

Lower On-Treatment Low-Density Lipoprotein Cholesterol and Major Adverse Cardiovascular Events in Women and Men: Pooled Analysis of 10 ODYSSEY Phase 3 Alirocumab Trials

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Background—In statin trials, men and women derived similar relative risk reductions in cardiovascular events per 39 mg/dL low-density lipoprotein cholesterol (LDL-C) reduction. We explored whether lower LDL-C levels and greater LDL-C percentage reductions than those achieved with statins are associated with reduced major adverse cardiovascular event (MACE) rates in women as well as men.

Methods and Results—Data pooled from 10 phase 3 ODYSSEY randomized trials (n=4983) comparing alirocumab with control (placebo/ezetimibe) were assessed for association between 39 mg/dL lower on-treatment LDL-C and percentage LDL-C change from baseline, and MACE risk by sex, using multivariable Cox regression. Mean baseline LDL-C was 135 mg/dL (women) and 121 mg/dL (men). Average on-treatment LDL-C levels with alirocumab, ezetimibe, and placebo were 71, 114, and 134 mg/dL, respectively, in women (n=1882) and 52, 93, and 122 mg/dL, respectively, in men (n=3090). Overall, 36.5% and 58.7% of women and men, respectively, achieved on-treatment LDL-C <50 mg/dL. Each 39 mg/dL lower LDL-C was associated with a 33% and 22% lower risk of MACE in women ($P=0.0209$) and men ($P=0.0307$), respectively, with no significant between-sex difference (P for heterogeneity=0.4597). Results were similar when analyzed per 50% LDL-C reduction, 24% ($P=0.1094$) and 29% ($P=0.0125$) lower MACE risk in women and men, respectively (P for heterogeneity=0.7499). Alirocumab was generally well tolerated in both sexes.

Conclusions—The present analysis reinforces the notion that both sexes derive a similar cardiovascular benefit from LDL-C lowering. Although women had slightly higher on-treatment LDL-C than men, both sexes showed a similar lower MACE risk with lower LDL-C. (*J Am Heart Assoc.* 2018;7:e009221. DOI: 10.1161/JAHA.118.009221.)

Key Words: cardiovascular disease risk factors • cardiovascular events • low-density lipoprotein cholesterol • proprotein convertase subtilisin/kexin type 9 • women

Lowering elevated levels of low-density lipoprotein cholesterol (LDL-C) is recommended to reduce cardiovascular risk in both men and women. However, women have lower absolute risk, and it is uncertain whether lowering LDL-C to very-low levels offers cardiovascular benefits in this population.^{1–3} This is at least partly attributable to the fact that women are often underrepresented in clinical outcome trials of lipid-lowering therapies.^{1–3} The strongest evidence

to date comes from the Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis of 27 statin trials (26.8% of 174 149 participants were women), which observed overall similar proportional reductions per 39 mg/dL lower LDL-C in both women and men at similar baseline risk of major vascular events,⁴ however, patients in these trials had higher on-treatment LDL-C and were treated with statins alone.

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Clinical Perspective

What Is New?

- Although women have a perceived lower absolute risk of cardiovascular disease than men, they derive similar relative benefits for each 39 mg/dL lowering of low-density lipoprotein cholesterol with alirocumab (a proprotein convertase subtilisin/kexin type 9 inhibitor).
- Lowering low-density lipoprotein cholesterol levels to <50 mg/dL in women was associated with a lower risk of major adverse cardiovascular events and was generally well tolerated.

What Are the Clinical Implications?

- Women who are at sufficiently high cardiovascular risk, and in whom low-density lipoprotein cholesterol remains elevated despite statins, may benefit from the addition of alirocumab to their usual standard of care.
- Achieving low-density lipoprotein cholesterol levels <50 mg/dL with alirocumab is similarly well tolerated in women and men.

Despite therapy with statins, patients with hypercholesterolemia often have suboptimal response, and cardiovascular risk remains.^{5,6} Cardiovascular events have been shown to be reduced when ezetimibe or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor is added to statin therapy to obtain lower LDL-C levels of 30 to 50 mg/dL.^{7,8} Furthermore, addition of a PCSK9 inhibitor to statin therapy has been shown to result in LDL-C levels <40 mg/dL with suggested regression of atherosclerosis.⁹

Analyses from the ODYSSEY phase 3 clinical trial program reported a substantial proportion of patients having LDL-C reductions to levels of <50 mg/dL¹⁰ and some to <25 mg/dL¹¹ with the PCSK9 inhibitor alirocumab added, in the most part, to background statin therapy with or without other lipid-lowering therapy. In addition, a continuous relationship between lower on-treatment LDL-C (including levels <50 mg/dL) and lower incidence of major adverse cardiovascular events (MACE) was observed.¹⁰ In the present analysis of data pooled from the 10 ODYSSEY phase 3 trials, we assessed whether lower levels of on-treatment LDL-C would be associated with a lower risk of MACE in women and compared these results with observations in men. In addition, we explored the association between percentage reductions in LDL-C levels from baseline and risk of MACE in both women and men. More importantly, the populations we studied in this analysis are at an overall lower risk than those in the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) and ODYSSEY Outcomes (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab)

trials,^{8,12} and include ezetimibe controls. Hence, evidence of benefit in a lower-risk population, especially in women who are often perceived to be at lower cardiovascular risk and therefore perhaps benefit less from LDL-C lowering, would be an important additional piece of data informing the wider clinical community.

Methods

Study Design and Patient Populations

Patient data (women and men) were pooled from 10 international, randomized, double-blind, multicenter, controlled (placebo or ezetimibe) phase 3 ODYSSEY trials; trial names and identifiers are reported in Table 1. Details of the design of each of these studies have been reported previously (Figure 1).^{13–21} The data, analytic methods, and study materials for this secondary analysis will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Briefly, individuals were eligible for trial recruitment if they were aged ≥ 18 years, had established atherosclerotic cardiovascular disease (ASCVD), had heterozygous familial hypercholesterolemia (HeFH), or had other cardiovascular risk factors (depending on the study), with inadequately controlled LDL-C. At the time of screening, most patients were receiving maximally tolerated statin therapy with or without other lipid-lowering therapy (74.6%). Two trials were performed in patients who were not receiving background statin therapy (MONO and ALTERNATIVE trials, Figure 1).

For inclusion in the trials, patients had to have LDL-C ≥ 70 mg/dL (for those with prior cardiovascular disease) or LDL-C ≥ 100 mg/dL (for those without cardiovascular disease but with other risk factors). Exceptions were the LONG TERM (LDL-C ≥ 70 mg/dL, all patients at high risk), HIGH FH (LDL-C ≥ 160 mg/dL, patients with HeFH), MONO (LDL-C ≥ 100 mg/dL, moderate-risk patients), and ALTERNATIVE (LDL-C ≥ 70 mg/dL for very-high risk or ≥ 100 mg/dL for moderate- or high-risk patients) trials. All individuals presenting with baseline triglycerides >400 mg/dL were excluded.

Eligible patients were randomized in a 1:1 or 2:1 ratio to subcutaneous (SC) alirocumab, 75/150 mg dose titration (where alirocumab, 75 mg every 2 weeks [Q2W], was increased to 150 mg Q2W at week 12 if LDL-C at week 8 was ≥ 70 mg/dL; or, in OPTIONS I, OPTIONS II, and ALTERNATIVE trials, ≥ 70 or 100 mg/dL, depending on cardiovascular risk), 150 mg Q2W, or control (placebo or ezetimibe) for double-blind treatment periods of 24 to 104 weeks.

