ORIGINAL RESEARCH ARTICLE

Reductions in Atherogenic Lipids and Major Cardiovascular Events

A Pooled Analysis of 10 ODYSSEY Trials Comparing Alirocumab With Control

BACKGROUND: A continuous relationship between reductions in low-density lipoprotein cholesterol (LDL-C) and major adverse cardiovascular events (MACE) has been observed in statin and ezetimibe outcomes trials down to achieved levels of 54 mg/dL. However, it is uncertain whether this relationship extends to LDL-C levels <50 mg/dL. We assessed the relationship between additional LDL-C, non–high-density lipoprotein cholesterol, and apolipoprotein B100 reductions and MACE among patients within the ODYSSEY trials that compared alirocumab with controls (placebo/ezetimibe), mainly as add-on therapy to maximally tolerated statin.

METHODS: Data were pooled from 10 double-blind trials (6699 patient-years of follow-up). Randomization was to alirocumab 75/150 mg every 2 weeks or control for 24 to 104 weeks, added to background statin therapy in 8 trials. This analysis included 4974 patients (3182 taking alirocumab, 1174 taking placebo, 618 taking ezetimibe). In a post hoc analysis, the relationship between average on-treatment lipid levels and percent reductions in lipids from baseline were correlated with MACE (coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, or unstable angina requiring hospitalization) in multivariable analyses.

RESULTS: Overall, 33.1% of the pooled cohort achieved average LDL-C <50 mg/dL (44.7%–52.6% allocated to alirocumab, 6.5% allocated to ezetimibe, and 0% allocated to placebo). In total, 104 patients experienced MACE (median time to event, 36 weeks). For every 39 mg/dL lower achieved LDL-C, the risk of MACE appeared to be 24% lower (adjusted hazard ratio, 0.76; 95% confidence interval, 0.63–0.91; *P*=0.0025). Percent reductions in LDL-C from baseline were inversely correlated with MACE rates (hazard ratio, 0.71; 95% confidence interval, 0.57–0.89 per additional 50% reduction from baseline; *P*=0.003). Strengths of association materially similar to those described for LDL-C were observed with achieved non–high-density lipoprotein cholesterol and apolipoprotein B100 levels or percentage reductions.

CONCLUSIONS: In a post hoc analysis from 10 ODYSSEY trials, greater percentage reductions in LDL-C and lower on-treatment LDL-C were associated with a lower incidence of MACE, including very low levels of LDL-C (<50 mg/dL). These findings require further validation in the ongoing prospective ODYSSEY OUTCOMES trial.

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Clinical Perspective

What Is New?

- Cardiovascular benefits of statins and add-on lipid-lowering therapy extend only to low-density lipoprotein cholesterol (LDL-C) levels of ≈54 mg/dL. We investigated whether this relationship extends below 50 mg/dL using data from the ODYSSEY trials of alirocumab (proprotein convertase subtilisin/kexin type 9 monoclonal antibody) versus placebo/ezetimibe.
- About half of alirocumab-treated patients achieved LDL-C <50 mg/dL. For each 39 mg/dL lower achieved LDL-C, MACE incidence fell by 24%, and 50% reductions in LDL-C from baseline reduced MACE by 29%.
- Similar associations were observed with non–high-density lipoprotein cholesterol and apolipoprotein B achieved levels, percentage reductions, and MACE.
- Low LDL-C levels were not associated with excess treatment-emergent adverse events.

What Are the Clinical Implications?

- These analyses provide further reassurance about the safety and cardiovascular benefit of achieving even further reductions in LDL-C with alirocumab beyond what was previously achieved with statins and ezetimibe.
- Limitations include the low number of events (104), the limited duration of the studies (24–104 weeks), and the post hoc nature of this analysis.
- If the forthcoming outcomes trials of PCSK9 inhibitors such as alirocumab demonstrate additional reduction in MACE with further LDL-C reduction, then guideline committees may investigate lower LDL-C goals or a larger reduction in LDL-C from untreated baseline for those at highest risk of MACE.

Statins have been the cornerstone of global lipid modification guidelines for the prevention of major adverse cardiovascular events (MACE).[1] With accumulating evidence, each subsequent iteration of clinical guidelines has extended statin indications and recommended the achievement of progressively lower low-density lipoprotein cholesterol (LDL-C) goals[2–4] or, most recently, percentage reductions in LDL-C with the most potent statins.[5] Recently, the IMPROVE-IT trial (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) demonstrated that further reductions in LDL-C to a mean of 54 mg/dL with a nonstatin lipid-lowering therapy in statin-treated individuals provided additional reductions in MACE,[6] supporting the concept that lower LDL-C levels are better and consistent with observational data from several statin trials.[7–9]

Inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9) offer the prospect of achieving even lower LDL-C levels than ezetimibe when added to statins. Data from the phase 3 ODYSSEY trial program, in which average achieved LDL-C levels of <50 mg/dL were observed when alirocumab was added to statin therapy,[10–12] allow the exploration of changes in event rates at much lower LDL-C levels than previously analyzed.

