Lower On-Treatment Low-Density Lipoprotein Cholesterol is Associated with Lower Cardiovascular Risk in Very High-Risk Patients with Atherosclerotic Cardiovascular Disease: Analyses from the ODYSSEY Trials

Kausik K Ray,[1] Antonio J Vallejo-Vaz,[1] Henry N Ginsberg,[2] Michael H Davidson,[3] Robert H Eckel,[4] L Veronica Lee,[5] Laurence Bessac,[6] Robert Pordy,[7] Alexia Letierce,[8] Christopher P Cannon[9]

[1]*Imperial Centre for Cardiovascular Disease Prevention, Imperial College London, London, UK;* [2]*Columbia University, New York, NY, USA;* [3]*Department of Medicine, University of Chicago Medicine, Chicago, IL, USA;* [4]*University of Colorado, Anschutz Medical Campus, Aurora, CO, USA;* [5]*Sanofi, Bridgewater, NJ, USA;* [6]*Sanofi, Paris, France;* [7]*Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA;* [8]*Sanofi, Chilly-Mazarin, France;* [9]*Baim Institute for Clinical Research, Boston, MA, USA*

Background

- Individuals with hypercholesterolemia and established atherosclerotic cardiovascular disease (ASCVD) are considered to be at high risk of further ASCVD events.[1,2]
- Reducing levels of low-density lipoprotein cholesterol (LDL-C) with statins or ezetimibe has been shown to reduce ASCVD risk.[3,4] However, even with maximally tolerated statin therapy and ezetimibe, elevated LDL-C levels may persist.[5,6]
- Alirocumab, a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, has been approved for treating patients with clinical ASCVD and elevated LDL-C despite maximally tolerated statin by the US Food and Drug Administration.[7] Alirocumab is also approved for lowering LDL-C in Europe.[8]
- Analysis of data from 10 Phase 3 ODYSSEY trials (which compared alirocumab 75 or 150 mg every 2 weeks with placebo or ezetimibe, mostly on a background of maximally tolerated statin, for 24–104 weeks) showed a continuous relationship between lower on-treatment LDL-C and major adverse cardiovascular events (MACE); for every 39 mg/dL lower average LDL-C level achieved, the risk of MACE was reduced by 24% (adjusted hazard ratio [HR] 0.76, 95% confidence interval [CI]: 0.63–0.91; *P*=0.0025).[9]
- In this analysis of the ODYSSEY trials, we assessed the relationship between lower on-treatment LDL-C levels and MACE in very high-risk patients with ASCVD including those with polyvascular disease (PoVD), diabetes mellitus (DM), or reduced estimated glomerular filtration rate (eGFR).

Methods

- This pooled analysis included patients with ASCVD from 10 ODYSSEY trials (trial names and identifiers are given under Table 1). ASCVD was defined as coronary heart disease (CHD), ischemic stroke, or peripheral arterial disease (PAD), all of presumed atherosclerotic origin.[1]
- For further analysis, patients with ASCVD were analyzed in high-risk subgroups including patients with DM, eGFR <60 mL/min/1.73 m^2, or PoVD. DM was defined based on medical history. PoVD was defined as a history of multiple cardiovascular events in a single bed (separated by ≥30 days) or >1 affected vascular bed (irrespective of the time the event occurred).
- Baseline and safety data are presented for alirocumab and control (pooled placebo or ezetimibe) groups. For analysis of on-treatment LDL-C, data are presented separately for alirocumab, placebo and ezetimibe. For analysis of MACE, which correspond to few events overall, data have been pooled together for alirocumab, placebo and ezetimibe.
- 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 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. MACE rates were derived from a Poisson model adjusted for baseline characteristics and average on-treatment LDL-C.

Results

- Of 4983 patients randomized in the ODYSSEY trials, 3511 patients (70.5%) had a history of ASCVD. Furthermore, 984 patients had ASCVD+DM, 663 patients had ASCVD+eGFR <60 mL/min/1.73 m^2, and 945 patients had PoVD.
- Baseline characteristics of patients with ASCVD were similar between the alirocumab and control groups (Table 1); this was also seen for the high-risk subgroups (data not shown).

