receptors available to remove apoB-containing lipoproteins from circulation, potentially including Lp(a) [31]. Statins also increase the number of LDL receptors, but most studies show little effect of statins on Lp(a), suggesting that Lp(a) is not primarily cleared through the LDL receptor following PCSK9 inhibition [6]. As both statins and PCSK9 inhibitors reduce apoB and LDL-C, but have differential effects on Lp(a), it is unlikely that merely reducing the apoB100 substrate for Lp(a) is the explanation. Recent in vitro studies using human hepatoma HepG2 cells by Raal et al. showed that Lp(a) competes with LDL for the LDL receptor and non-LDL receptor mediated clearance, but much higher doses of Lp(a) are required to prevent LDL binding than the converse [25]. Hence, the preferred substrate for the LDL receptor is LDL rather than Lp(a). Reyes-Soffer et al. showed that treatment with alirocumab increased the fractional clearance of Lp(a) by 25%, indicating that while the LDL receptor was likely involved in the clearance of Lp(a), there had to be other receptors involved [32].

We did not observe a significant relationship between lower on-study Lp(a) and MACE. This is analogous to a recent analysis of the high-intensity statin study SATURN, which did not find an association between Lp(a) levels (neither baseline nor on-study levels nor by levels below *vs.* above 50 mg/dL) and coronary progression (changes in percent coronary atheroma volume) [33]. However, as in the ODYSSEY trials [6], most patients in SATURN had Lp(a) levels < 50 mg/dL (baseline median 17.4 mg/dL), i.e. below the upper 80th percentile of Lp(a), *vs.* higher levels which are associated with the largest cardiovascular risk [1].

Both Lp(a) and LDL contain a cholesterol cargo and are considered atherogenic [1]. In statistical models that compared like for like, Lp(a) had a weaker strength of association with MACE compared with LDL-C [4]. It should be remembered that we standardized our reduction in Lp(a) as 25%, which was associated with a non-significant 8% lower risk of CVD after controlling for LDL-C. Furthermore, whilst we were underpowered, there was a suggestion that greater reductions in Lp(a), such as 50%, might provide greater reductions in CVD risk when Lp(a) is high, since per 25% reduction in Lp(a) the HRs were 0.60 ($p = 0.0201$) *vs.* 0.94 ($p = 0.3837$) for patients with baseline Lp(a) ≥50 mg/dL *versus* those below (p-interaction = 0.0549; Fig. 4A). This would suggest that any therapeutic approach to reducing Lp(a) should be targeted towards a population with very high baseline Lp(a) levels and should have a magnitude of absolute reduction that is considerably larger than that observed with PCSK9 inhibitors. Therapies such as antisense oligonucleotides against apo(a), which reduce Lp(a) by up to 92%, are perhaps more likely to offer the best meaningful approaches to reducing Lp(a) [34].

The present findings should not detract from the wealth of observational data on Lp(a). Indeed, large-scale observational studies have indicated a non-linear association between Lp(a) levels and cardiovascular risk [2]. In particular, the risk appears more marked at levels > 50 mg/dL, with many consensus statements recommending screening for Lp(a) [1]. More recently, genetic studies that are free from potential confounding have demonstrated strong and likely causal associations with CVD [35,36]. The final proof of causality is the test for reversibility in randomized controlled trials, and this has been lacking with respect to the evidence base for Lp(a). There was therefore considerable interest when it was observed that PCSK9 inhibition reduced Lp(a). However, it has not been possible to prospectively study the effect of reducing Lp(a) on cardiovascular events, as PCSK9 inhibitors do not specifically reduce Lp(a) without affecting LDL-C and other lipids. While we have attempted to account for these statistically, we cannot exclude the possibility that the Lp(a) reductions observed do not contribute to CVD reduction.

Limitations of the present study must be considered, including the relatively low median baseline level of Lp(a) as discussed above and modest achieved Lp(a) reductions, the limited follow-up time (24–104 weeks), the small number of MACE (n = 104), and the limited number of patients in subgroups stratified by baseline Lp(a) ≥50 *vs.* < 50 mg/dL, which may have diminished the power to show a significant association between the different Lp(a) measurements and MACE. Furthermore, this analysis is *post hoc*, resulting from pooled data from several trials, and hypothesis-generating. We corrected LDL-C for the cholesterol content of Lp(a), which may be 30–45% of the mass of Lp(a) depending on the individual [18]. Although other studies used similar adjustments to assess Lp(a) cholesterol [19,20], there is an inherent variation because the molecular masses of different Lp(a) isoforms vary; a larger apo(a) isoform with an identical mass concentration as a smaller Lp(a) isoform represents a lower Lp(a) particle concentration and provides an overestimate of the amount of cholesterol in the particle [37,38]. The ODYSSEY OUTCOMES trial in 18,924 patients with recent acute coronary syndrome has recently shown that alirocumab significantly reduces cardiovascular events compared with placebo, and may provide further information about the association of both Lp(a) and LDL-C-lowering with the risk of MACE [23].

