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Associations between lower levels of low-density lipoprotein cholesterol and cardiovascular events in very high-risk patients: Pooled analysis of nine ODYSSEY trials of alirocumab *versus* control

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HIGHLIGHTS

- Prior atherosclerotic cardiovascular disease (ASCVD) puts patients at high risk.
- Comorbidities such as diabetes/chronic kidney/polyvascular disease increase risk.
- Alirocumab reduces LDL-C by a similar amount in ASCVD with/without comorbidities.
- Per 39 mg/dL lower LDL-C, risk reduced by 30–35% with comorbidities *vs.* 9% without.
- Absolute benefit from lower LDL-C with alirocumab greatest for ASCVD + comorbidities.

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ABSTRACT

Background and aims: Guidelines recommend high-intensity statins for patients with atherosclerotic cardiovascular disease (ASCVD). Subgroups with comorbidities that increase cardiovascular risk, such as diabetes mellitus (DM), chronic kidney disease (CKD) or polyvascular disease (PoVD), may derive greater absolute benefit from addition of non-statin therapies. We assessed the relationship between lower low-density lipoprotein cholesterol (LDL-C) and major adverse cardiovascular events (MACE) risk reduction during alirocumab phase III ODYSSEY trials among these subgroups.

Methods: Patient data were pooled from nine trials comparing alirocumab with control (placebo/ezetimibe), predominantly on background maximally tolerated statin. Patients with baseline ASCVD were stratified into subgroups with DM, CKD or PoVD, or without comorbidities, and between-group relative and absolute benefits were compared.

Results: Among 3505 patients with ASCVD, 1573 had no comorbidities, 981 had DM, 660 had CKD and 943 had PoVD, with overlap between comorbidities; mean baseline LDL-C levels were 119 (ASCVD overall), 123, 117, 114 and 113 mg/dL, respectively. Overall, each 39 mg/dL lower on-study LDL-C was associated with a 25% lower MACE risk, hazard ratio 0.75 (95% confidence interval, 0.62–0.90, $p = 0.0023$), with a similar lower risk observed in each very high-risk subgroup (DM, CKD or PoVD; 30–35%) but not in the subgroup without these comorbidities (9%). Absolute benefits were greater for very high-risk subgroups; lowering LDL-C from 120 to

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40 mg/dL would result in 2.76–4.35 fewer MACE/100 patient-years *versus* 0.3 for no comorbidities.
Conclusions: Among patients with ASCVD and mean baseline LDL-C > 100 mg/dL, patients with DM, CKD or PoVD appeared to derive greater absolute cardiovascular benefits from further LDL-C reduction than those without.

1. Introduction

Statins are first-line therapy in patients with atherosclerotic cardiovascular disease (ASCVD) for the secondary prevention of additional ASCVD events [1]. Among patients with ASCVD, event rates vary considerably [2,3] and it is now recognised that the total cardiovascular (CV) risk is markedly higher among individuals with ASCVD and concomitant high-risk phenotypes such as diabetes mellitus (DM), chronic kidney disease (CKD) and polyvascular disease (PoVD) [4,5].

The 2016 American College of Cardiology (ACC) decision pathway and the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Task Force specifically identified the presence of these comorbidities as scenarios in which the addition of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor could be considered if low-density lipoprotein cholesterol (LDL-C) levels were high despite maximally tolerated statin therapy [6,7]. Furthermore, the 2018 ACC/American Heart Association (AHA) Cholesterol Guideline provides specific recommendations for the management of patients in the newly defined "very high risk of ASCVD" category, including those with a history of multiple major ASCVD events, or one major ASCVD event and multiple high-risk conditions; these guidelines state that it is reasonable to add a PCSK9 inhibitor on top of ezetimibe and maximally tolerated statin therapy when LDL-C remains ≥70 mg/dL [1].

In the recently completed CV outcomes trial, ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), in 18 924 patients with recent acute coronary syndrome (ACS), the PCSK9 inhibitor alirocumab significantly reduced CV events relative to placebo [8]. However, as of yet, subanalyses of high-risk subgroups from this study are not available. In this *post-hoc* analysis of patient data from nine ODYSSEY trials of alirocumab, we investigated the relationship between lower on-study LDL-C and major adverse cardiovascular events (MACE) in high-risk patients with ASCVD, considered to be at very high risk due to the presence of comorbid conditions such as DM, CKD or PoVD, to validate the 2016 ACC decision pathway, the ESC/EAS Task Force statement and the 2018 ACC/AHA cholesterol treatment guideline [1,6,7].

2. Materials and methods

2.1. Study design and patient populations

This *post-hoc* analysis pooled data for patients enrolled in nine phase III ODYSSEY trials (for trial names and identifiers, see Table 1). Trial designs (for overview see Supplementary Table 1) and primary results have been reported previously [9–15]. Briefly, the nine trials recruited individuals aged ≥18 years with hypercholesterolaemia and established coronary heart disease (CHD) or CHD-risk equivalents, and/or heterozygous familial hypercholesterolaemia or other CV risk factors. At screening, most patients were receiving maximally tolerated statin therapy with or without other lipid-lowering therapy, except for one trial in which patients with statin intolerance received no background statin therapy (see Supplementary Table 1). Patients were randomised in a 1:1 or 2:1 ratio (depending on the study) to subcutaneous alirocumab or control (placebo or ezetimibe) for double-blind treatment periods of 24–104 weeks. Seven trials used an alirocumab dose of 75 mg every 2 weeks (Q2W), which was adjusted to 150 mg Q2W at Week 12 if predefined LDL-C levels were not achieved by Week 8; in two trials, only alirocumab 150 mg Q2W was used. LDL-C levels at baseline and at 4-week intervals up to Week 16, then at Weeks 24, 36, 52, 64, 78, 88 and 104 were calculated using the Friedewald equation [16]. In cases in which triglycerides were > 400 mg/dL, LDL-C was determined by beta-quantification. However, these values were not included in this analysis. All study protocols were approved by the corresponding local independent review board and enrolled individuals provided written informed consent prior to study treatment in each trial.