LDL-C levels were calculated using the Friedewald equation at baseline and at 4-week intervals up to week 16, then at weeks 24, 36, 52, 64, 78, 88, and 104. In those cases where triglycerides were >400 mg/dL, LDL-C was determined by β quantification.

Table 1. Baseline Characteristics of Patients Pooled From 10 Phase 3 ODYSSEY Trials (Randomized Population)

Characteristics	Women (n=1887)		Men (n=3096)	
	Alirocumab (n=1192)	Control (n=695)*	Alirocumab (n=1996)	Control (n=1100)*
Age, mean±SD, y	60.2±11.4	60.8±10.9	59.1±11.0	59.4±10.8
Race, white	1049 (88.0)	611 (87.9)	1835 (91.9)	1009 (91.7)
BMI, mean±SD, kg/m ²	30.2±6.5	30.6±6.5	30.0±5.2	30.0±5.0
HeFH	410 (34.4)	216 (31.1)	468 (23.4)	246 (22.4)
Diabetes mellitus	401 (33.6)	240 (34.5)	583 (29.2)	308 (28.0)
ASCVD [†]	715 (60.0)	403 (58.0)	1551 (77.7)	842 (76.5)
CHD	610 (51.2)	355 (51.1)	1455 (72.9)	801 (72.8)
Ischemic stroke/TIA	123 (10.3)	47 (6.8)	143 (7.2)	81 (7.4)
PAD	49 (4.1)	37 (5.3)	81 (4.1)	38 (3.5)
Current smoker	225 (18.9)	124 (17.8)	374 (18.7)	225 (20.5)
Background LLT				
Statin only	759 (63.7)	422 (60.7)	1294 (64.8)	687 (62.5)
Statin+ezetimibe	211 (17.7)	110 (15.8)	329 (16.5)	181 (16.5)
Statin+other LLT (no ezetimibe)	141 (11.8)	83 (11.9)	276 (13.8)	145 (13.2)
Ezetimibe (no statin)	0	0	0	0
Other LLT (no statin/ezetimibe)	16 (1.3)	25 (3.6)	31 (1.6)	27 (2.5)
No LLT/no statin	65 (5.5)	55 (7.9)	66 (3.3)	60 (5.5)
Statin intensity [‡]				
High	644 (54.0)	329 (47.3)	1113 (55.8)	618 (56.2)
Moderate	306 (25.7)	186 (26.8)	552 (27.7)	282 (25.6)
Low	160 (13.4)	97 (14.0)	234 (11.7)	110 (10.0)
Baseline LDL-C, mean±SD, mg/dL				
Calculated LDL-C	134.5±53.8	135.7±56.5	120.7±43.0	120.4±43.0
Subjects with HeFH	159.6±62.5	162.2±66.1	150.8±54.1	151.5±50.8
Subjects without HeFH	121.4±43.2	123.8±53.847.1	111.5±34.1	111.4±35.9

Data are given as number (percentage) unless otherwise indicated. Pooled data of all randomized women and men in 10 phase 3 ODYSSEY trials, including 5 placebo-controlled trials: COMBO I, NCT01644175; LONG TERM, NCT01507831; HIGH FH, NCT01617655; FH I, NCT01623115; and FH II, NCT01709500; and 5 ezetimibe-controlled trials: COMBO II, NCT01644188; MONO, NCT01644474; ALTERNATIVE, NCT01709513; OPTIONS I, NCT01730040; and OPTIONS II, NCT01730053. ASCVD indicates 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; PAD, peripheral artery disease; TIA, transient ischemic attack.

*Control=placebo or ezetimibe.

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

[‡]High: atorvastatin, 40 to 80 mg; rosuvastatin, 20 to 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.

Individual study protocols were approved by the corresponding local independent review board, and all enrolled individuals provided written informed consent before study treatment in each trial.

Statistical Analysis

Baseline characteristics

Baseline patient data are presented stratified by sex, treatment (alirocumab), and the control comparator in each of the studies, placebo or ezetimibe. For continuous

variables, data are presented as means and SDs, or median and interquartile range for data that are not normally distributed.

LDL-C distribution

Changes in LDL-C levels with treatment were assessed in women and men in the pooled population stratified by treatment allocation (ie, alirocumab or control [placebo or ezetimibe]). Data were pooled from the safety population of the 10 ODYSSEY trials, including all randomized patients who received at least 1 full or partial dose of study treatment.

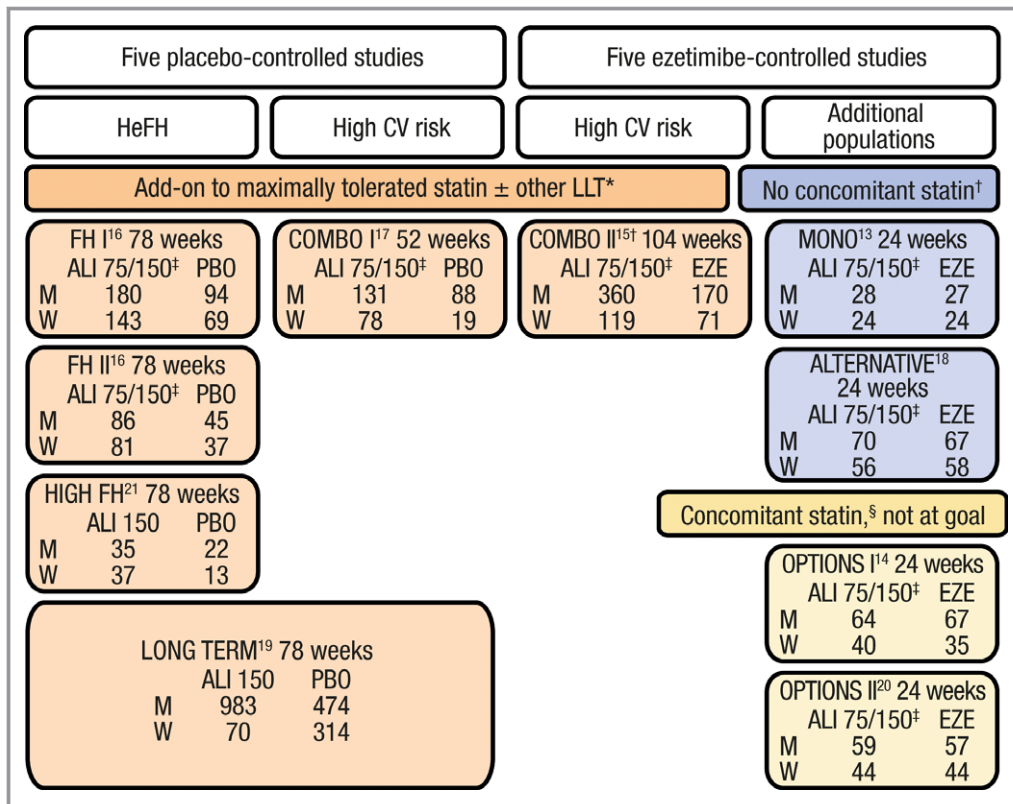


Figure 1. Overview of the study designs of the 10 ODYSSEY trials (n=4983) included in this analysis. *Maximally tolerated statin defined as atorvastatin, 40 to 80 mg; rosuvastatin, 20 to 40 mg; or simvastatin, 80 mg. No other nonstatin lipid-lowering therapies (LLTs) were allowed in COMBO II. †Two studies were performed without background statin: ALTERNATIVE, in patients with documented statin intolerance (other LLTs were allowed in ALTERNATIVE, except for ezetimibe [EZE]); and MONO, a monotherapy study performed without background statin or any other LLT. ‡Alirocumab (ALI), 75/150 mg every 2 weeks (Q2W), indicates studies using a dose adjustment strategy, whereby ALI, 75 mg Q2W, was increased to 150 mg Q2W at week 12 if low-density lipoprotein cholesterol at week 8 was ≥70 mg/dL (or, in OPTIONS I, OPTIONS II, and ALTERNATIVE, ≥70 or 100 mg/dL, depending on cardiovascular [CV] risk). §Concomitant statin (with or without other LLT): in OPTIONS I, atorvastatin, 20 or 40 mg; in OPTIONS II, rosuvastatin, 10 or 20 mg. HeFH indicates heterozygous familial hypercholesterolemia; M, men; PBO, placebo; W, women.