Table 1. Baseline characteristics of patients with ASCVD randomized to treatment with alirocumab or control (placebo or ezetimibe)

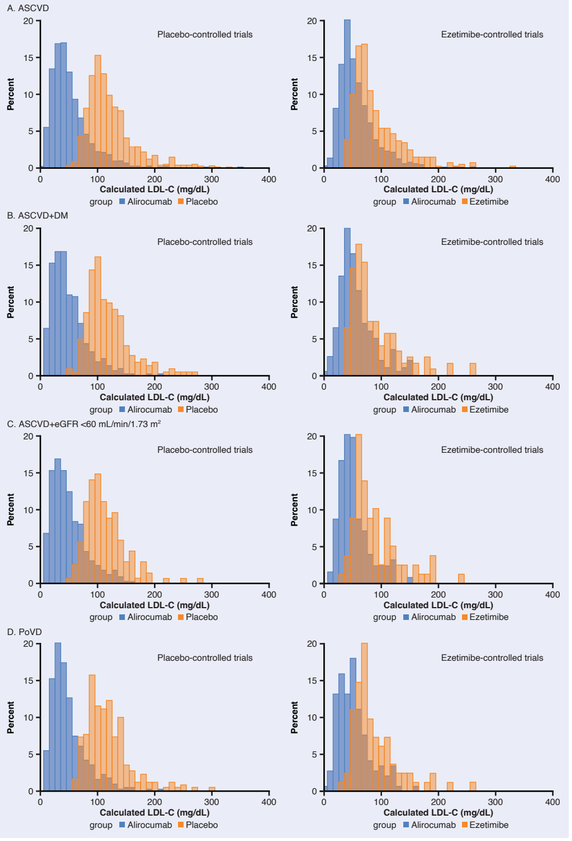
	ASCVD (N=3511)	
	Alirocumab (n=2266)	**Control (n=1245)**
Age, years, mean ± SD	61.7 ± 9.8	61.8 ± 9.6
Males, n (%)	1551 (68.4)	842 (67.6)
Race, white, n (%)	2065 (91.1)	1141 (91.6)
BMI, kg/m^2, mean ± SD	30.1 ± 5.4	30.3 ± 5.3
HeFH, n (%)	385 (17.0)	216 (17.3)
Diabetes, n (%)	639 (28.2)	347 (27.9)
ASCVD, n (%)[†]	2266 (100.0)	1245 (100.0)
CHD	2065 (91.1)	1156 (92.9)
Ischemic stroke	266 (11.7)	128 (10.3)
PAD	130 (5.7)	75 (6.0)
eGFR, mL/min/1.73 m^2, mean ± SD	74.4 ± 18.0	74.8 ± 18.2
Patients with baseline eGFR <60 mL/min/1.73 m^2, n (%)	447 (19.7)	216 (17.3)
Current smoker, n (%)	447 (19.7)	254 (20.4)
High-dose statin, n (%)[‡]	1299 (57.3)	717 (57.6)
LLT other than statin, n (%)[§]	679 (30.0)	388 (31.2)
Baseline LDL-C, mg/dL, mean ± SD	118.9 ± 42.1	119.4 ± 45.6

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 to 80 mg, rosuvastatin 20 to 40 mg, or simvastatin 80 mg. [§]In combination with statins or not.
BMI, body mass index; HeFH, heterozygous familial hypercholesterolemia; LLT, lipid-lowering therapy; SD, standard deviation.

Association between LDL-C levels and MACE

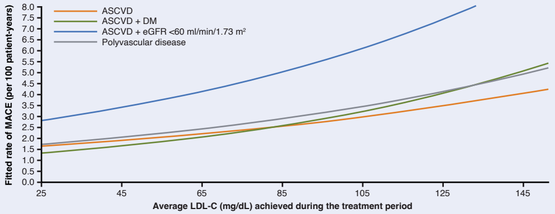
- Baseline mean LDL-C levels were 119 mg/dL for the overall pooled ASCVD population, 114 mg/dL for the ASCVD+DM subgroup, 113 mg/dL for the ASCVD+eGFR <60 mL/min/1.73 m^2 subgroup, and 116 mg/dL for the PoVD subgroup.
- Average on-treatment LDL-C levels were lower with alirocumab than control in the overall ASCVD population and in each high-risk subgroup (Figure 1).