In addition, percent reduction in LDL-C has been cited as being important in some guidelines,[5,13,14] and because patients in the ODYSSEY trials have already had their LDL-C reduced by 30% to 50% with statins, these trials allow us to explore the relationship between further percentage reductions in LDL-C and risk. Therefore, we assessed whether the relationship between LDL-C and risk extends to very low levels of LDL-C (<50 mg/dL) in the ODYSSEY trial program. We hypothesized that, among patients already receiving maximally tolerated statin therapy, both lower achieved LDL-C and greater percentage reductions from baseline would translate into lower rates of MACE. Furthermore, because many guidelines increasingly recommend non–high-density lipoprotein cholesterol (non–HDL-C) or apolipoprotein B100 (apoB) as potential alternatives to LDL-C for assessing the efficacy of lipid-lowering therapy, we provide similar analyses using these lipid parameters for comparison.[4,15,16]

METHODS

Patient Population

The phase 3 ODYSSEY trial designs have been reported previously.[6,11,12,17–22] Patients were enrolled if they had established atherosclerotic cardiovascular disease (ASCVD) or high cardiovascular risk such as heterozygous familial hypercholesterolemia with LDL-C inadequately controlled on their existing treatment (statin/other lipid-lowering therapy/diet). The main exclusion criteria were baseline LDL-C <70 mg/dL for those with ASCVD and very high risk and <100 mg/dL for high-risk patients without ASCVD at screening. Individuals with triglyceride levels >400 mg/dL were excluded (for further details on inclusion and exclusion criteria, see Table I in the online-only Data Supplement). For the present analysis, data were pooled from 10 phase 3 ODYSSEY trials (Figure I in the online-only Data Supplement). Patients were randomized to receive alirocumab or control (placebo or ezetimibe) with double-blind treatment periods of 24 to 104 weeks. Six of the 10 studies, representing ≈80% of the population, had a minimum study duration of 52 weeks. All study protocols were approved by the relevant local independent review boards, and all participating patients provided written informed consent.

Lipid Measurements

LDL-C was calculated with the Friedewald equation unless triglycerides were >400 mg/dL, when it was determined by β quantification. ApoB levels in serum were determined from immunonephelometry by a central laboratory (Medpace Reference Laboratories, Cincinnati, OH, and Leuven, Belgium, except for the LONG TERM study, which used Covance Central

Laboratories, Indianapolis, IN, and Geneva, Switzerland) and non–HDL-C via subtraction of HDL-C from total cholesterol.

MACE Definitions

MACE were defined as per the primary end point of the ODYSSEY OUTCOMES study[23]: coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, or unstable angina requiring hospitalization. Cardiovascular events were adjudicated by a central Clinical Events Committee[12] (The same committee is involved in the ODYSSEY OUTCOMES trial[23]). Unstable angina considered here was limited to those with definite evidence of the ischemic condition; that is a small proportion of unstable angina events qualified (see the definition of unstable angina in the online-only Data Supplement).

Statistical Analysis

Baseline Characteristics and Distribution of Lipid Parameters

Baseline data were pooled for all randomized patients and presented stratified according to whether the studies were placebo controlled or ezetimibe controlled. For continuous variables, the data are reported as mean and SD or median and interquartile range if they were not normally distributed. The distribution of LDL-C, non–HDL-C, and apoB levels at baseline and the average on-treatment levels or average percentage reductions in these parameters during the study treatment period are depicted graphically and analyzed with descriptive statistics comparing treatment groups (alirocumab versus placebo or versus ezetimibe).These include only patients in the safety population, that is patients who were randomized and received at least 1 dose or part of a dose of study treatment.

Lipid Changes and Risk of MACE

Regardless of treatment allocation, patients were pooled into 1 overall cohort, and the relationship between LDL-C and MACE during the treatment period was assessed with achieved LDL-C levels during treatment and percentage reductions in LDL-C from baseline. Average on-treatment LDL-C or the mean percentage reduction during the treatment period was determined from the area under the curve (using the trapezoidal method), taking into account all LDL-C values up to end of the treatment period or the occurrence of MACE, whichever came first.

The relation between on-treatment LDL-C and MACE was assessed with a multivariable Cox regression model with adjustment for age, sex, diabetes mellitus, history of myocardial infarction or stroke, baseline LDL-C, and smoking status, as previously published.[24] Hazard ratios (HRs) and 95% confidence intervals (CI) were calculated for every 39 mg/dL lower LDL-C to provide a comparison with the CTT (Cholesterol Treatment Trialists' Collaboration) meta-regression line.[25] Similar analyses were conducted for the percentage reduction in LDL-C from baseline and subsequent risk of MACE with HRs and 95% CIs expressed for each 50% reduction in LDL-C.

To assess the shape of association, the adjusted rates of MACE and associated 95% CIs were determined from a multivariate Poisson model and depicted graphically as a function of average LDL-C levels or average percentage reduction during

treatment. Instead of using all available lipid measurements (average LDL-C levels or reductions), we conducted sensitivity analyses with only LDL-C values and percentage reduction at week 4 and subsequent events after the exclusion of events that occurred before week 4. Last, analyses similar to those described above were conducted for non–HDL-C or apoB. All analyses were generated with SAS version 9.4, and all tests and CIs were 2 sided.

Safety Analysis

For safety, treatment-emergent adverse events (TEAEs) were defined as those events occurring from the first dose of study treatment up to 70 days after the last dose. The principal analyses compared randomized treatment with alirocumab and control. We also explored the strength of association between any TEAE and LDL-C levels or percentage reductions in LDL-C using multivariable logistic regression, after adjusting for the same covariates included in the MACE analyses. Data are reported as odds ratio and 95% CI per 39-mg/dL difference or 50% reduction in LDL-C. The shape of the association was also depicted graphically with adjusted TEAE rate and associated 95% CI plotted against average LDL-C levels or percentage LDL-C reductions derived from multivariate logistic regression models.

