Lower On-Treatment Low-Density Lipoprotein Cholesterol is Associated with Lower Cardiovascular Risk in Women: Analyses from the ODYSSEY Trials of Alirocumab versus Control

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Background

- In statin trials, women and men at similar risk of major adverse cardiovascular events (MACE) derived statistically significant reductions in risk (16% and 22%, respectively) for each 39 mg/dL reduction in low-density lipoprotein cholesterol (LDL-C); rate ratio (RR) was 0.84 (99% confidence interval [CI] 0.78–0.91) for women and 0.78 (99% CI 0.75–0.81) for men, both *P*<0.0001 (*P*-heterogeneity adjusted by sex 0.331).[1]
- Alirocumab, a proprotein convertase subtilisin/kexin type 9 inhibitor, was shown to significantly reduce LDL-C at doses of 75 or 150 mg every 2 weeks versus placebo or ezetimibe in Phase 3 ODYSSEY clinical trials.[2,3]
- Previous analysis of data from 10 ODYSSEY trials showed a continuous relationship between lower on-treatment LDL-C (including levels <50 mg/dL) and lower incidence of MACE.[3]
- In this analysis of the alirocumab ODYSSEY trials, we explored whether lower LDL-C levels would be associated with a lower rate of MACE in women as well as in men.

Methods

- Data from women and men patients were pooled from 10 ODYSSEY trials (double-blind periods of 24–104 weeks) which included a total of 4983 randomized patients.
- Patients in the trials had atherosclerotic cardiovascular disease (ASCVD) or cardiovascular (CV) risk factors with LDL-C not adequately controlled (most patients were receiving background of maximally tolerated statin therapy with or without other lipid-lowering therapies [LLTs]). See Table 1 for trial names and identifiers.
- Average LDL-C during treatment was determined from the area under the curve (using trapezoidal method), taking into account all LDL-C values up to the end of the treatment period or occurrence of MACE (defined as coronary heart disease [CHD] death, nonfatal myocardial infarction [MI], ischemic stroke, or unstable angina requiring hospitalization), whichever came first.
- Risk of MACE was assessed per 39 mg/dL lower mean on-treatment LDL-C determined from a multivariate Cox model. Rates of MACE were also fitted by a Poisson model in men and women, adjusted for baseline characteristics and average on-treatment LDL-C.

Results

- The 10 trials included a total of 1887 women (38% of the total population; Table 1).

Table 1. Baseline characteristics of patients with ASCVD or CV risk factors treated with alirocumab or control (placebo or ezetimibe), randomized population

	Female (n=1887)		Male (n=3096)	
	Alirocumab (n=1192)	Control (n=695)	Alirocumab (n=1996)	Control (n=1100)
Age, years, mean ± SD	60.2 ± 11.4	60.8 ± 10.9	59.1 ± 11.0	59.4 ± 10.8
Race, white, n (%)	1049 (88.0)	611 (87.9)	1835 (91.9)	1009 (91.7)
BMI, kg/m^2, mean ± SD	30.2 ± 6.5	30.6 ± 6.5	30.0 ± 5.2	30.0 ± 5.0
HeFH, n (%)	410 (34.4)	216 (31.1)	468 (23.4)	246 (22.4)
Diabetes, n (%)	401 (33.6)	240 (34.5)	583 (29.2)	308 (28.0)
ASCVD,† n (%)	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, n (%)	225 (18.9)	124 (17.8)	374 (18.7)	225 (20.5)
High-dose statin,‡ n (%)	644 (54.0)	329 (47.3)	1113 (55.8)	618 (56.2)
LLT other than statin,§ n (%)	371 (31.1)	219 (31.5)	636 (31.9)	353 (32.1)
Baseline LDL-C, mg/dL, mean ± SD	134.5 ± 53.8	135.7 ± 56.5	120.7 ± 43.0	120.4 ± 43.0
Baseline LDL-C, HeFH	159.6 ± 62.5	162.2 ± 66.1	150.8 ± 54.1	151.5 ± 50.8
Baseline LDL-C, non-FH	121.4 ± 43.2	123.8 ± 47.1	111.5 ± 34.1	111.4 ± 35.9

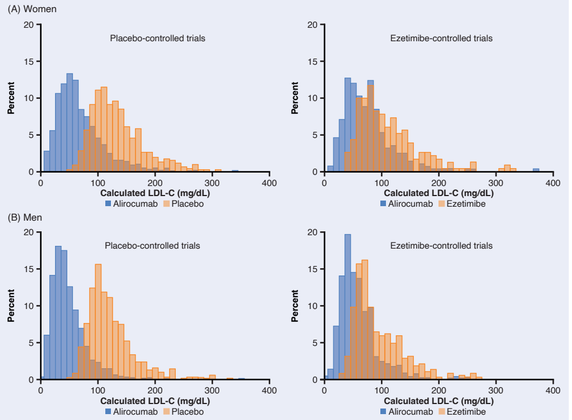
Data pooled from 10 randomized Phase 3 trials, including five placebo-controlled trials: COMBO I, NCT01644175; LONG TERM, NCT01507831; HIGH FH, NCT01617655; FH I, NCT01623115; and FH II, NCT01709500; and five ezetimibe-controlled trials: COMBO II, NCT01644188; MONO, NCT01644474; ALTERNATIVE, NCT01709513; OPTIONS I, NCT01730040; and OPTIONS II, NCT01730053. †Patients may be counted in ≥1 category. ‡Atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg. §In combination with statins or not.
BMI, body mass index; HeFH, heterozygous familial hypercholesterolemia; SD, standard deviation; PAD, peripheral arterial disease; TIA, transient ischemic attack.