Figure 1. Average LDL-C levels during treatment in patients with ASCVD (A) and very high-risk subgroups (B–D) in pools according to control used



- Achieved average LDL-C was correlated with MACE rates in the overall ASCVD cohort and in the high-risk subgroups (Figure 2).

Figure 2. Adjusted rate of MACE by average LDL-C achieved during the treatment period in all patients with ASCVD and in high-risk subgroups with comorbid DM, PoVD, or eGFR <60 mL/min/1.73 m^2 at baseline (multivariate analysis adjusted on baseline characteristics, safety population; pool of 10 Phase 3 ODYSSEY trials)



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 event, 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.

- In the overall ASCVD population, a 39 mg/dL lower LDL-C level was associated with a 25% lower risk of MACE, HR 0.75 (95% CI: 0.62–0.90), with a similar trend seen in the very high-risk ASCVD subgroups (Figure 3).

Figure 3. Relationship between MACE and each 39 mg/dL lower average LDL-C in very high-risk ASCVD subgroups (safety population; pool of 10 Phase 3 ODYSSEY trials)

Population	n	HR (95% CI) per 39 mg/dL lower LDL-C	Lower risk	Higher risk	Adjusted rate (%) of MACE per 100 patient-years (95% CI): Mean achieved LDL-C 40 mg/dL	Mean achieved LDL-C 79 mg/dL	Mean achieved LDL-C 120 mg/dL
Overall ASCVD	3503	0.75 (0.62 to 0.90)			1.81 (1.12 to 2.94)	2.44 (1.59 to 3.76)	3.34 (2.11 to 5.28)
Polyvascular disease	943	0.71 (0.49 to 1.01)			1.94 (0.75 to 5.01)	2.75 (1.18 to 6.37)	3.96 (1.63 to 9.60)
ASCVD + DM	980	0.65 (0.49 to 0.86)			1.55 (0.67 to 3.58)	2.41 (1.12 to 5.19)	3.83 (1.72 to 8.54)
ASCVD + eGFR <60 mL/min/1.73 m^2	660	0.69 (0.48 to 1.00)			3.26 (1.27 to 8.35)	4.77 (2.07 to 11.00)	7.13 (2.93 to 17.35)

HR calculated using Cox multivariable regression analysis, adjusted for age, gender, diabetes (except for the ASCVD+DM 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 under treatment.

- The relationship between MACE and selected baseline variables and average LDL-C in patients with ASCVD is shown in Table 2. Being older and having diabetes were significant factors associated with MACE.

Table 2. Relationship between MACE and selected baseline variables and average LDL-C during the treatment period in patients with ASCVD (safety population; pool of 10 Phase 3 ODYSSEY trials)

	Categories	n	n events (%/year)	HR (95% CI)	*P*-value
Age	Per 10-year increase	3503		1.33 (1.07–1.66)	0.0117
Gender	Male	2389	71 (2.1)	Referent	0.2446
	Female	1114	29 (1.9)	0.77 (0.49–1.20)	
Diabetes	No	2523	58 (1.6)	Referent	0.0012
	Yes	980	42 (3.2)	1.94 (1.30–2.90)	
Prior history of MI/stroke	No	1344	36 (2.0)	Referent	0.6099
	Yes	2159	64 (2.1)	1.11 (0.74–1.68)	
Baseline LDL-C	Per 39 mg/dL decrease	3503		1.12 (0.89–1.40)	0.3420
Current smoker	No	2803	81 (2.1)	Referent	0.7165
	Yes	700	19 (1.9)	1.10 (0.66–1.84)	
Average LDL-C during treatment period	Per 39 mg/dL decrease	3503		0.75 (0.62–0.90)	0.0022

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. Average LDL-C during the treatment period determined from the area under the curve (using trapezoidal method), taking into account all values up to end of treatment period or occurrence of MACE event, whichever came first. 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

- The safety profile of alirocumab in patients with ASCVD was similar to that seen with control, except for a higher rate of injection-site reactions with alirocumab (Table 3). The safety profile was also similar between alirocumab and control in the high-risk subgroups (data not shown).