RESULTS

Baseline Characteristics

The baseline characteristics of individual studies are shown in Table II in the online-only Data Supplement, and the pooled summary of placebo and ezetimibe comparator trials is shown in Table 1. In the placebo-controlled trials, 2318 patients were treated with alirocumab and 1174 were treated with placebo; in the ezetimibe-controlled trials, 864 were treated with alirocumab and 618 were treated with ezetimibe. Hence, a total of 4974 patients were included in the lipid and MACE analyses described below. Overall, the average age was ≈60 years, with patients being mostly white and having an average body mass index of ≈30 kg/m². Approximately two thirds were male; one third had diabetes mellitus; two thirds had a history of ASCVD; and about one fifth were smokers. One third of participants in the placebo-controlled trials had heterozygous familial hypercholesterolemia.

Baseline Lipids

Baseline lipid values for individual studies are reported in Table III in the online-only Data Supplement. Pooled mean baseline LDL-C levels ranged from 123.2 to 126.8 mg/dL; non–HDL-C, between 154.2 and 156.9 mg/dL; and apoB, between 101.8 and 104.3 mg/dL (Table 1). As expected, the distribution of baseline lipids at randomization was fairly similar between the alirocumab and control groups (Figure II in the online-only Data Supplement).

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Table 1. Baseline Characteristics

	Placebo-Controlled Trials		Ezetimibe-Controlled Trials*	
	Alirocumab (n=2324)	Placebo (n=1175)	Alirocumab (n=864)	Ezetimibe (n=620)
Age, mean (SD), y	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/m²	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 mellitus, n (%)	699 (30.1)	355 (30.2)	283 (32.8)	192 (31.0)
ASCVD, n (%)†	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)
Statin intensity, n (%)				
High‡	1327 (57.1)	682 (58.0)	430 (49.8)	265 (42.7)
Moderate§	650 (28.0)	314 (26.7)	208 (24.1)	152 (24.5)
Low¶	344 (14.8)	177 (15.1)	47 (5.4)	27 (4.4)
No statins	0	0	178 (20.6)	176 (28.4)
Missing	3 (0.1)	2 (0.2)	1 (0.1)	0
Baseline lipids, mean (SD), mg/dL				
LDL-C	126.8 (46.3)	126.8 (44.8)	123.2 (51.5)	125.5 (56.9)
Non–HDL-C	155.7 (49.6)	155.5 (48.5)	154.2 (57.2)	156.9 (64.1)
ApoB	104.3 (29.0)	104.0 (28.5)	101.8 (30.7)	102.5 (32.2)

ApoB indicates apolipoprotein B100; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CHD, coronary heart disease; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; non–HDL-C, non–high-density lipoprotein cholesterol; PAD, peripheral artery disease, and TIA, transient ischemic attack. Pooled data of all randomized patients from the 10 trials included in this analysis.

*In combination with statins or not.
†Patients may be in >1 category.
‡Atorvastatin 40 to 80 mg, rosuvastatin 20 to 40 mg, or simvastatin 80 mg.
§Atorvastatin 20 to <40 mg, rosuvastatin 10 to <20 mg, or simvastatin 40 to <80 mg.
¶Atorvastatin <20 mg, rosuvastatin <10 mg, or simvastatin <40 mg.

Lipid Levels During Treatment

Figure 1 illustrates the distribution of different lipid parameters during treatment. The mean LDL-C levels achieved during treatment were as follows: in placebo-controlled studies, 56.9 and 126.5 mg/dL among those treated with alirocumab and placebo, and in ezetimibe-controlled studies, 64.0 and 100.9 mg/dL in those treated with alirocumab and ezetimibe, respectively (Table 2; individual trial data in Table IV in the online-only Data Supplement). Corresponding values for non–HDL-C and apoB are shown in Table 2. Similar results were obtained when week 4 achieved lipids were used instead of average levels throughout the entire study duration (Table V in the online-only Data Supplement).

Overall, 33.1% of patients achieved an average LDL-C <50 mg/dL during treatment. In placebo-controlled studies, 52.6% of alirocumab-treated and 0% of placebo-treated patients achieved LDL-C levels <50 mg/dL. In the ezetimibe-controlled studies, the corresponding figures were 44.7% for the alirocumab and 6.5% for the ezetimibe arm, respectively. Thus, when all patients were pooled, the overall distribution of each lipid parameter during treatment largely reflected the greater proportion of patients achieving very low levels of LDL-C, non–HDL-C, and apoB in the alirocumab group (Figure III in the online-only Data Supplement).