Average LDL-C during treatment or percentage reductions in LDL-C from baseline were determined from the area under the curve (using trapezoidal method), incorporating all LDL-C values up to the end of the treatment period or occurrence of MACE, whichever occurred first.

LDL-C and risk of MACE

MACE were defined according to the primary end point of the ODYSSEY OUTCOMES trial as the composite of coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, or diagnosis of unstable angina (limited to events with evidence of ischemia and fulfilling additional severity criteria, requiring hospitalization or emergency department visit until at least the following day), whichever came first.^{10,12} As per the ODYSSEY OUTCOMES trial, all cardiovascular events were adjudicated by a central Clinical Events Committee.¹⁹

Patients were pooled into 2 overall cohorts (women and men) that had received alirocumab or control, and the relationship between LDL-C and MACE during the treatment period was assessed by average achieved on-treatment LDL-C and percentage reductions in LDL-C from baseline.

Analysis of the relationship between on-treatment LDL-C and the composite of MACE end points was conducted using a multivariate Cox regression model with adjustment for differences in baseline characteristics (age, diabetes mellitus, history of myocardial infarction or ischemic stroke, baseline LDL-C, and smoking status), as previously published²²; in addition, for the present analysis, the HeFH status of individuals was included in the model. The risk of MACE (hazard ratio [HR] and 95% confidence interval [CI]) was assessed for every 39 mg/dL (1.0 mmol/L) lower mean on-

treatment LDL-C (to facilitate comparison with the CTT Collaboration meta-regression line).²³

Comparable analyses were used to assess the relationship between percentage reduction in LDL-C from baseline and risk of MACE, with HR and 95% CI expressed for each 50% reduction in LDL-C.

The adjusted rates of MACE and associated 95% CIs were also determined from a multivariate Poisson model in women and men and were depicted graphically as a function of average on-treatment LDL-C levels or average percentage reduction during treatment.

Analyses were generated using SAS, version 9.4. All tests and CIs were 2 sided, and statistical significance was defined as a $P < 0.05$.

Safety assessments

Treatment-emergent adverse events, which occurred during the period from the first dose of study treatment up to 70 days after the patient's last injection, were summarized using descriptive statistics. The safety analysis compared the occurrence of events (incidence rate) in women and men randomized to receive alirocumab or control (placebo or ezetimibe).

Results

Baseline Characteristics

Among the total pooled population of 4983 randomized individuals from the 10 ODYSSEY trials, 38% ($n=1887$) were women and 62% ($n=3096$) were men (Table 1). In total, 1192 women were randomized to alirocumab, and 695 were randomized to control; the corresponding figures for men were 1996 and 1100, respectively. Median (quartile 1, quartile 3) duration of follow-up was similar for women, 78.7 (32.7, 86.1) weeks, and men, 86.0 (48.3, 86.3) weeks (ie, 1.5 and 1.7 years, respectively).

Baseline demographic and clinical characteristics stratified by the pooled alirocumab and control (placebo or ezetimibe) groups for both women and men are shown in Table 1. Both women and men had a similar mean age of ≈ 60 years and a body mass index of 30 kg/m². A slightly higher proportion of women than men had diabetes mellitus at baseline, although the proportions between the alirocumab and control groups were comparable in women (33.6% and 34.5%, respectively) and in men (29.2% and 28.0%, respectively). Approximately 1 in 3 women had HeFH in the alirocumab and control groups, compared with ≈ 1 in 4 men. In contrast, fewer women (60.0% and 58.0%) than men (77.7% and 76.5%) presented with ASCVD in the pooled alirocumab and control groups, respectively. The proportion of patients receiving high-intensity statin treatment ranged from 47% to 56% of each pooled cohort of women and men stratified by treatment group (Table 1).

Baseline and On-Treatment LDL-C and Percentage Reductions From Baseline

Baseline overall mean LDL-C levels in the pooled alirocumab and control groups were higher in women (134.5 and 135.7 mg/dL, respectively) than in men (120.7 and 120.4 mg/dL, respectively). Among participants with HeFH, baseline mean LDL-C levels were ≈ 40 mg/dL higher than those without HeFH in both women and men (Table 1).

In the 8 studies that used alirocumab 75/150 mg Q2W, the alirocumab dose was increased from 75 to 150 mg Q2W at week 12 in significantly more women than men (35.7% versus 23.8%; $P < 0.0001$).

During follow-up, average LDL-C levels were markedly lower with alirocumab than either placebo (Figure 2A) or ezetimibe (Figure 2B) in women and men. Mean average on-treatment LDL-C levels with alirocumab, ezetimibe, and placebo were 71, 114, and 134 mg/dL, respectively, in women ($n=1882$), and 52, 93, and 122 mg/dL, respectively, in men ($n=3090$); overall mean achieved LDL-C levels were 91.9 and 72.8 mg/dL in women and men, respectively.

The distribution of the average percentage change from baseline in LDL-C by treatment is shown for women and men in Figure 2C and 2D. In placebo-controlled trials (Figure 2C), mean percentage change from baseline was greater in alirocumab-treated women and men (-48.3% and -60.0% , respectively) than in those who received placebo (4.3% and 1.7%, respectively); similarly, in ezetimibe-controlled trials (Figure 2D), treatment with alirocumab led to greater LDL-C percentage reductions in both women and men (-42.3% and -50.9% , respectively) compared with treatment with ezetimibe (-16.8% and -18.6% , respectively).

Considerably more alirocumab-treated women and men (36.5% and 58.7%, respectively) achieved average on-treatment LDL-C < 50 mg/dL than those who received placebo (0.0% and 0.0%, respectively) or ezetimibe (3.9% and 8.0%, respectively) (Figure 3).

Association Between On-Treatment LDL-C Levels and MACE

Among the overall pooled population of 1882 women and 3090 men treated with alirocumab or control, representing 6699 patient-years of exposure, 104 first MACE were reported, including 20 coronary heart disease deaths, 64 nonfatal myocardial infarctions, 16 ischemic strokes, and 4 episodes of unstable angina;¹⁰ more men than women reported each event (Table 2). The median time to first event was 36 weeks.