- Baseline characteristics of the pooled population were generally similar between treatment groups (Table 1). In the alirocumab and control groups, 34.4 and 31.1% of women had HeFH compared with 23.4 and 22.4% of men, and 60.0 and 58.0% of women had ASCVD compared with 77.7% and 76.5% of men (Table 1).
- There was a trend for higher baseline LDL-C values in women versus men for both patients with and without HeFH (Table 1).

Association between LDL-C levels and MACE

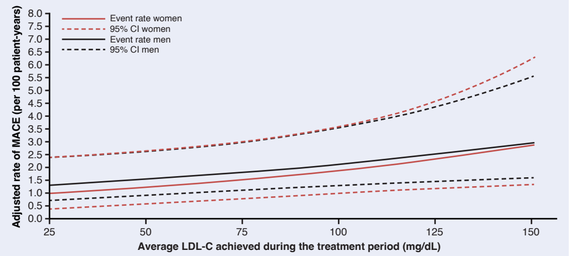
- Average on-treatment LDL-C levels were lower with alirocumab than control in women and men (Figure 1).
  - Average on-treatment LDL-C levels with alirocumab, ezetimibe, and placebo were 71, 114, and 134 mg/dL, respectively, in women (n=1882), and 52, 93, and 122 mg/dL, respectively, in men (n=3090).

Figure 1. Average LDL-C levels in A) women and B) men during treatment with alirocumab, placebo, or ezetimibe (safety populations)



- Average on-treatment LDL-C was correlated with the rate of MACE in both women and men (Figure 2).

Figure 2. Adjusted rate of MACE by average LDL-C achieved during the treatment period in women and men (multivariate analysis adjusted on baseline characteristics; safety population)

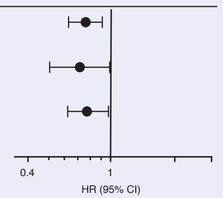


Event rate and 95% CI determined from a multivariate Poisson model, with adjustment for age, diabetes, prior history of MI or stroke, baseline LDL-C and smoking status. Average LDL-C during the treatment period determined from the area under the curve (using trapezoidal method), taking into account all LDL-C values up to end of treatment 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.

- Each 39 mg/dL lower on-treatment LDL-C was associated with a 29% lower risk of MACE in women (*P*=0.0459), and a 22% lower risk of MACE in men (*P*=0.0297), with no significant difference between women and men (*P*-heterogeneity 0.6427) (Figure 3).

Figure 3. Risk of MACE associated with each 39 mg/dL on-treatment reduction in LDL-C in women and men

Population	n	Adjusted HR (95% CI) per 39 mg/dL lower LDL-C	*P*-value†
Overall cohort	4972	0.76 (0.63–0.91)	0.0025
Women	1882	0.71 (0.51–0.99)	0.0459
Men	3090	0.78 (0.63–0.98)	0.0297



†*P*-values are for each 39 mg/dL decrease in LDL-C. HR calculated using multivariable Cox regression, adjusted for age, diabetes mellitus, prior MI/stroke, baseline LDL-C, and smoking.

- Overall, results were similar when analyzed by average percent reductions in LDL-C; hazard ratio (HR) (95% CI) per 50% reduction in LDL-C was 0.78 (0.54–1.12; *P*=0.1822) for women and 0.71 (0.54–0.93; *P*=0.0122) for men (*P*-heterogeneity 0.6678).
- Inclusion of HeFH in the model had no notable effect on the findings (Table 2).

Table 2. Relationship between MACE, selected baseline characteristics, and average achieved LDL-C during the treatment period (safety population; pool of 10 Phase 3 ODYSSEY trials)

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

†*P*-values are for each 39 mg/dL decrease in LDL-C. ‡Heterogeneity test compares results for women and men. n = number of patients; n event (%/year) = number of patients with at least one 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 post-baseline lipid value, lipid value at baseline was used; two patients with missing baseline LDL-C were excluded from the multivariate analysis.

Safety

- Alirocumab was generally well tolerated and showed a similar safety profile in women and men (Table 3).

Table 3. Safety summary of patients exposed to study treatment (pool of 10 Phase 3 ODYSSEY trials)

	Women (n=1882)		Men (n=3092)	
n (%)	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 ≥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	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)

†Control = placebo or ezetimibe. SAE, serious adverse event; TEAE, treatment emergent adverse event.

- Compared with control, the frequency of injection-site reactions was increased with alirocumab in both women (8.0% vs 6.2%) and men (4.9% vs 2.9%).

Conclusions

- This analysis of the global pool of Phase 3 trials of alirocumab (conducted in high-risk patients with elevated LDL-C levels receiving, for the most part, background statin therapy) showed that:
  - Women had slightly higher baseline and on-treatment LDL-C levels than men.
  - Both women and men showed a lower risk of MACE with lower LDL-C levels.
- Alirocumab was generally well tolerated with no differences in safety in women versus men.
- Study findings are observational, *post hoc*, and based on a small number of MACE events; however, the large (≈18,000 patients) ongoing ODYSSEY OUTCOMES study will provide further information on the association between lower on-treatment LDL-C and lower cardiovascular risk in women as well as men.

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