Only patients with ASCVD, defined as CHD, ischaemic stroke or peripheral arterial disease, were included in this analysis; these patients had been included in the ODYSSEY trials if their baseline LDL-C was ≥70 mg/dL at screening. Regardless of study treatment, alirocumab or control (placebo or ezetimibe), patients with ASCVD were further stratified by the presence or absence of additional high-risk comorbidities: those without DM, CKD or PoVD were the high-risk ASCVD and no comorbidities group, and very high-risk patients were categorised into subgroups with DM (ASCVD + DM), CKD (ASCVD + CKD) or PoVD (ASCVD + PoVD). DM was defined based on careful review of medical history, CKD was defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 and PoVD was defined as a history of multiple CV events in a single bed (separated by ≥ 30 days) or multiple affected vascular beds (irrespective of the time the event occurred). Note that the ODYSSEY trials excluded patients with eGFR < 30 mL/min/1.73 m^2. Patients could have several of these comorbidities and subgroups are not mutually exclusive (Supplementary Fig. 1).

2.2. Statistical analysis

2.2.1. Baseline characteristics

Baseline patient data are presented in the safety population (all patients who were randomised and received at least one dose of study treatment) stratified by treatment (alirocumab) and the control comparator in each of the individual studies (placebo or ezetimibe) for the overall high-risk population and the very high-risk subgroups. For all continuous baseline variables, values are presented as means and standard deviations (SD), or median and interquartile range for baseline variables that are not normally distributed.

2.2.2. Low-density lipoprotein cholesterol

Changes in on-study LDL-C levels were assessed in each very high-risk subgroup of the pooled ASCVD population stratified by treatment allocation, alirocumab or control (placebo or ezetimibe). Patient data were pooled from the safety population of the nine ODYSSEY trials, which included all randomised patients who received at least one dose or partial dose of study treatment.

Average LDL-C during the study or percentage reductions in LDL-C from baseline were determined from the area under the curve (using the trapezoidal method), incorporating all LDL-C values up to the end of the treatment-emergent adverse event period (last injection of study treatment + 10 weeks) or first occurrence of MACE, whichever event occurred first. Patients had a median of nine (5–11 depending on the study and duration) LDL-C measures; the majority of LDL-C measurements (97.3%) were on-treatment with a small proportion (2.7%) during the post-treatment period (as MACE were assessed until the end of study, including the 10 weeks after last injection, the area under the curve included all available LDL-C values assessed during the same period of time).

2.2.3. Low-density lipoprotein cholesterol and risk of MACE

As per the primary endpoint of the ODYSSEY OUTCOMES study [8],

Table 1
Baseline characteristics of patients pooled by ASCVD and stratified by high-/very high-risk status from nine ODYSSEY trials (safety population); control = placebo/ezetimibe.