In summary, we observed that compared with placebo or ezetimibe, treatment with alirocumab significantly reduced Lp(a) levels and although the reduction from baseline in absolute terms was small, there was an associated 12% lower risk of MACE per each 25% decrease in Lp(a) levels when adjusted by baseline characteristics. However, this association was no longer significant when reduction in Lp(a)-corrected LDL-C was accounted for; the mean reduction in LDL-C was ~52% in this population [7]. These results suggest that Lp(a) reduction with monoclonal antibodies to PCSK9 may add only modest additional cardiovascular benefit on top of LDL-C-lowering in a population with otherwise “normal” average baseline Lp(a) levels when the treatment produces only modest absolute reductions in Lp(a) but large reductions in LDL-C. Patients' baseline Lp(a) levels may provide insight into expected cardiovascular outcomes; those with higher baseline levels may derive significant benefit. Reducing the risk of MACE by targeting Lp(a)

may require more potent therapies which reduce Lp(a) to a greater degree [39] and/or higher initial Lp(a) levels; both of these approaches are likely to offer greater absolute reductions in Lp(a), which is consistent with genetic studies [4].

Conflicts of interest

Prof. Ray acknowledges support from the NIHR Imperial Biomedical Research Centre, and has received significant research grants from Pfizer, Inc., Amgen, Sanofi, Regeneron Pharmaceuticals, Inc., and MSD Pharma outside of the submitted work; modest honoraria from Cipla, Algorithm, Sanofi, Amgen, Boehringer Ingelheim, Takeda, and Pfizer Inc.; and modest consultant/advisory board fees from Takeda, MedCo, AstraZeneca, Resverlogix, Kowa, AbbVie, Eli Lilly, Sanofi, Amgen, Boehringer Ingelheim, Esperion, Cerenis, Akcea, and Regeneron Pharmaceuticals, Inc.

Dr Vallejo-Vaz is involved in a research project funded by grants from Amgen, Sanofi, MSD, and Pfizer to the European Atherosclerosis Society/Imperial College London, outside of the submitted work; and has received honoraria for lectures from Amgen, Mylan and Akcea, and non-financial support from Regeneron Pharmaceuticals, Inc., outside of the submitted work.

Dr Ginsberg has received significant research grants from Merck, Sanofi, Regeneron Pharmaceuticals, Inc., and Amgen; and modest consultant/advisory board fees from Amarin, Amgen, AstraZeneca, Bristol- Myers Squibb, GlaxoSmithKline, Ionis, Janssen, Kowa, Merck, Novartis, Sanofi, Regeneron Pharmaceuticals, Inc., and Pfizer, Inc.

Dr Davidson has received significant speaker bureau fees from Sanofi, Regeneron Pharmaceuticals, Inc., and Amgen; significant honoraria from Sanofi, Regeneron Pharmaceuticals, Inc., and Amgen; and modest consultant/advisory board fees from Sanofi, Regeneron Pharmaceuticals, Inc., and Amgen.

Dr Louie is an employee of and shareholder in Regeneron Pharmaceuticals, Inc.

Dr Bujas-Bobanovic and Dr Minini are employees of and shareholders in Sanofi.

Dr Eckel has received modest consultant/advisory board fees from Novo Nordisk; and significant consultant/advisory board fees from Regeneron Pharmaceuticals, Inc. and Sanofi.

Dr Cannon has received significant research grants from Amgen, BoehringerIngelheim, Bristol-Myers Squibb, Daiichi Sankyo, Janssen, and Merck; and consultant fees from Alnylam, Amarin, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Eisai, Janssen, Kowa, Merck, Pfizer, Inc., Regeneron Pharmaceuticals, Inc., and Sanofi.

Financial support

This analysis was funded by Sanofi and Regeneron Pharmaceuticals, Inc. The sponsors were involved in the study design, collection, analysis, and interpretation of data, as well as data checking of information provided in the manuscript. The authors were responsible for all content and editorial decisions, and received no honoraria related to the development of this publication.

Author contributions

KK Ray, AJ Vallejo-Vaz, HN Ginsberg, MH Davidson, MJ Louie, M Bujas-Bobanovic, RH Eckel, and CP Cannon contributed to the study concept, data analysis and interpretation, and in drafting the manuscript. P Minini was involved in statistical analysis and interpretation. All authors provided critical review of drafts and approved the final version for submission.

Acknowledgments

The authors thank the patients, their families, and all investigators involved in the ODYSSEY studies included in this analysis. The following people from the study sponsors provided editorial comments on the manuscript: Michael Howard, MBA, L. Veronica Lee, MD, and Corinne Hanotin, MD (Sanofi); and Robert Pordy, MD, Carol Hudson, MS, and Eva-Lynne Greene, MS (Regeneron Pharmaceuticals, Inc.). Additional statistical analysis was performed by Jonas Mandel and Alexia Letierce, Sanofi, France. Medical writing support under the direction of the authors was provided by Mark R. Vogel, MA, and Nila Bhana, MSc, of Prime (Knutsford, UK), supported by Sanofi and Regeneron Pharmaceuticals, Inc., according to Good Publication Practice guidelines (http://annals.org/aim/article/2424869/good-publication-practice-communicating-company-sponsored-medical-research-gpp3).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.06.896.

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