Regardless of sex, average on-treatment LDL-C correlated directly with the rate of MACE (Figure 4A). With each 39 mg/dL lower on-treatment LDL-C achieved, there was an

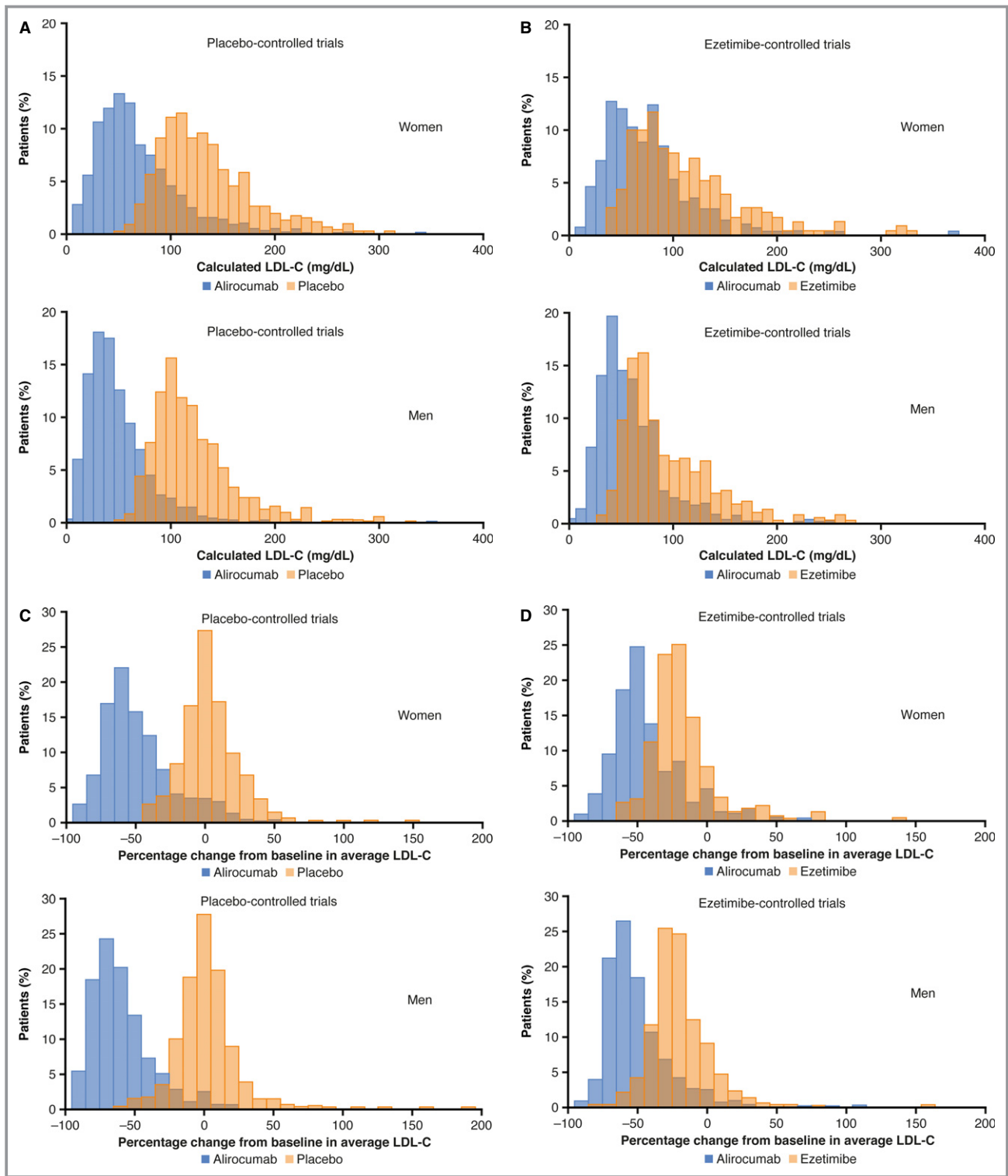


Figure 2. Average low-density lipoprotein cholesterol (LDL-C) levels in women and men in placebo-controlled (A) and ezetimibe-controlled (B) trials, and distribution of percentage change in average LDL-C in women and men in placebo-controlled (C) and ezetimibe-controlled (D) trials during treatment with alirocumab.

associated 26% lower risk of MACE in the overall population (HR, 0.74; 95% CI, 0.62–0.89; $P=0.0016$), a 33% lower risk of MACE in women (HR, 0.67; 95% CI, 0.48–0.94; $P=0.0209$),

and a 22% lower risk of MACE in men (HR, 0.78; 95% CI, 0.63–0.98; $P=0.0307$), with no significant between-sex difference (P for heterogeneity=0.4597; Figure 4B). The

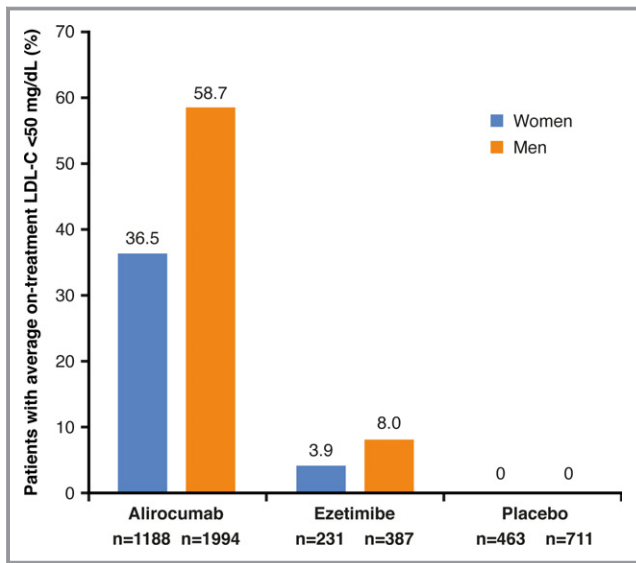


Figure 3. Proportion of alirocumab- or control-treated women and men with average on-treatment low-density lipoprotein cholesterol (LDL-C) <50 mg/dL.

relationship between MACE, selected baseline characteristics, and average achieved LDL-C during treatment in women and men is shown in Table 3.

The results for analysis by average percentage reductions in LDL-C showed that the percentage change in LDL-C from baseline was inversely correlated with the rate of MACE (Figure 5A). HR (95% CI) per 50% reduction in LDL-C was 0.70 (0.56–0.88) (*P*=0.0020) for the overall population; 0.76 (0.54–1.06) (*P*=0.1094) for women; and 0.71 (0.54–0.93) (*P*=0.0125) for men. There was no significant between-sex difference (*P* for heterogeneity=0.7499; Figure 5B and further details on the multivariate analysis in Table 4).

Considering the Poisson model used, as expected, the absolute risk reduction for MACE is not constant but rather

log-linear (Figure 6); hence, the absolute risk reduction is not proportional to the average LDL-C reduction because the slope of the curve increases with average LDL-C. In addition, the curves for men and women are not parallel, and the absolute risk reduction differs between men and women, even for an identical average LDL-C reduction. As such, as shown in Figure 6, in men, an average achieved LDL-C of 50 mg/dL compared with 100 mg/dL corresponded to a reduction of 0.60 events per 100 patient-years. By contrast, among women, the difference in rates was smaller, a decrease of 0.26 events per 100 patient-years for those with an average achieved LDL-C of 50 versus 100 mg/dL.

Safety

Overall, alirocumab was generally well tolerated and demonstrated a similar safety profile in women and men (Table 5). The incidence of treatment-emergent adverse events was consistent between pooled alirocumab and control (placebo or ezetimibe) groups in both women (79.4% and 81.4%, respectively) and men (78.5% and 77.0%, respectively). The frequency of injection-site reactions was increased with alirocumab compared with control in both women (8.0% versus 6.2%) and men (4.9% versus 2.9%); however, most of these adverse events were mild in intensity and transient. Notably, urinary tract infections occurred in more alirocumab- and control-treated women (8.5% and 10.1%, respectively) than men (2.4% and 1.8%, respectively).