Percent Reductions in Lipids From Baseline

Figure 2 depicts the distribution of the average percentage change from baseline in LDL-C, non–HDL-C, and apoB during the trials. The average percentage change in LDL-C from baseline during treatment was –55.4% for
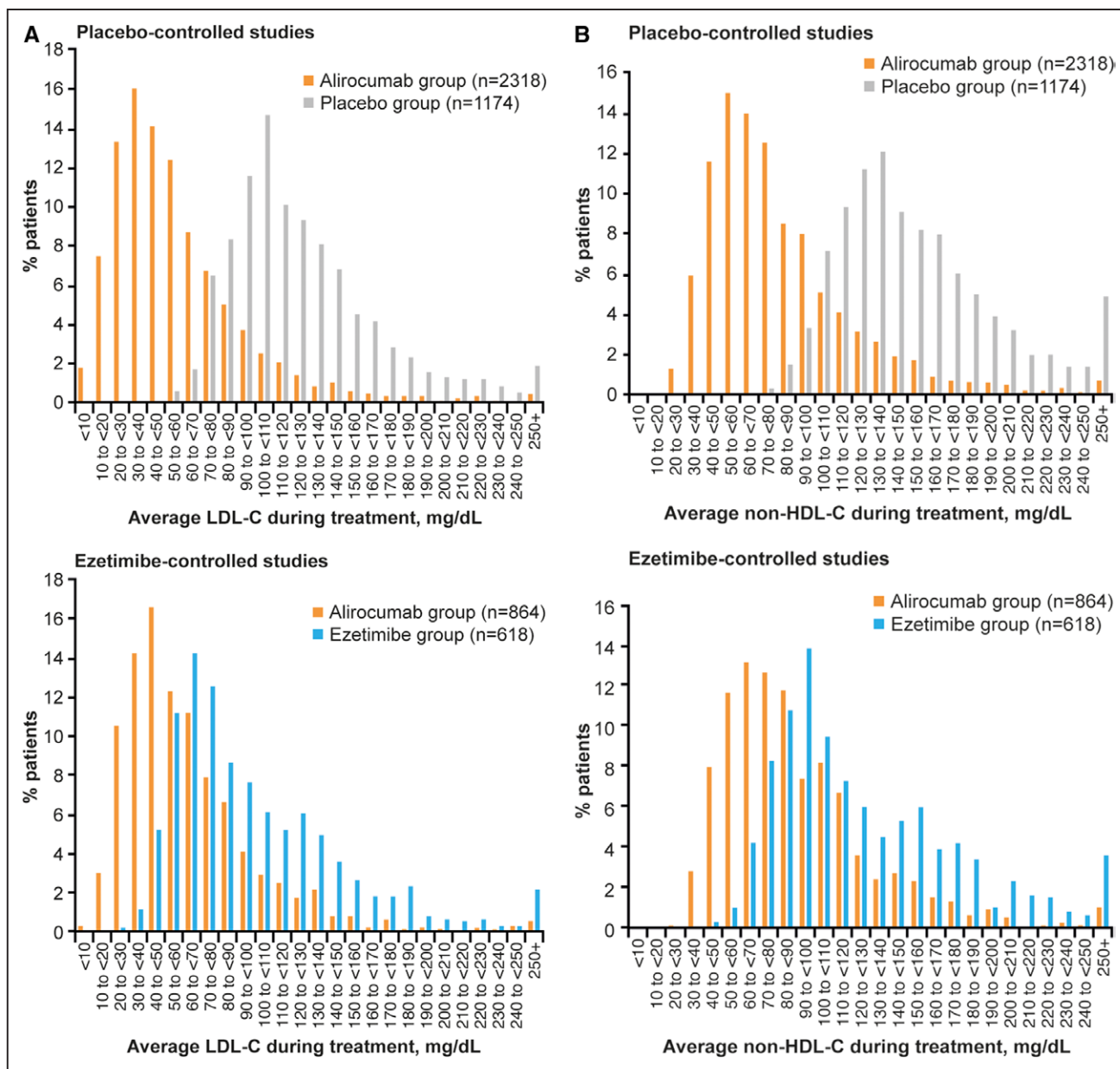
Figure 1. Distribution of achieved levels of low-density lipoprotein cholesterol (LDL-C; A), non–high-density lipoprotein cholesterol (non–HDL-C; B), and apolipoprotein B100 (apoB; C) during treatment stratified by control group.
For patients with no postbaseline lipid measurement, baseline values were used. CI indicates confidence interval; and MACE, major adverse cardiovascular event.

alirocumab and 2.7% for placebo in placebo-controlled trials and −48.1% with alirocumab and −18.0% with ezetimibe in ezetimibe-controlled trials (Table 2; individual trial data in Table IV in the online-only Data Supplement). Corresponding results for non–HDL-C and apoB are shown in Table 2 and Table IV in the online-only Data Supplement. When week 4 percentage reductions were assessed rather than the average reductions over the course of the trial, similar values were observed (Table V in the online-only Data Supplement). The combined distribution plot (Figure III in the online-only Data Supplement) reflected mainly the greater reductions in lipids achieved

with alirocumab versus the relatively modest reductions observed with ezetimibe and with placebo-treated patients largely remaining unchanged from baseline.

On Treatment Lipid Levels and MACE

A total of 104 first MACE were reported: 20 coronary heart disease deaths, 64 nonfatal myocardial infarctions, 16 ischemic strokes, and 4 unstable angina episodes occurred (median time to event, 36 weeks) among 4974 patients treated during a total of 6699 patient-years of follow-up. A lower risk of MACE was observed with lower

Table 2. Achieved Lipid Levels and Percentage Reductions During Treatment and Relationship to MACE

	Placebo-Controlled Trials		Ezetimibe-Controlled Trials		Pool of All Patients From the Trials			
	Alirocumab (n=2318)	Placebo (n=1174)	Alirocumab (n=864)	Ezetimibe (n=618)	Category	n	HR (95% CI)	P Value
Average achieved, mg/dL					MACE vs Average Achieved Level			
LDL-C	56.9 (38.8)	126.5 (43.9)	64.0 (42.4)	100.9 (50.8)	Per 39-mg/dL difference	4972	0.76 (0.63–0.91)	0.0025
Non–HDL-C	82.0 (41.8)	156.0 (47.2)	91.1 (45.6)	128.5 (55.2)	Per 42-mg/dL difference	4974	0.77 (0.65–0.93)	0.0056
ApoB	57.1 (29.1)	104.1 (28.1)	64.9 (28.1)	89.2 (31.0)	Per 27-mg/dL difference	4871	0.72 (0.60–0.86)	0.0002
Average change from baseline, %					MACE vs Percentage Change in Average Level			
LDL-C	−55.4 (23.5)	2.7 (25.7)	−48.1 (23.8)	−18.0 (28.9)	Per 50% reduction	4972	0.71 (0.57–0.89)	0.0030
Non–HDL-C	−46.9 (20.7)	2.6 (21.1)	−40.3 (20.1)	−16.8 (20.5)	Per 50% reduction	4974	0.71 (0.52–0.97)	0.0323
ApoB	−45.5 (22.8)	2.2 (24.0)	−35.9 (20.9)	−12.0 (20.1)	Per 50% reduction	4871	0.68 (0.54–0.85)	0.0008