	ASCVD (N = 3505)		ASCVD + DM (n = 981)		ASCVD + CKD (n = 660)		ASCVD + PoVD (n = 943)		ASCVD + no comorbidities[a] (n = 1573)	
	Alirocumab (n = 2262)	Control (n = 1243)	Alirocumab (n = 636)	Control (n = 345)	Alirocumab (n = 446)	Control (n = 214)	Alirocumab (n = 602)	Control (n = 341)	Alirocumab (n = 1009)	Control (n = 564)
Age, years, mean ± SD	61.7 ± 9.8	61.8 ± 9.6	63.8 ± 8.9	62.9 ± 9.2	67.5 ± 8.8	68.1 ± 9.0	62.7 ± 9.6	63.1 ± 9.5	59.2 ± 9.7	59.6 ± 9.4
Male, n (%)	1550 (68.5)	841 (67.7)	413 (64.9)	219 (63.5)	271 (60.8)	126 (58.9)	446 (74.1)	247 (72.4)	709 (70.3)	382 (67.7)
Race, White, n (%)	2063 (91.2)	1139 (91.6)	541 (85.1)	294 (85.2)	417 (93.5)	195 (91.1)	550 (91.4)	313 (91.8)	946 (93.8)	531 (94.1)
BMI, kg/m^2, mean ± SD	30.1 ± 5.4	30.3 ± 5.3	32.0 ± 6.0	32.4 ± 5.7	30.5 ± 5.4	30.5 ± 5.6	30.0 ± 5.3	29.6 ± 4.8	29.1 ± 4.9	29.6 ± 5.2
HeFH, n (%)	385 (17.0)	216 (17.4)	47 (7.4)	37 (10.7)	51 (11.4)	24 (11.2)	99 (16.4)	42 (12.3)	228 (22.6)	135 (23.9)
DM, n (%)	637 (28.2)	346 (27.8)	636 (100.0)	345 (100.0)	158 (35.4)	79 (36.9)	181 (30.1)	95 (27.9)	0 (0.0)	0 (0.0)
ASCVD, n (%)[b]										
CHD	2061 (91.1)	1154 (92.8)	568 (89.3)	309 (89.6)	405 (90.8)	196 (91.6)	581 (96.5)	329 (96.5)	910 (90.2)	519 (92.0)
Ischaemic stroke/TIA	266 (11.8)	128 (10.3)	88 (13.8)	40 (11.6)	66 (14.8)	31 (14.5)	137 (22.8)	74 (21.7)	65 (6.4)	35 (6.2)
PAD	130 (5.7)	74 (6.0)	50 (7.9)	29 (8.4)	29 (6.5)	18 (8.4)	76 (12.6)	47 (13.8)	34 (3.4)	12 (2.1)
eGFR, mL/min/1.73 m^2, mean ± SD	74.4 ± 18.0	74.9 ± 18.2	72.8 ± 20.4	73.3 ± 20.4	50.4 ± 7.4	50.0 ± 7.6	72.4 ± 18.1	73.0 ± 18.8	80.4 ± 13.8	79.8 ± 15.1
Baseline eGFR < 60 mL/min/1.73 m^2, n (%)	446 (19.7)	214 (17.2)	158 (24.8)	79 (22.9)	446 (100)	214 (100)	146 (24.3)	73 (21.4)	0	0
Current smoker, n (%)	447 (19.8)	254 (20.4)	115 (18.1)	64 (18.6)	57 (12.8)	28 (13.1)	120 (19.9)	79 (23.2)	223 (22.1)	118 (20.9)
Statin intensity n (%)[c]										
High	1298 (57.4)	716 (57.6)	324 (50.9)	179 (51.9)	233 (52.2)	122 (57.0)	356 (59.1)	197 (57.8)	608 (60.3)	342 (60.6)
Moderate	618 (27.3)	331 (26.6)	199 (31.3)	108 (31.3)	146 (32.7)	55 (25.7)	173 (28.7)	97 (28.4)	246 (24.4)	132 (23.4)
Low	273 (12.1)	140 (11.3)	90 (14.2)	46 (13.3)	57 (12.8)	29 (13.6)	65 (10.8)	38 (11.1)	113 (11.2)	58 (10.3)
No statins	73 (3.2)	54 (4.3)	23 (3.6)	12 (3.5)	10 (2.2)	8 (3.7)	8 (1.3)	9 (2.6)	42 (4.2)	30 (5.3)
Missing	0 (0.0)	2 (0.2)	0	0	0	0	0	0	0	2 (0.4)
LLT other than statin, n (%)[d]	677 (29.9)	387 (31.1)	166 (26.1)	87 (25.2)	138 (30.9)	67 (31.3)	193 (32.1)	95 (27.9)	310 (30.7)	192 (34.0)
Baseline LDL-C, mg/dL, mean ± SD	118.9 ± 42.1	119.4 ± 45.6	113.7 ± 36.2	114.8 ± 43.5	111.7 ± 36.2	114.3 ± 47.1	115.5 ± 37.7	117.7 ± 41.8	123.7 ± 47.1	122.7 ± 46.8

Pooled data of all randomised subjects in nine phase III ODYSSEY trials, including five placebo-controlled trials: COMBO I, NCT01644175; LONG TERM, NCT01507831; HIGH FH, NCT01617655; FH I, NCT01623115; and FH II, NCT01709500; and four ezetimibe-controlled trials: COMBO II, NCT01644188; ALTERNATIVE, NCT01709513; OPTIONS I, NCT01730040; and OPTIONS II, NCT01730053.
ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CHD, coronary heart disease; CKD, chronic kidney disease, defined as eGFR < 60 mL/min/1.73 m^2; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; PAD, peripheral artery disease; PoVD, polyvascular disease, defined as a history of multiple cardiovascular events in a single bed (separated by ≥ 30 days) or ≥1 affected peripheral vascular bed (irrespective of the time the event occurred) in which peripheral vascular bed includes PAD, intermittent claudication (linked to PAD), revascularisation procedure or surgery, critical limb ischaemia or thrombolysis for PAD; SD, standard deviation; TIA, transient ischaemic attack.

[a] No DM, CKD or PoVD.

[b] Patients may be counted in ≥1 category.

[c] High: atorvastatin 40–80 mg, rosuvastatin 20–40 mg or simvastatin 80 mg; moderate: atorvastatin 20 to < 40 mg, rosuvastatin 10 to < 20 mg or simvastatin 40 to < 80 mg; low: atorvastatin < 20 mg, rosuvastatin < 10 mg or simvastatin < 40 mg.

[d] In combination with statins or not.

MACE were defined as CHD death, nonfatal myocardial infarction, ischaemic stroke or diagnosis of unstable angina (limited to events with evidence of ischaemia and fulfilling additional severity criteria, requiring hospitalisation or emergency room visit until at least the following day); all CV events were adjudicated by a central Clinical Events Committee [3,12].