Discussion

The PCSK9 inhibitor alirocumab is a fully human monoclonal antibody to PCSK9 that has been shown in the ODYSSEY phase 3 clinical trial program to significantly reduce LDL-C

Table 2. Summary of MACE Reported in Women and Men Treated With Alirocumab or Control: Data Pooled From 10 Phase 3 ODYSSEY Trials (Safety Population)

MACE	Women (n=1882)		Men (n=3092)		Overall (n=4974)	P value [†]
	Alirocumab (n=1188)	Control (n=694)*	Alirocumab (n=1994)	Control (n=1098)*		
CHD death	4 (0.34)		16 (0.80)		20 (0.40)	
Nonfatal MI	23 (1.94)		41 (2.06)		64 (1.29)	
Nonfatal IS	2 (0.16)		14 (0.70)		16 (0.32)	
UA requiring hospitalization	1 (0.08)		3 (0.15)		4 (0.08)	
Total/treatment	15 (1.26)	15	50 (2.51)	24		0.3237
Total	30 (2.54)		74 (2.39)		104	0.0991

Data are given as number (percentage). CHD indicates coronary heart disease; IS, ischemic stroke; MACE, major adverse cardiovascular events; MI, myocardial infarction; UA, unstable angina.

*Control=placebo or ezetimibe.

[†]Comparison by log-rank test.

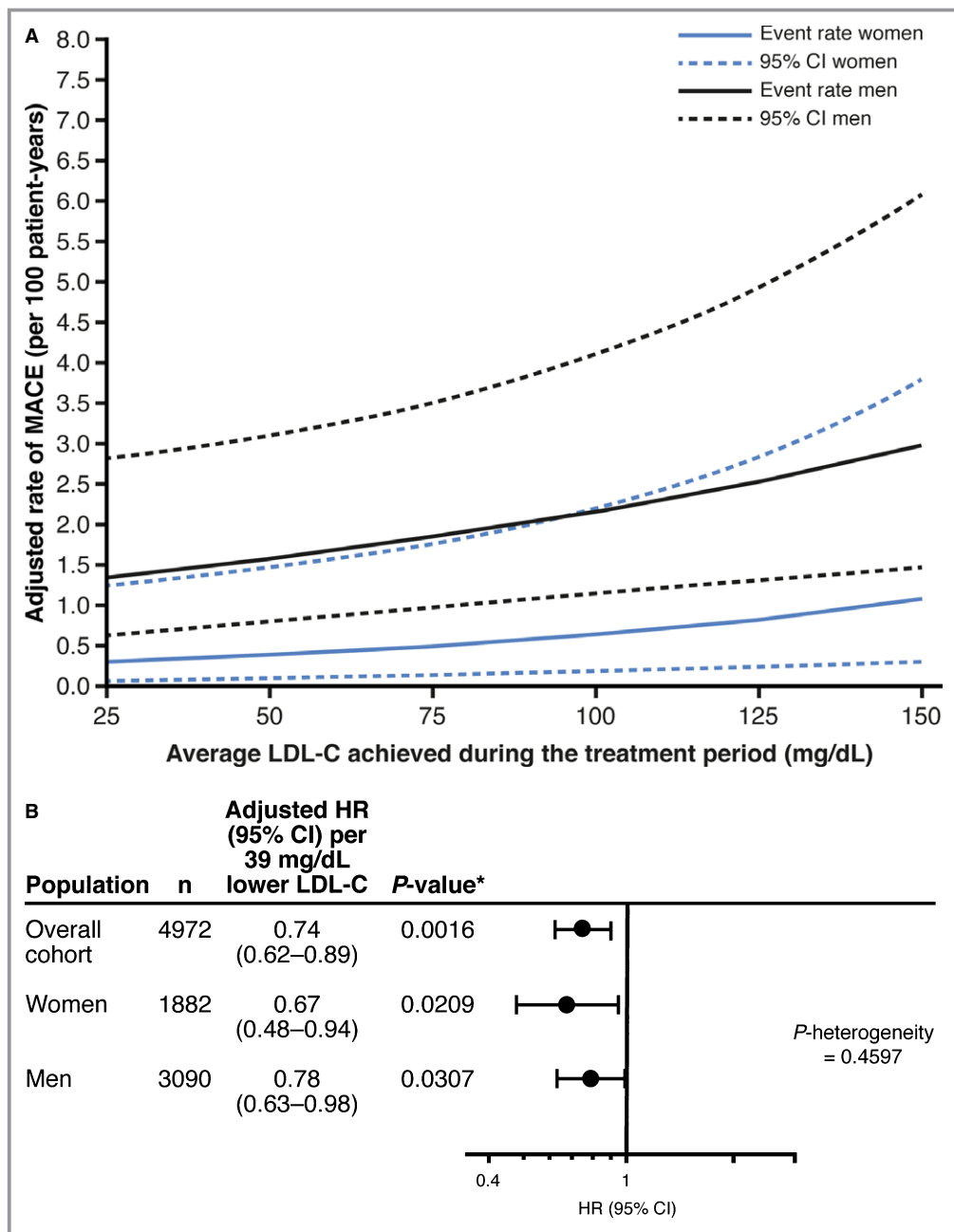


Figure 4. A, Adjusted rate of major adverse cardiovascular events (MACE) in women and men by average on-treatment low-density lipoprotein cholesterol (LDL-C). B, Risk of MACE associated with each 39 mg/dL on-treatment reduction in LDL-C in women and men. Event rate and 95% confidence interval (CI) determined from a multivariate Poisson model, with adjustment for age, diabetes mellitus, history of myocardial infarction (MI)/stroke, baseline LDL-C, heterozygous familial hypocholesterolemia (HeFH), and smoking status. Average LDL-C during the treatment period was determined from the area under the curve (using trapezoidal method), considering all LDL-C values up to the end of treatment period or occurrence of MACE, whichever came first. For patients with no postbaseline LDL-C, LDL-C at baseline was used; 2 patients with missing baseline LDL-C were excluded from the multivariate analysis. **P* values are for each 39 mg/dL decrease in LDL-C. Hazard ratio (HR) calculated using multivariate Cox regression analysis, adjusted for age, diabetes mellitus, prior MI/ischemic stroke, baseline LDL-C, HeFH, and smoking status.

levels, including to levels of <50 mg/dL, in a significant proportion of patients when added to background statin therapy, with or without other lipid-lowering therapy.¹⁰ In the

present analysis of a pooled cohort from 10 ODYSSEY phase 3 trials of alirocumab versus ezetimibe or placebo (added to background statin therapy in most patients), including 33.1%

Table 3. Relationship Between MACE, Selected Baseline Characteristics, and Average Achieved On-Treatment LDL-C in Women and Men (Safety Population)