ApoB indicates apolipoprotein B100; CI, confidence interval; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; and non–HDL-C, non–high-density lipoprotein cholesterol. Lipids are mean (SD). HR, 95% CI, and P value were determined from a multivariate Cox model. Multivariate analysis was adjusted on baseline characteristics (age, sex, diabetes mellitus, history of myocardial infarction/stroke, baseline LDL-C, and smoking status). Average LDL-C during the treatment period was determined from the area under the curve (with the trapezoidal method), taking into account all LDL-C values up to the end of the treatment period or occurrence of MACE, whichever came first. For patients with no postbaseline LDL-C, LDL-C at baseline was used. Note that 2 patients with missing baseline LDL-C and 3 with missing baseline apoB were excluded from the multivariate analysis.

More recently, the American College of Cardiology/American Heart Association guidelines and the UK National Institute for Health and Care Excellence guidelines have argued that most statin trials have tested whether a certain percentage reduction in LDL-C translates into a reduction in clinical events rather than an LDL-C goal and thus recommended LDL-C reductions of at least 30% to 50% for those at elevated risk, again on the basis of what is achievable with the most potent statins.[5,13] Until recently, it was uncertain from trial data whether consistently achieving LDL-C levels <70 mg/dL or achieving further percentage reductions in LDL-C after maximizing statins would translate into a lower risk of MACE.

The IMPROVE-IT trial extended our evidence base beyond statins, demonstrating that LDL-C levels on average 54 mg/dL with ezetimibe plus statins further reduced MACE compared with the achievement of an LDL-C of ≈70 mg/dL with statins alone.[6] The risk reduction observed in the IMPROVE-IT trial was also entirely consistent with the absolute reduction in LDL-C that would have been predicted by the CTT statin-derived regression line, supporting the notion that LDL-C reduction by statins and ezetimibe confers similar benefits and that the real determinant of the relative risk reduction is the magnitude of the change in LDL-C rather than the mechanism by which this change is achieved. If the findings of IMPROVE-IT are considered as a further percentage re-

duction in LDL-C, then they support the notion that, starting with a baseline LDL-C of ≈70 mg/dL, a further 20% reduction in LDL-C translates into a 6% to 7% lower risk of MACE. However, the question remains as to whether the additional percentage reduction in LDL-C (of 50% to 60%) and even lower on-treatment LDL-C level (<50 mg/dL) that can be achieved by adding a PCSK9 inhibitor to a statin will be associated with a lower risk of MACE.

The present analysis reports data from 10 randomized trials in the ODYSSEY trial program, providing information on 6699 patient-years of exposure, and suggests that there is continuous relationship between average on-treatment LDL-C and MACE with no evidence of discernable attenuation even at low achieved levels of LDL-C (<50 mg/dL). Furthermore, for every additional 39 mg/dL lower LDL-C achieved with either alirocumab or ezetimibe (on top of maximally tolerated statins in most patients), there was a further 24% lower risk of MACE (HR, 0.76; 95% CI, 0.63–0.91). This is remarkably similar to the CTT point estimate of a 22% risk reduction (rate ratio, 0.78; 95% CI, 0.76–0.80) for every 39-mg/dL reduction in LDL-C achieved with statins.[25]