Regardless of study treatment, alirocumab or control (placebo/ezetimibe), the relationship between LDL-C and MACE during the study

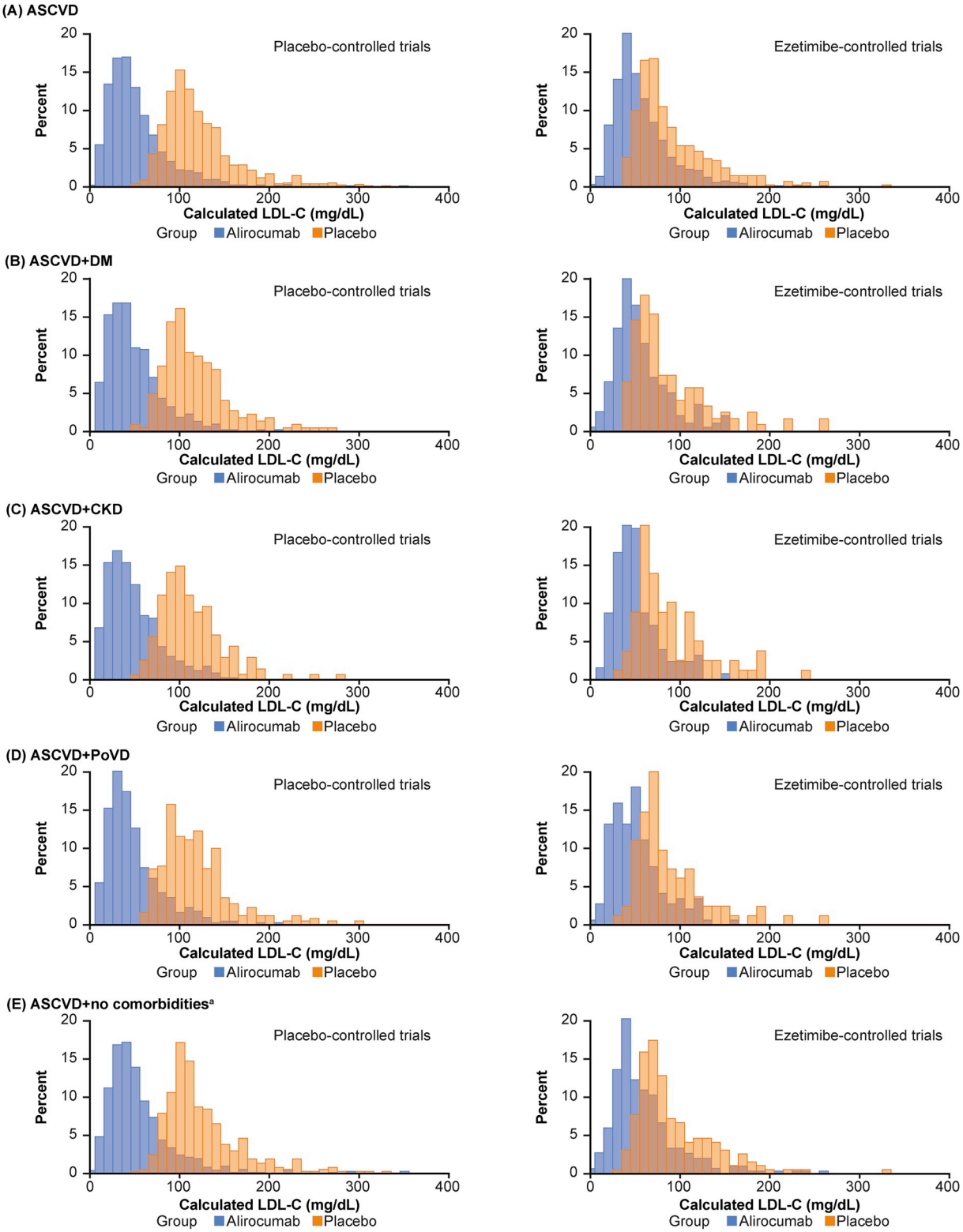

Fig. 1. Average achieved on-study LDL-C levels in patients with (A) ASCVD and (B–E) in high-/very high-risk subgroups in pools according to control (placebo or ezetimibe).

[a]No DM, CKD or PoVD. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease, defined as eGFR < 60 mL/min/1.73 m^2; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; PoVD, polyvascular disease.

period was assessed by average lower achieved (per 39 mg/dL) on-study LDL-C and percentage (per 50%) reduction in LDL-C from baseline for each high-/very high-risk subgroup. The relationship between on-study LDL-C and the composite of MACE endpoints was assessed by stratified analyses using a multivariate Cox regression model with adjustment for differences in baseline characteristics (including age, gender, DM, CKD, PoVD, prior history of myocardial infarction or ischaemic stroke, baseline LDL-C and smoking status), as previously specified by Wiviott et al. [17], with the exception that for each subgroup the associated variable was not adjusted for, e.g., for the ASCVD + DM subgroup, adjustment for DM was not included but adjustment for PoVD and CKD were. The risk of MACE was assessed for every 39 mg/dL lower mean on-study LDL-C, and hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to enable comparison with the Cholesterol Treatment Trialists (CTT) Collaboration meta-regression line [18].

Adjusted rates of MACE and associated 95% CIs were also determined from a multivariate Poisson model adjusted for baseline characteristics and average on-study LDL-C, and depicted graphically as a function of average on-study LDL-C levels or average percentage reduction during the study. Analyses were generated using SAS version 9.4, and all tests and CIs were two-sided.

2.2.4. Safety assessments

Treatment-emergent adverse events, defined as those which occurred during the period from the first dose of study treatment up to 70 days after the last injection, were summarised using descriptive statistics. The safety analysis compared the occurrence of events (incidence rate) in patients with ASCVD and each very high-risk subgroup randomised to receive alirocumab or control (placebo or ezetimibe).