Variable	Categories	Women				Men				P Value (Heterogeneity Test)
		No. of Patients	No. of Events (%/Year)	HR (95% CI)	P Value	No. of Patients	No. of Events (%/Year)	HR (95% CI)	P Value	
Age	Per 10-y increase	1882		0.96 (0.64–1.42)	0.8294	3090		1.69 (1.30–2.18)	<0.0001	...
HeFH	No	1256	28 (1.8)	Referent	0.0280	2379	61 (1.9)	Referent	0.9758	...
	Yes	626	2 (0.2)	0.18 (0.04–0.83)		711	13 (1.3)	0.99 (0.50–1.97)		
Diabetes mellitus	No	1243	14 (0.9)	Referent	0.0820	2205	46 (1.5)	Referent	0.1076	...
	Yes	639	16 (1.9)	1.93 (0.92–4.06)		885	28 (2.4)	1.49 (0.92–2.41)		
History of MI/stroke	No	1269	9 (0.6)	Referent	0.0007	1529	30 (1.5)	Referent	0.3181	...
	Yes	613	21 (2.6)	4.11 (1.82–9.27)		1561	44 (1.9)	1.27 (0.79–2.04)		
Baseline LDL-C	Per 39 mg/dL decrease	1882		1.22 (0.81–1.84)	0.3343	3090		1.06 (0.81–1.41)	0.6576	...
Current smoker	No	1533	23 (1.2)	Referent	0.9833	2492	62 (1.8)	Referent	0.9996	...
	Yes	349	7 (1.5)	1.01 (0.41–2.49)		598	12 (1.4)	1.00 (0.53–1.88)		
Average LDL-C achieved during treatment period	Per 39 mg/dL decrease	1882		0.67 (0.48–0.94)	0.0209	3090		0.78 (0.63–0.98)	0.0307	0.4597

No. of events (%/year)=number of patients with at least 1 event and crude (unadjusted) percentage of patients with event per year. HR, 95% CI, and P value determined from a multivariate Cox model. Multivariate analysis adjusted on baseline characteristics and stratified by sex. For patients with no postbaseline lipid value, lipid value at baseline was used; 2 patients with missing baseline LDL-C were excluded from the multivariate analysis. CI indicates confidence interval; HeFH, heterozygous familial hypercholesterolemia; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MI, myocardial infarction.

of patients with an on-treatment LDL-C level <50 mg/dL, we observed that, although women had slightly higher baseline and on-treatment LDL-C levels than men, both women and men showed a significant and similar lower risk of MACE with lower achieved LDL-C levels (lower on-treatment LDL-C or greater percentage reductions in LDL-C from baseline). The relationship between MACE and LDL-C levels in women and men in the present analysis is consistent with those in the overall pooled ODYSSEY phase 3 trial population in which a 24% relative risk reduction in MACE was observed per 39 mg/dL lower achieved LDL-C.¹⁰ Treatment with alirocumab was generally well tolerated in both women and men.

Current guidelines acknowledge that there is still insufficient evidence in women, compared with men, for the benefit of lowering elevated levels of LDL-C, especially among those women without cardiovascular disease and with lower LDL-C

levels.^{2,3,19} Our results, including patients with and without a history of ASCVD, add to prior evidence from statin trials suggesting a similar benefit of LDL-C-lowering on cardiovascular events in both women and men (with the additional consideration that our results also included patients treated with the PCSK9 inhibitor alirocumab and around one third of patients had an on-treatment LDL-C <50 mg/dL). Our results are consistent with those reported by the large CTT Collaboration meta-analysis of 27 statin trials, which observed that women and men at similar baseline risk of major vascular events derive comparable relative reductions in risk with LDL-C-lowering (16% and 22%, respectively; both $P<0.0001$; adjusted P for heterogeneity=0.331) for each 39 mg/dL reduction in LDL-C levels with statins;⁴ this was also consistent in both women and men stratified by history of vascular disease.

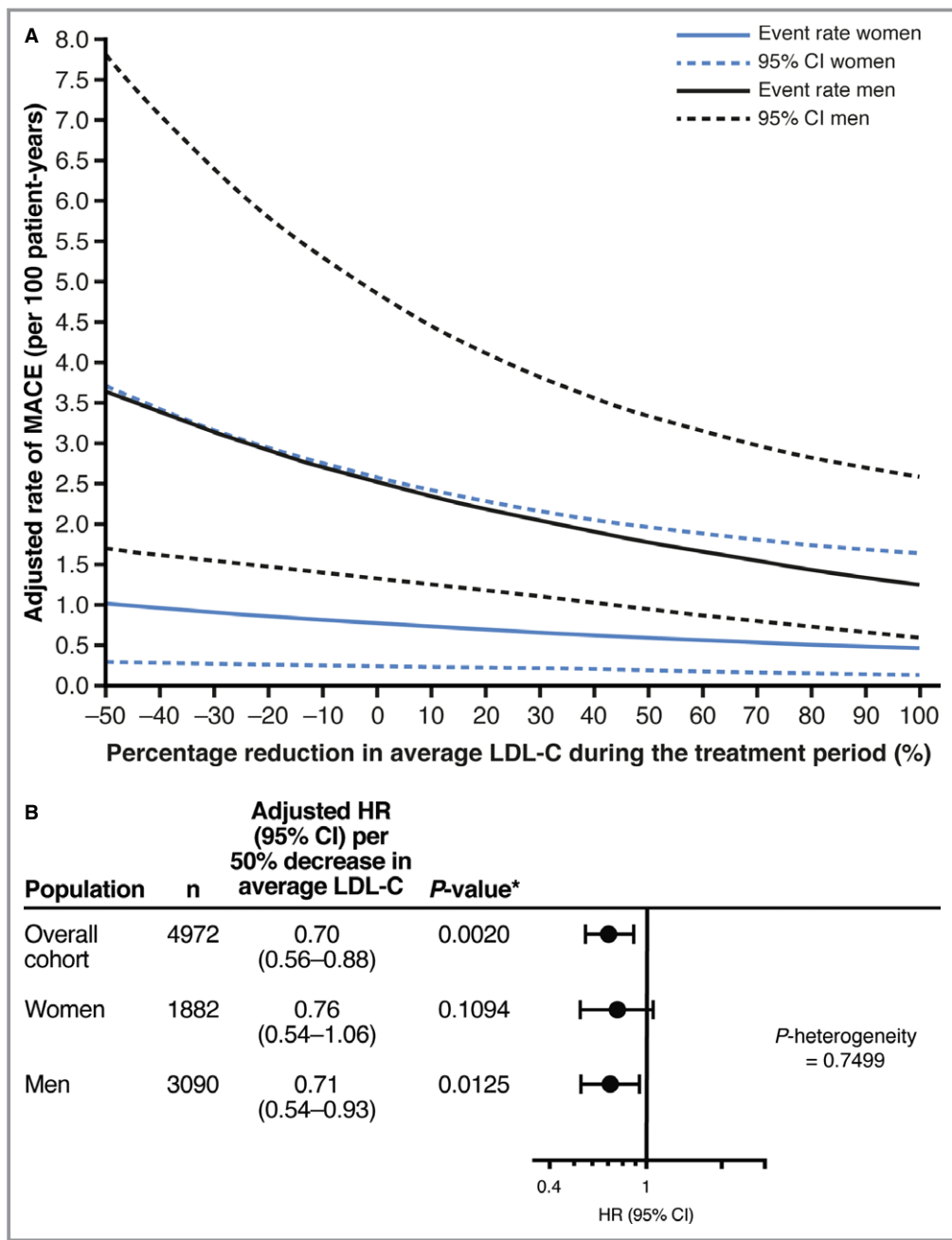


Figure 5. A, Adjusted rate of major adverse cardiovascular events (MACE) in women and men by percentage change from baseline in average low-density lipoprotein cholesterol (LDL-C). B, Risk of MACE associated with percentage reduction in average LDL-C (per 50% decrease) in women and men. Event rate and 95% confidence interval (CI) determined from a multivariate Poisson model, with adjustment for age, diabetes mellitus, history of myocardial infarction (MI)/stroke, baseline LDL-C, heterozygous familial hypocholesterolemia (HeFH), and smoking status. Percentage change from baseline in average LDL-C during treatment period (whatever the duration of the treatment period). For patients with no postbaseline LDL-C, LDL-C at baseline was used; 2 patients with missing baseline LDL-C were excluded from the multivariate analysis. *P values are for each 50% decrease in LDL-C. Hazard ratio (HR) was calculated using multivariate Cox regression analysis, adjusted for age (for the overall cohort only), diabetes mellitus, prior MI/ischemic stroke, baseline LDL-C, HeFH, and smoking status.