Similarly, we observed an inverse relationship with additional percentage reductions in LDL-C and MACE without evidence of attenuation of benefit for greater percentage reductions in LDL-C. In multivariable regression analyses, each 50% incremental reduction in LDL-C on top of statins was associated with a further
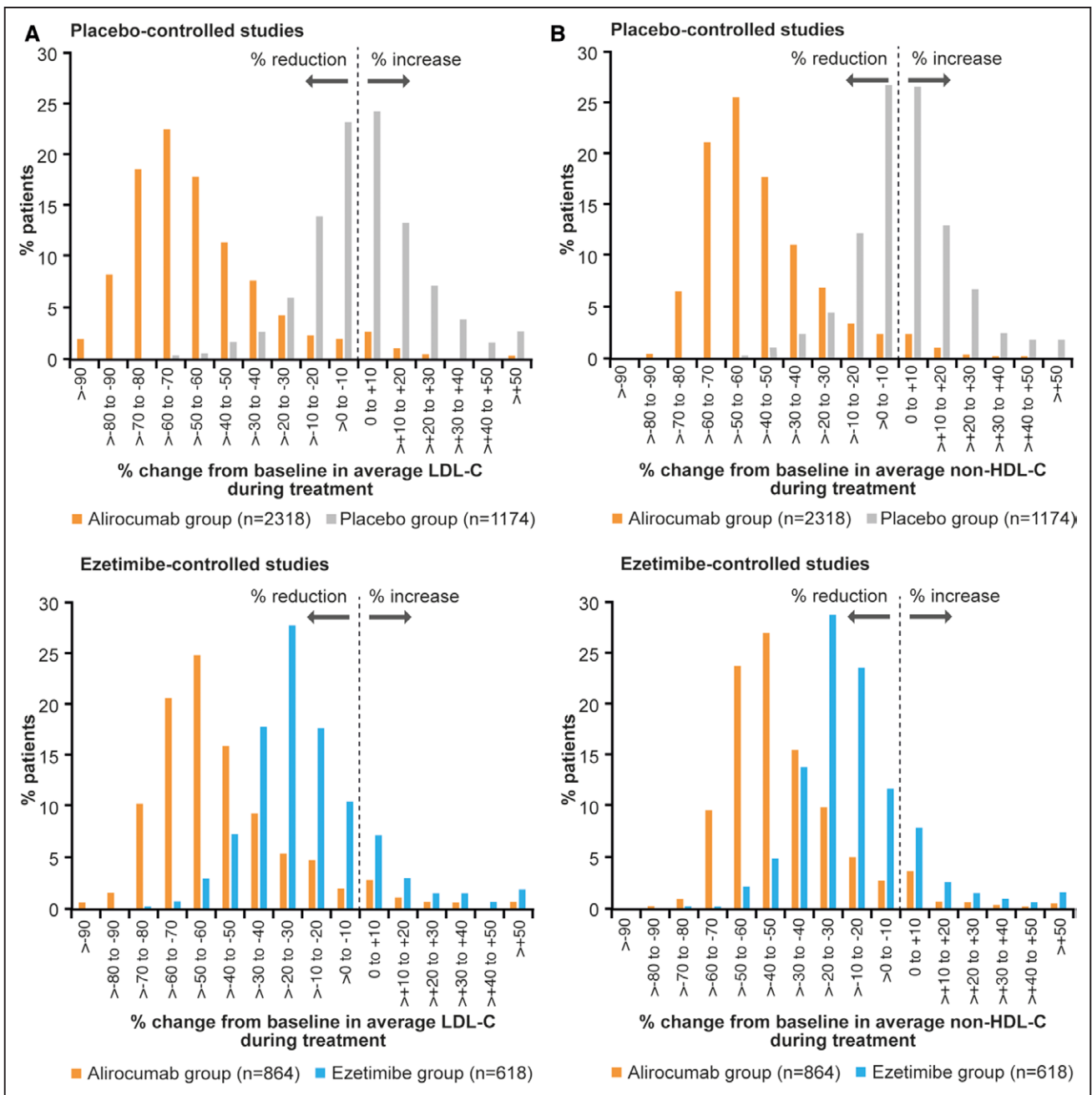
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Figure 2. Distribution of the percentage reductions in low-density lipoprotein cholesterol (LDL-C; A), non–high-density lipoprotein cholesterol (non–HDL-C; B), and apolipoprotein B100 (apoB; C) from baseline during treatment stratified by control group.
For patients with no postbaseline lipid measurement, baseline values were used. Two patients with missing baseline LDL-C and 3 patients with missing baseline apoB were excluded from the analysis. CI indicates confidence interval.

29% reduction in the risk of MACE (HR, 0.71; 95% CI, 0.57–0.89).

There was a significant correlation between LDL-C and non–HDL-C, between LDL-C and apoB, and between non–HDL-C and apoB (all *P*<0.0001). As with LDL-C, we observed a continuous relationship between lower achieved levels of both non–HDL-C and apoB with lower rates of MACE (HR, 0.77; 95% CI, 0.65–0.93 per

42-mg/dL difference; and HR, 0.72; 95% CI, 0.60–0.86 per 27-mg/dL difference, respectively), with no discernable evidence of attenuation at lower levels. Furthermore, greater percentage reductions in non–HDL-C and apoB were also associated with a lower risk of MACE with no evidence of attenuation of benefit.

Our findings are consistent with epidemiological studies in statin-naïve populations that have suggested a
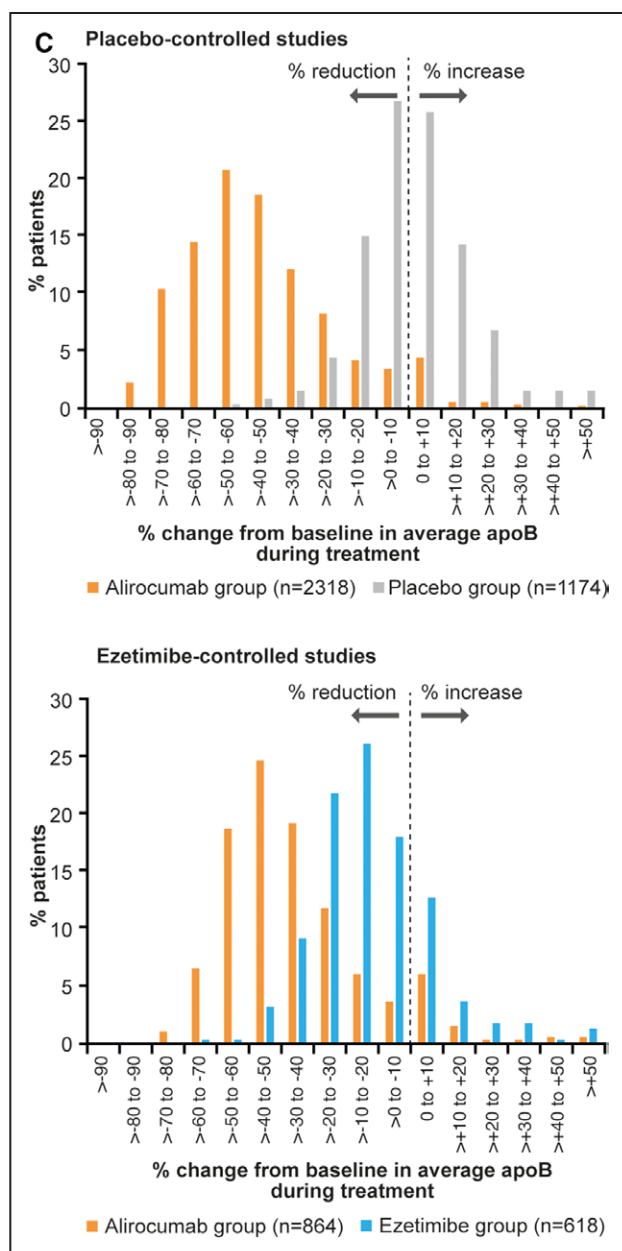
Figure 2 Continued.