3. Results

3.1. Baseline characteristics

A total of 4880 patients were randomised in the nine ODYSSEY trials (Supplementary Table 1), among whom 72% (n = 3505) had a history of ASCVD (Table 1). Within this pooled cohort of patients with ASCVD, 28% had DM, 19% CKD and 27% PoVD. The overlap between comorbidities is shown in Supplementary Fig. 1. Overall, 2262 patients with ASCVD were randomised to alirocumab and 1243 to control. Baseline characteristics of patients in the overall ASCVD cohort were similar between the alirocumab and control groups; this was also seen for the very high-risk subgroups (Table 1).

3.2. Percentage change from baseline in LDL-C levels

Mean baseline LDL-C levels were generally similar among the alirocumab and control groups for the overall pooled ASCVD population (118.9 and 119.4 mg/dL, respectively), each very high-risk subgroup (range 111.7–117.7 mg/dL), and the subgroups with ASCVD + no comorbidities (123.7 and 122.7 mg/dL; Table 1). During the studies, average LDL-C levels were markedly lower with alirocumab than placebo or ezetimibe in the overall ASCVD population (Fig. 1A) and for each subgroup: ASCVD + DM (Fig. 1B), ASCVD + CKD (Fig. 1C), ASCVD + PoVD (Fig. 1D) and ASCVD + no comorbidities (Fig. 1E). Average LDL-C levels during study for the overall ASCVD population and for each subgroup (ASCVD + DM, ASCVD + CKD, ASCVD + PoVD and ASCVD + no comorbidities) are shown in Table 2.

In the overall ASCVD population, mean percentage change from baseline in average LDL-C during the study period was significantly lower with alirocumab than control, placebo (−57.4% *vs.* 2.2%) or ezetimibe (−49.9% *vs.* −17.2%). This was also seen in the ASCVD + no comorbidities subgroup with alirocumab *versus* control (placebo or ezetimibe), and for each very high-risk subgroup: ASCVD + DM, ASCVD + CKD and ASCVD + PoVD (Table 2).

3.3. Association between on-study LDL-C levels and MACE

Among the overall pooled population of 3505 patients with ASCVD treated with alirocumab or control, representing 6699 patient-years of exposure, there were a total of 100 first MACE (median time to first

Table 2
Relationship between MACE incidence rate, average achieved LDL-C and percentage change from baseline during the study period in patients with ASCVD, with or without other cardiovascular risk factors (safety population).

	Placebo-controlled trials (n = 2445)		Ezetimibe-controlled trials (n = 1060)		Pool of patients (N = 3505)			
On-study LDL-C	Alirocumab (n = 1611)	Placebo (n = 834)	Alirocumab (n = 651)	Ezetimibe (n = 409)	Category (reduction)	n	HR (95% CI)	*p* value
ASCVD overall								
Achieved, mean (SD), mg/dL	51.3 (35.0)	121.4 (42.5)	57.6 (34.1)	90.8 (43.6)	Per 39 mg/dL	3503	0.75 (0.62–0.90)	0.0023
Change, mean (SD), %	−57.4 (22.8)	2.2 (27.4)	−49.9 (23.3)	−17.2 (33.0)	Per 50%	3503	0.71 (0.57–0.88)	0.0023
ASCVD + DM, n	437	222	199	123				
Achieved, mean (SD), mg/dL	48.7 (30.3)	117.9 (37.7)	55.7 (30.1)	87.5 (44.2)	Per 39 mg/dL	980	0.65 (0.49–0.87)	0.0034
Change, mean (SD), %	−56.7 (24.3)	2.8 (27.1)	−48.2 (27.4)	−15.6 (34.6)	Per 50%	980	0.63 (0.43–0.92)	0.0167
ASCVD + CKD, n	320	135	126	79				
Achieved, mean (SD), mg/dL	49.3 (30.3)	115.1 (45.7)	51.4 (26.1)	89.0 (40.8)	Per 39 mg/dL	660	0.70 (0.48–1.01)	0.0571
Change, mean (SD), %	−56.6 (23.5)	0.5 (23.8)	−50.5 (21.5)	−15.7 (26.2)	Per 50%	660	0.68 (0.42–1.09)	0.1075
ASCVD + PoVD, n	458	260	144	81				
Achieved, mean (SD), mg/dL	48.0 (30.3)	116.7 (38.5)	51.9 (28.7)	89.3 (41.3)	Per 39 mg/dL	943	0.70 (0.49–1.00)	0.0516
Change, mean (SD), %	−59.1 (21.7)	1.1 (21.4)	−52.2 (22.6)	−22.3 (17.9)	Per 50%	943	0.66 (0.43–1.02)	0.0597
ASCVD + no comorbidities, n	706	368	303	409				
Achieved, mean (SD), mg/dL	54.4 (40.1)	125.5 (44.4)	61.7 (38.8)	93.0 (43.7)	Per 39 mg/dL	1572	0.91 (0.65–1.29)	0.5995
Change, mean (SD), %	−56.9 (22.7)	3.0 (32.3)	−49.6 (21.6)	−16.8 (36.5)	Per 50%	1572	0.80 (0.52–1.21)	0.2864

n = number of patients. HR, 95% CI and *p* value determined from a multivariate Cox model adjusted for baseline characteristics. Average LDL-C and percentage change from baseline during the study period (double-blind treatment period plus up to 10-week follow-up period) were determined from the area under the curve (using trapezoidal method), including all values up to the end of the study period or occurrence of MACE, whichever came first. For patients with no post-baseline LDL-C, baseline LDL-C data were used; two patients with missing baseline LDL-C data were excluded from the multivariate analysis.
ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease, defined as eGFR < 60 mL/min/1.73 m^2; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MI, myocardial infarction; PAD, peripheral artery disease; PoVD, polyvascular disease, defined as a history of multiple cardiovascular events in a single bed (separated by ≥ 30 days) or ≥1 affected peripheral vascular bed (irrespective of the time the event occurred) in which peripheral vascular bed includes PAD, intermittent claudication (linked to PAD), revascularisation procedure or surgery, critical limb ischaemia or thrombolysis for PAD; SD, standard deviation.

event was 36 weeks), including 16 CHD deaths, 45 non-fatal myocardial infarctions, 16 non-fatal ischaemic strokes and three episodes of unstable angina.