Incremental lowering of LDL-C with other nonstatin lipid-lowering medication added to statin therapy has also been shown to similarly improve cardiovascular outcomes in

women and men. In IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), a trial of simvastatin plus ezetimibe versus simvastatin alone, in which

Table 4. Relationship Between MACE, Selected Baseline Characteristics, and Percentage Change From Baseline in LDL-C in Women and Men (Safety Population)

Variable	Categories	Women				Men				P Value (Heterogeneity Test)
		No. of Patients	No. of Events (%/Year)	HR (95% CI)	P Value	No. of Patients	No. of Events (%/Year)	HR (95% CI)	P Value	
Age	Per 10-y increase	1882		0.96 (0.65–1.43)	0.8434	3090		1.70 (1.31–2.21)	<0.0001	...
HeFH	No	1256	28 (1.8)	Referent	0.0367	2379	61 (1.9)	Referent	0.9819	
	Yes	626	2 (0.2)	0.20 (0.04–0.90)		711	13 (1.3)	1.01 (0.51–1.99)		
Diabetes mellitus	No	1243	14 (0.9)	Referent	0.0781	2205	46 (1.5)	Referent	0.1096	...
	Yes	639	16 (1.9)	1.95 (0.93–4.09)		885	28 (2.4)	1.48 (0.92–2.39)		
History of MI/stroke	No	1269	9 (0.6)	Referent	0.0008	1529	30 (1.5)	Referent	0.3008	...
	Yes	613	21 (2.6)	4.08 (1.80–9.23)		1561	44 (1.9)	1.28 (0.80–2.06)		
Baseline LDL-C	Per 39 mg/dL decrease	1882		0.91 (0.64–1.27)	0.5669	3090		0.89 (0.70–1.13)	0.3531	...
Current smoker	No	1533	23 (1.2)	Referent	0.9098	2492	62 (1.8)	Referent	0.9770	...
	Yes	349	7 (1.5)	1.05 (0.43–2.60)		598	12 (1.4)	1.01 (0.54–0.93)		
% reduction in average LDL-C	Per 50% decrease	1882		0.76 (0.54–1.06)	0.1094	3090		0.71 (0.54–0.93)	0.0125	0.7499

No. of events (%/year)=number of patients with at least 1 event and crude (unadjusted) percentage of patients with event per year. HR, 95% CI, and P value determined from a multivariate Cox model. Multivariate analysis adjusted on baseline characteristics and stratified by sex. Percentage reductions in average LDL-C from baseline were determined from the area under the curve (using trapezoidal method), incorporating all LDL-C values up to the end of the treatment period or occurrence of MACE, whichever event occurred first. For patients with no postbaseline lipid value, lipid value at baseline was used; 2 patients with missing baseline LDL-C were excluded from the multivariate analysis. CI indicates confidence interval; HeFH; heterozygous familial hypercholesterolemia; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MI, myocardial infarction.

patients in the former group achieved mean on-treatment LDL-C of 53 mg/dL, the Kaplan-Meier event rate for cardiovascular events at 7 years was 31% and 33% in women and men, respectively, with simvastatin plus ezetimibe, compared with 34% and 35%, respectively, with simvastatin monotherapy (HR [95% CI], 0.88 [0.79–0.99] in women and 0.95 [0.89–1.01] in men; $P_{\text{interaction}}=0.267$).⁷ A recent prespecified analysis of IMPROVE-IT demonstrated a numerically greater relative risk reduction in the total number of primary cardiovascular events with ezetimibe/simvastatin than placebo/simvastatin in women (n=4416) compared with men (n=13 728; 19% and 6%, respectively [$P_{\text{interaction}}=0.08$]).²⁴ Similarly, in our study, there was a greater reduction in risk of MACE in women compared with men (33% and 22%, respectively), with no significant between-sex difference (P for heterogeneity=0.4597). However, in our study population, the absolute risk in women was considerably lower and

despite similar relative benefits, they therefore derived less absolute benefit from, for example, LDL-C differences of 50 versus 100 mg/dL. Thus, in the population studied, generally the absolute gains are less; albeit present, while in the population in which the treatment is likely to be used, the absolute risks are more likely to be higher. Such factors may affect costs (eg, at current prices, although our results show that the relative benefits in women are similar to that seen in men, the absolute benefits are less). Hence, at current costs, alirocumab treatment in women will be less cost-effective; however, among women with higher absolute risk and, for example, higher LDL-C, there will be greater absolute benefit, which may translate to greater cost-effectiveness.

Also, recently, similar to our results with alirocumab, a clinical outcomes trial of another PCSK9 inhibitor, evolocumab, in patients with ASCVD (the FOURIER trial) reported similar relative risk reductions in cardiovascular events in

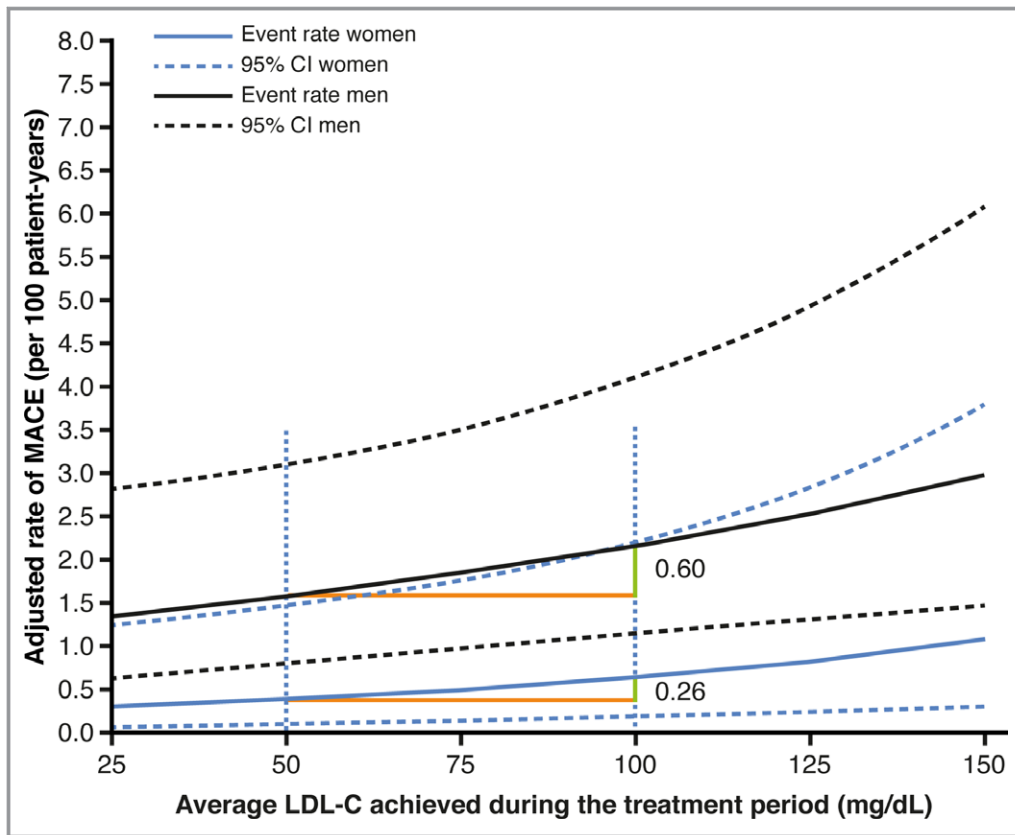


Figure 6. Absolute difference in rates of major adverse cardiovascular events (MACE) for average on-treatment low-density lipoprotein cholesterol (LDL-C) values of 50 and 100 mg/dL in women and men. CI indicates confidence interval.