continuous relationship between LDL-C, non–HDL-C, and apoB and risk[28] with no apparent attenuation of the relationship, as well as data from the statin trials in which a continuous relationship between on-treatment LDL-C, non–HDL-C, and MACE[29] has been observed without evidence of a threshold. Although LDL-C continues to be the main target of lipid-lowering strategies, levels of non–HDL-C and apoB have been shown to more closely correlate with risk of MACE because these parameters more accurately reflect the actual number of circulating atherogenic particles or their cholesterol content, particularly in patients with elevated triglycerides who likely have elevations in non-LDL atherogenic particles.[30] Our findings showed materially similar benefit with reductions

in each parameter, in part as a result of the collinearity of the parameters and the relatively small number of events.

Prior work by Robinson et al[31,32] has demonstrated that the benefit of lipid-lowering therapy is also related to the percentage reduction in LDL-C and non–HDL-C with consistent benefits between statins. Although high-intensity statins have offered us the scope of a 50% reduction in LDL-C, the addition of a PCSK9 inhibitor to statin therapy offers us a further 50% to 60% reduction in these parameters on top of statins, or ≈75% to 80% total reduction from the patient's untreated baseline LDL-C level. Consistent with this rationale is the recent 2016 American College of Cardiology pathway for the addition of nonstatin therapies for those individuals with high absolute risk and high LDL-C levels despite maximally tolerated statin therapy.[14] Our observation that high-risk patients with LDL-C levels between 120 and 130 mg/dL, despite maximally tolerated statin, derive benefit from a further 50% reduction in LDL-C or lower achieved absolute levels lends support to the consensus statement.

As we approach the possibility of achieving lower LDL-C levels consistently with PCSK9 inhibition, concerns have been raised about the potential safety of achieving very low levels of LDL-C (eg, <50 mg/dL). The present phase 3 clinical trial analyses provide further data on the overall safety of alirocumab and lower LDL-C levels not being associated with an increase in total adverse events. These findings add to earlier observations from high-intensity statin trials that have also failed to demonstrate any relationship adverse events and lower achieved LDL-C levels.[24,33,34]

Limitations

The limitations of the present analysis merit consideration. It is important to note that, although adverse consequences of very low LDL-C were not identified in these trials, the long-term effects of very low levels of LDL-C induced by PCSK9 inhibitors are unknown. Moreover, although these data are derived from randomized, controlled trials, the analyses are observational in nature and derived from a relatively small number of events. Therefore, we cannot exclude the potential for confounding as an explanation for the observed associations. We have attempted to take these into account by statistical adjustment and by conducting sensitivity analyses using alternative methodology that have produced materially similar findings. Furthermore, the 10 studies pooled differed most notably in the prevalence of heterozygous familial hypercholesterolemia, diabetes mellitus, age, history of myocardial infarction or stroke, and baseline LDL-C. Studies derived principally from patients with heterozygous familial hypercholesterolemia tended to include patients who were a decade younger, had fewer patients with diabetes mellitus, and tended to have patients with higher baseline LDL-C levels. Similarly, in trials without background
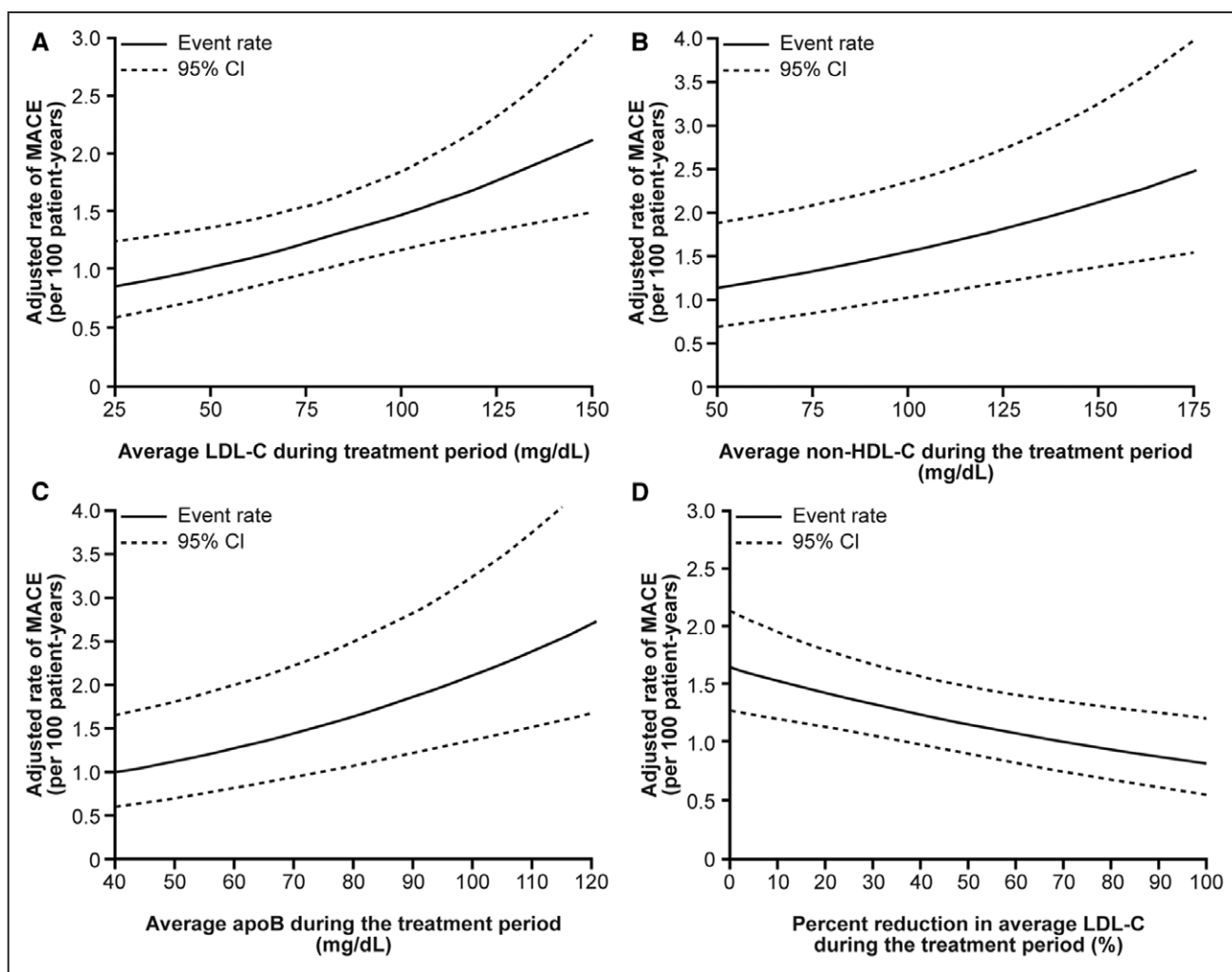
Figure 3. Relationship between on-treatment lipids and reductions in lipid levels with major adverse cardiovascular events (MACE).
A through **C** show adjusted MACE rate by achieved levels of low-density lipoprotein cholesterol (LDL-C), non–high-density lipoprotein cholesterol (non–HDL-C), and apolipoprotein B (apoB), respectively, during follow-up. Corresponding results for percent reductions are shown in **D** through **F**, respectively. Multivariate analysis was adjusted for baseline characteristics (age, sex, diabetes mellitus, history of myocardial infarction/stroke, baseline LDL-C, and smoking status). CI indicates confidence interval.