For the overall ASCVD cohort, for those with ASCVD and no comorbidities, and in the very high-risk subgroups, average on-study LDL-C correlated with the rate of MACE (Fig. 2). For the overall cohort, a 39 mg/dL lower achieved LDL-C level was associated with a 25% lower risk of MACE, HR 0.75 (95% CI 0.62–0.90, $p = 0.0023$), with a similar trend seen in all three very high-risk ASCVD subgroups (Fig. 3): DM, HR 0.65 (95% CI 0.49–0.87, $p = 0.0034$); CKD, HR 0.70 (95% CI 0.48–1.01, $p = 0.0571$) or PoVD, HR 0.70 (95% CI 0.49–1.00, $p = 0.0516$). By contrast, for the subgroup of patients with ASCVD and no comorbidities, the strength of association per 39 mg/dL lower on-study LDL-C and MACE was more modest (HR 0.91, 95% CI 0.65–1.29, $p = 0.5995$).

The relationship between MACE, baseline variables and average achieved LDL-C during the study in patients with ASCVD is shown in Supplementary Table 2; DM and CKD were significant factors associated with MACE. For each very high-risk subgroup, there were no baseline characteristics significantly associated with MACE, except for CKD and LDL-C for the subgroup ASCVD + PoVD (data not shown).

3.4. Percentage reduction in LDL-C and MACE

In the overall population of patients with ASCVD, average percentage reduction in LDL-C was significantly inversely correlated with the incidence rate of first MACE (HR 0.71, 95% CI 0.57–0.88 per 50% reduction in LDL-C, $p = 0.0023$; Table 2), with diabetes and CKD the only baseline characteristics significantly associated with MACE (Supplementary Table 3). Likewise, in patients with ASCVD + DM, there was a significant association between 50% reduction in LDL-C and MACE incidence rate (HR 0.63, 95% CI 0.43–0.92, $p = 0.0167$; Table 2). Associations between average percentage reduction in LDL-C and incidence of first MACE were not statistically significant for the other subgroups (Table 2).

3.5. Safety

The safety profile of alirocumab in patients with ASCVD was similar to that seen with control (placebo or ezetimibe), except for a higher rate of injection-site reactions in alirocumab-treated patients (Supplementary Table 4). Nevertheless, injection-site reactions tended to be mild in intensity and transient. The safety profile was also similar between alirocumab and control in the very high-risk subgroups (Supplementary Table 4).

4. Discussion

Recent consensus statements and guideline updates specifically identified the presence of high-risk comorbidities as scenarios in which the addition of a PCSK9 inhibitor should be considered if LDL-C levels remain high despite maximally tolerated statin therapy [1,6,7]. The present *post-hoc* analysis of nine ODYSSEY phase III trials of alirocumab *versus* control (predominantly on background statin therapy) provides support for these recommendations by showing that, within a relatively short-time frame, these very high-risk patient groups have a lower risk of MACE with lower achieved LDL-C.

Among patients with ASCVD, each 39 mg/dL lower on-study LDL-C was associated with a 25% lower risk of MACE with no evidence of heterogeneity across very high-risk subgroups. Almost 30% of patients with ASCVD in the population analysed had DM. Among this very high-risk subgroup, absolute rates of MACE over 100 patient-years varied from 4.70 among those with an LDL-C of 120 mg/dL (mostly representing patients on statins only) to 1.94 among those with an LDL-C of 40 mg/dL (mostly patients on statins and alirocumab), representing an absolute difference in risk of 2.76 per 100 patient-years. The data lend support to the American Association of Clinical Endocrinologists/American College of Endocrinology [19] guidelines which define subjects with DM and ASCVD as at extreme risk and recommend LDL-C targets of < 55 mg/dL. Furthermore, in the IMPROVE-IT trial of ezetimibe added to statin therapy in patients with hypercholesterolaemia and ACS, the CV benefit of incremental lowering of LDL-C was more pronounced in absolute and relative terms among patients with DM