women (HR [95% CI], 0.81 [0.69–0.95]) and men (HR [95% CI], 0.86 [0.80–0.94]) ($P_{\text{interaction}}=0.48$), among those treated with evolocumab (median on-treatment LDL-C, 30 mg/dL) versus placebo over 26 months of follow-up.⁸ Later analysis from the overall FOURIER cohort has shown a strong relationship between lower achieved LDL-C, including to very-low LDL-C levels, and a progressive reduction of cardiovascular events,²⁵ consistent with our observation of a lower rate of MACE in women and men with lower on-treatment LDL-C levels (Figure 4A). In line with results from the FOURIER trial⁸ and the CTT Collaboration,⁴ in our study, the P for heterogeneity between men and women was not significant for overall effects. Our analysis, therefore, provides complementary data for alirocumab on safety and efficacy, particularly for the relationship between LDL-C and MACE in women and men. Furthermore, although the CTT Collaboration had a greater number of women than our study (4416 versus 1887), the LDL-C achieved was much higher; the findings in our analysis, therefore, add to earlier results. Indeed, demonstration of a continuum of benefit through to very-low levels of LDL-C, in a lower-risk population in this pooled analysis than the populations studied in the FOURIER⁸ and ODYSSEY OUTCOMES¹² trials, should be considered complimentary data.

In the present analysis of the pooled cohort from the ODYSSEY phase 3 trials, a larger proportion of women had HeFH than men. This reflects the trial populations in the individual studies (Figure 1). Roughly equivalent proportions of women and men with HeFH were recruited into the familial hypercholesterolemia (FH)-specific trials, whereas a greater proportion of men (mainly with ASCVD) were recruited into the trials of high cardiovascular risk (non-FH) patients. The risk of MACE in the present analysis was adjusted by both presence of HeFH and history of myocardial infarction/stroke. In addition, sensitivity analysis, including or excluding HeFH from the models, did not materially change the results (data on file).

A previous analysis of the ODYSSEY trials showed that individuals with higher baseline LDL-C levels, higher body mass index, younger age (<50 years), and higher free PCSK9 levels (>400 ng/mL) are more likely to require a dose increase from 75 to 150 mg Q2W.²⁶ In our study, baseline LDL-C tended to be higher in women than men, and significantly more women than men required a dose increase at week 12; however, mean percentage reductions from baseline in LDL-C with alirocumab were $\approx 10\%$ greater in men than in women, possibly reflecting the greater proportion of women with HeFH.

Table 5. Safety Summary of Women and Men Treated With Alirocumab or Control: Data Pooled From 10 Phase 3 ODYSSEY Trials (Safety Population)

Variable	Women (n=1882)		Men (n=3092)	
	Alirocumab (n=1188)	Control (n=694)*	Alirocumab (n=1994)	Control (n=1098)*
TEAEs	943 (79.4)	565 (81.4)	1565 (78.5)	846 (77.0)
Treatment-emergent SAEs	168 (14.1)	112 (16.1)	364 (18.3)	176 (16.0)
TEAEs leading to death	4 (0.3)	4 (0.6)	18 (0.9)	18 (1.6)
TEAEs leading to discontinuation	95 (8.0)	52 (7.5)	133 (6.7)	81 (7.4)
TEAEs in $\geq 5\%$ of patients				
Arthralgia	49 (4.1)	47 (6.8)	111 (5.6)	55 (5.0)
Back pain	55 (4.6)	42 (6.1)	101 (5.1)	54 (4.9)
Bronchitis	64 (5.4)	40 (5.8)	74 (3.7)	38 (3.5)
Dizziness	61 (5.1)	30 (4.3)	56 (2.8)	49 (4.5)
Headache	80 (6.7)	45 (6.5)	82 (4.1)	43 (3.9)
Influenza	73 (6.1)	41 (5.9)	111 (5.6)	45 (4.1)
Injection-site reaction	95 (8.0)	43 (6.2)	97 (4.9)	32 (2.9)
Myalgia	59 (5.0)	44 (6.3)	114 (5.7)	50 (4.6)
Nasopharyngitis	114 (9.6)	66 (9.5)	229 (11.5)	117 (10.7)
Upper respiratory tract infection	81 (6.8)	51 (7.3)	143 (7.2)	83 (7.6)
Urinary tract infection	101 (8.5)	70 (10.1)	48 (2.4)	20 (1.8)

Data are given as number (percentage). SAE indicates serious adverse event; TEAE, treatment-emergent adverse event.

*Control=placebo or ezetimibe.

Several limitations of the present study merit consideration. For instance, although the present data are derived from randomized controlled trials, these are observational post hoc analyses, based on postrandomization groups, including a relatively reduced number (n=104) of MACE; a low sample size (n=4983), particularly women (n=1887); and a limited duration of follow-up (up to 72 weeks). The data were pooled from 10 trials that, although they had similar inclusion/exclusion criteria, differed in characteristics, such as the prevalence of HeFH, history of ASCVD, or baseline LDL-C. Therefore, although we have performed multivariate adjustments for baseline characteristics, we cannot fully rule out the potential for confounding factors influencing the results. In the pooled cohort, women had ≈ 10 to 15 mg/dL higher baseline LDL-C than men; among the factors that might have partly influenced these data is a higher proportion of patients with HeFH among women or a potentially perceived lower cardiovascular risk among women (lower rates of ASCVD at baseline compared with men; thus, they were potentially being treated less intensively). Nevertheless, because our analyses were adjusted for baseline LDL-C, we do not expect that baseline LDL-C levels ultimately accounted for our results. Finally, treatment duration was limited, ranging from 24 to 104 weeks.

In summary, within the present cohort studied, women derived slightly higher on-treatment levels of LDL-C and slightly lower LDL-C percentage reductions than men. Despite this, the present analysis reinforces the notion that both women and men derive a similar benefit from LDL-C-lowering in terms of cardiovascular risk reduction and provides further evidence of the safety and cardiovascular benefit of achieving lower LDL-C levels with alirocumab in both women and men.

Forthcoming results from the recently completed ODYSSEY Outcomes trial, which investigated the effect of alirocumab on cardiovascular outcomes in a large cohort of patients after acute coronary syndrome (n=18 924, ≈ 3 years of follow-up), are expected to provide further information on the effects of lower on-treatment LDL-C levels on cardiovascular risk in the overall cohort and in both women and men.¹²

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