statin therapy, baseline LDL-C was higher. Therefore, a potential critique of the analyses of achieved LDL-C and MACE could be that patients who achieve lower LDL-C had lower baseline LDL-C and lower risk than patients at higher baseline LDL-C levels. However, we controlled for baseline LDL-C in all analyses; thus, we do not believe that baseline LDL-C levels accounted for our findings. Furthermore, we also assessed percentage reductions in LDL-C, which provided similar quantitative findings. Further reassurance of our methodology arises from the magnitude of the association observed between a 39-mg/dL difference in LDL-C and MACE, which is similar to the point estimate derived from the CTT meta-regression line and lies within its CIs. For the safety analysis, we looked only at overall TEAE rates to maximize power. More sophisticated

analyses looking at specific TEAEs would be more informative in larger trials with longer follow-up than the present pooled data.

Conclusions

These analyses provide further reassurance about the safety and cardiovascular benefit of achieving even further reductions in LDL-C, non–HDL-C, and apoB beyond what was previously achieved with statins alone. The results of the large cardiovascular outcomes studies with PCSK9 inhibitors such as ODYSSEY OUTCOMES are assessing whether PCSK9 inhibition with alirocumab on top of maximally tolerated statin therapy reduces MACE. If these trials demonstrate the effectiveness of further LDL-C reduction, then guideline committees may inves-
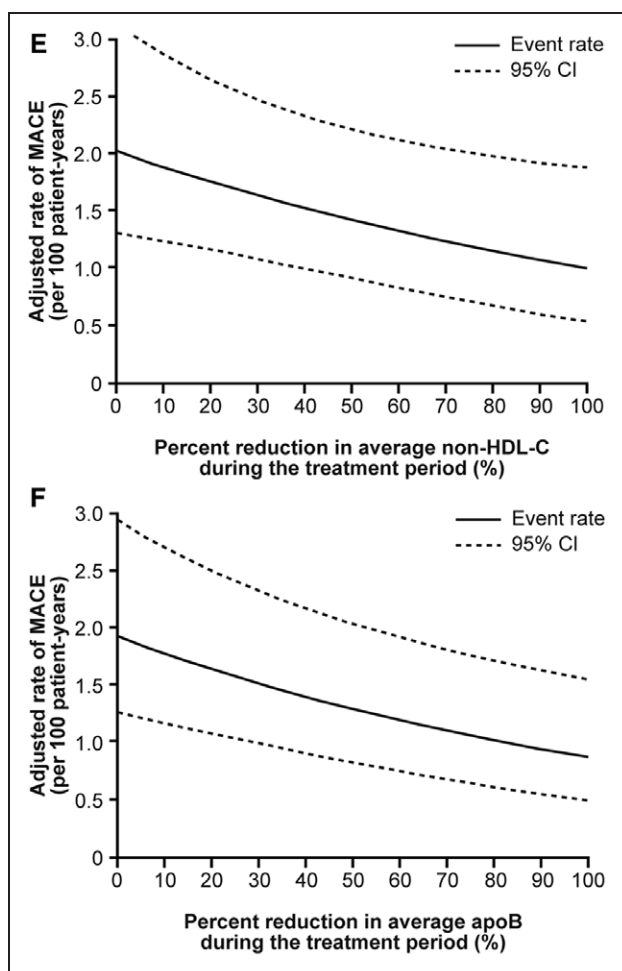
Figure 3 Continued.

tigate lower targets or a larger reduction in LDL-C from untreated baseline for those at highest risk of MACE.

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