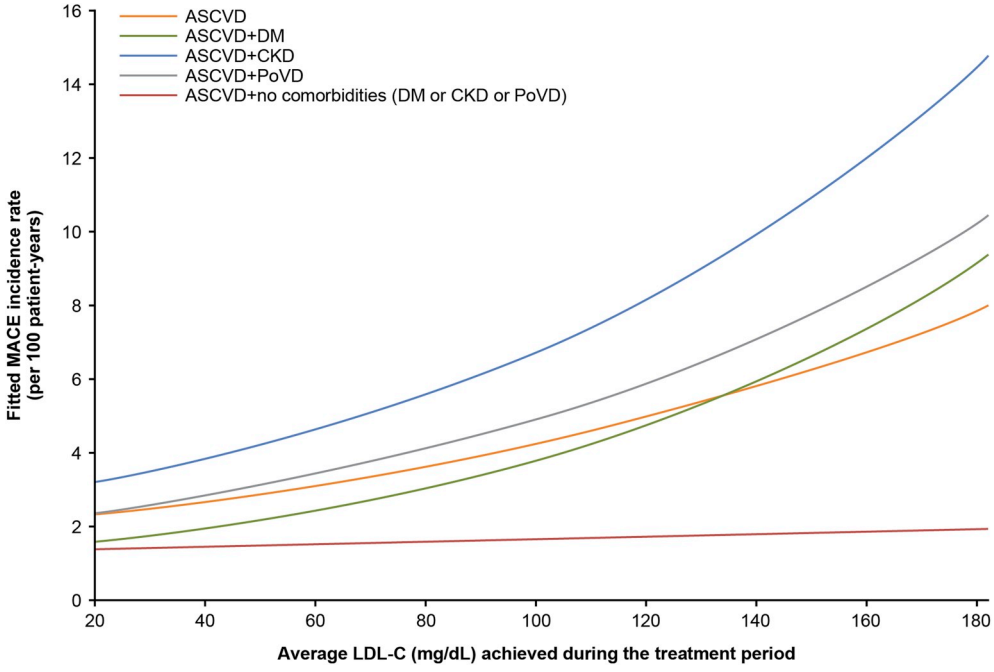

Fig. 2. Adjusted MACE incidence rate per 100 patient-years by average achieved on-study LDL-C levels in patients with ASCVD, with and without comorbidities: multivariate analysis adjusted on baseline characteristics (safety population).
Incidence rate (the number of patients having at least one new MACE event per 100 patient-years) determined from a multivariate Poisson model, with adjustment for age, gender, diabetes (except for the ASCVD + DM and the ASCVD + no comorbidities subgroups), CKD (except for the ASCVD + CKD and the ASCVD + no comorbidities subgroups), PoVD (except for the ASCVD + PoVD and the ASCVD + no comorbidities subgroups), prior history of MI or stroke, baseline LDL-C and smoking status. Average LDL-C during the study period was determined from the area under the curve (using trapezoidal method), taking into account all LDL-C values up to the end of the study period or occurrence of MACE, whichever came first. For patients with no post-baseline LDL-C, LDL-C at baseline was used; two patients with missing baseline LDL-C were excluded from the multivariate analysis. ASCVD, atherosclerotic vascular disease; CKD, chronic kidney disease, defined as eGFR < 60 mL/min/1.73 m^2; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; MI, myocardial infarction; PoVD, polyvascular disease.

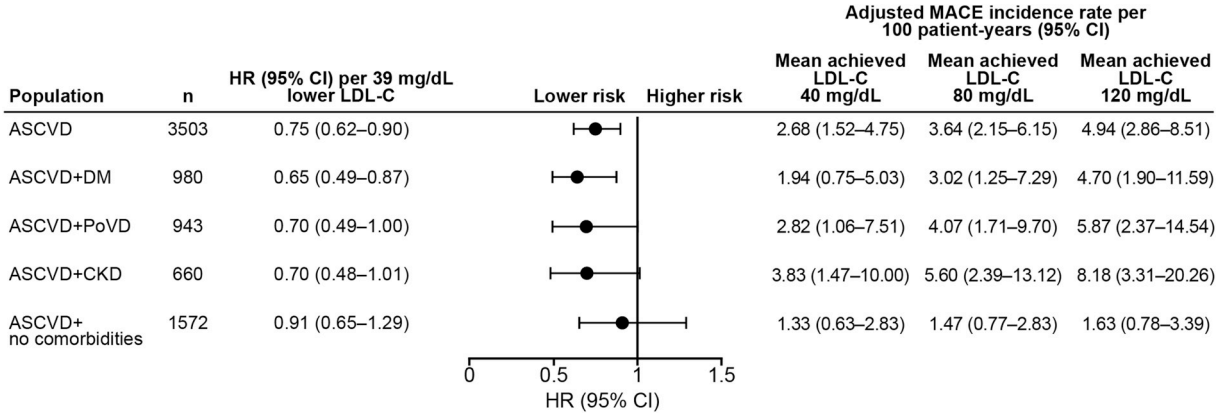

Fig. 3. Relationship between MACE incidence rate and each 39 mg/dL lower average LDL-C in high-/very high-risk ASCVD subgroups (safety population).
On the left side, HR calculated using Cox multivariable regression analysis, adjusted for age, gender, diabetes (except in the ASCVD + DM and the ASCVD + no comorbidities analysis), PoVD (except in the ASCVD + PoVD and the ASCVD + no comorbidities analysis), prior MI/stroke, baseline LDL-C and smoking. Adjusted rates of MACE obtained by a Poisson model adjusted for the same variables; rates are provided for a subject with averaged characteristics and different levels of LDL-C during the study period. ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease, defined as eGFR < 60 mL/min/1.73 m^2; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; MI, myocardial infarction; PoVD, polyvascular disease.

versus those without [20]. Further analysis of the same trial showed greater benefits among patients with PoVD [21]. These data are consistent with our hypothesis [2,22] that, among those with higher absolute risk and baseline LDL-C, there is higher absolute benefit even from therapies which provide only modest reductions in LDL-C, such as ezetimibe. Given that PCSK9 inhibitors provide greater percentage reductions in LDL-C, patients with higher baseline LDL-C should have even greater absolute reductions in LDL-C. As benefit is proportional to the duration of treatment and the absolute reduction in LDL-C, very high-risk subgroups with very high LDL-C should derive even greater benefits from a PCSK9 inhibitor than ezetimibe if assessed over the same time frame. This is supported by our findings when comparing on-study LDL-C levels of 40 and 80 mg/dL *versus* 120 mg/dL.

The REACH REGISTRY [5] identified those with PoVD as a group at particularly high risk of CV disease. More recently, data from prospective cohorts with prevalent vascular disease suggest that, even when achieving guideline-based control of blood pressure, LDL-C and lifestyle, these patients have the highest “residual risk”, suggesting that additional control of modifiable risk factors may be of benefit [2]. In the clinical outcomes trial of the PCSK9 inhibitor evolocumab (Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk [FOURIER]), patients with multivessel coronary artery disease were shown to be at higher baseline risk for major vascular events than those without and experienced greater absolute risk reductions from the same magnitude of LDL-C lowering [23]. In our analysis, among those with PoVD, absolute rates of MACE declined from a level of 5.87 at LDL-C of 120 mg/dL to 2.82 per 100 patients per year at 40 mg/dL, reflecting a risk difference of 3.05 fewer events per 100 patients per year with LDL-C 40 mg/dL *versus* 120 mg/dL.

The prevalence of CKD is increasing as patients age, and hypertension and diabetes increase in prevalence. The Study of Heart and Renal Protection (SHARP) trial demonstrated that the addition of ezetimibe to statin therapy reduced CV events *versus* placebo among patients with CKD [24]. These patients are often at the highest risk of CV events. The CTT meta-analysis of statin trials suggested that per 39 mg/dL LDL-C lowering there was a 23% (95% CI 0.72–0.83) lowering of risk among patients with eGFR < 60 mL/min/1.73 m^2 [18]. In our analysis, the patients with ASCVD and CKD appeared to have highest baseline risk; among this high-risk subgroup, lower on-study levels of LDL-C were associated with a lower rate of MACE. For instance, the incidence rate of MACE per 100 patient-years among those with an LDL-C 120 mg/dL was 8.18 and at 40 mg/dL it was 3.83, representing an absolute difference in rates of 4.35 per 100 patient-years.

In contrast to the above high-risk subgroups, patients with ASCVD without comorbidities appeared to derive smaller proportional benefits per 39 mg/dL lower on-study LDL-C (9%) and smaller absolute benefits from achievement of lower LDL-C levels. For instance, the rate of MACE was 1.63 events per 100 patient-years for LDL-C levels of 120 mg/dL *versus* 1.33 for those with an LDL-C of 40 mg/dL. Hence, in this analysis in patients with ASCVD without comorbidities, lowering LDL-C from 120 to 40 mg/dL would be expected to result in 0.3 fewer events/100 patient-years. By contrast, in patients with ASCVD with DM, CKD or PoVD, when LDL-C was lowered from 120 to 80 mg/dL, the absolute rate difference ranged from 1.68 to 2.58. When LDL-C was lowered further to 40 mg/dL, even greater differences were observed, ranging from 2.76 to 4.35.

The safety profiles of alirocumab and control were generally similar in patients with ASCVD and the very high-risk subgroups in this pooled analysis; consistent with the data observed in a previous larger study [12]. Given the cost differential of PCSK9 inhibitors to statins, the data support recommending PCSK9 inhibitors for individuals with very high risk and very high LDL-C despite maximally tolerated statin therapy [1,22].

The limitations of this study merit consideration. Of note, the limited treatment duration, as we know that the benefits of lipid lowering are about one-half in the first year as in subsequent years. Furthermore, the analyses are based on a small number of MACE (N = 100, with reduced numbers in the subgroups). Patients with severe CKD were excluded from the trials and it is not clear whether these findings can be extrapolated to more severe renal dysfunction. Nevertheless, the relationships between MACE and LDL-C levels in high-risk patients with ASCVD and very high-risk subgroups are consistent with those of the overall pooled population [3].

The *post-hoc* nature of this analysis means that these data are hypothesis generating for the benefits of greater reductions in LDL-C with alirocumab in very high-risk subgroups. However, the concept of greater absolute benefits and hence smaller numbers needed to treat has emerged from many subanalyses of the FOURIER trial [25,26]. In conclusion, the data support the notion that very high-risk patients with ASCVD and comorbidities, such as DM, CKD and PoVD, that increase CVD risk derive greater absolute benefits from achieving very low levels of LDL-C with alirocumab.

Conflicts of interest

All disclosures below relate to financial activities outside of the

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Michael H. Davidson: significant speaker's bureau fees from Amgen, Sanofi and Regeneron Pharmaceuticals, Inc.; significant honoraria from Amgen, Sanofi, and Regeneron Pharmaceuticals, Inc.; and consultant/advisory board fees from Amgen, Sanofi and Regeneron Pharmaceuticals, Inc.

Robert H. Eckel: modest consultant/advisory board fees from Merck, Kowa and Novo Nordisk; and significant consultant/advisory board fees from Regeneron Pharmaceuticals, Inc., and Sanofi.

Laurence Bessac, L. Veronica Lee and Alexia Letierce: employees of and shareholders in Sanofi.

Robert Pordy: employee of and shareholder in Regeneron Pharmaceuticals, Inc.

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Author contributions

AJ Vallejo-Vaz, KK Ray, HN Ginsberg, MH Davidson, RH Eckel, L. Veronica Lee, L Bessac, R Pordy and CP Cannon contributed to the study concept, data analysis and interpretation, and in drafting the manuscript. A. Letierce was involved in statistical analysis and interpretation. All authors provided critical review of drafts and approved the final version for submission.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.07.008.

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