Table 3. Safety analysis of patients with ASCVD (pool of 10 Phase 3 ODYSSEY trials)

	ASCVD (n=3505)	
n (%)	**Alirocumab (n=2262)**	**Control* (n=1243)**
TEAEs	1809 (80.0)	986 (79.3)
Treatment-emergent SAEs	458 (20.2)	247 (19.9)
TEAEs leading to death	19 (0.8)	21 (1.7)
TEAEs leading to discontinuation	164 (7.3)	99 (8.0)
TEAEs in ≥5% of patients		
Arthralgia	119 (5.3)	70 (5.6)
Back pain	107 (4.7)	67 (5.4)
Bronchitis	101 (4.5)	55 (4.4)
Diarrhoea	107 (4.7)	54 (4.3)
Dizziness	88 (3.9)	60 (4.8)
Headache	106 (4.7)	56 (4.5)
Hypertension	104 (4.6)	53 (4.3)
Influenza	108 (4.8)	53 (4.3)
Injection-site reaction	123 (5.4)	42 (3.4)
Myalgia	124 (5.5)	58 (4.7)
Nasopharyngitis	241 (10.7)	112 (9.0)
Pain in extremity	74 (3.3)	53 (4.3)
Upper respiratory tract infection	169 (7.5)	99 (8.0)
Urinary tract infection	99 (4.4)	56 (4.5)

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

Conclusions

- Based on available Phase 3 data, in very high-risk patients with ASCVD (~70% of the Phase 3 trial population) and mean baseline LDL-C >70 mg/dL, lower achieved LDL-C levels were associated with lower rates of MACE.
- Study findings are observational, *post hoc* and based on a small number of MACE events; however, the large (n=18,000 patients) ongoing prospective ODYSSEY OUTCOMES study will provide further information on the relationship between lower on-treatment LDL-C and lower cardiovascular risk in high-risk patients with clinical ASCVD.

References

1. Stone NJ et al. *J Am Coll Cardiol.* 2014;63:2889–2934.
2. Catapano AL et al. *Eur Heart J.* 2016;37:2999–3058.
3. Baigent C et al. *Lancet.* 2010;376:1670–1681.
4. Cannon CP et al. *N Engl J Med.* 2015;372:2387–2397.
5. Landmesser U et al. *Eur Heart J.* 2016 [Epub ahead of print].
6. Lloyd-Jones DM et al. *J Am Coll Cardiol.* 2016;68:92–125.
7. Praluent prescribing information (US). 2015. Available at: http://products.sanofi.us/praluent/praluent.pdf [Accessed Feb 2, 2017].
8. Praluent summary of product characteristics (EC). 2015. Available at: http://ec.europa.eu/health/documents/community-register/2015/20150923132812/anx_132812_en.pdf [Accessed Feb 2, 2017].
9. Ray KK et al. *Circulation.* 2016;134:1931–1943.

Acknowledgements

This study was funded by Sanofi and Regeneron Pharmaceuticals, Inc. Medical writing support and typesetting was provided by Prime, Knutsford, UK, funded by Sanofi and Regeneron Pharmaceuticals, Inc.

Disclosures

Kausik K Ray: Research grants from Pfizer, Amgen, Sanofi, Regeneron Pharmaceuticals, Inc., and MS; modest honoraria from Cipla, Algorithm, Sanofi, Amgen, Boehringer Ingelheim, Takeda, and Pfizer; and modest consultant/advisory board fees from Takeda, Medco, AstraZeneca, Resverlogix, Kowa, AbbVie, Inc., Eli Lilly, Sanofi, Amgen, Boehringer Ingelheim, and Regeneron Pharmaceuticals, Inc. **Antonio J Vallejo-Vaz:** No disclosures. **Henry N Ginsberg:** research grants from Merck, Sanofi, Regeneron Pharmaceuticals, Inc., and Amgen; and modest consultant/advisory board fees from Amarin, Amgen, AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline, Ionis, Janssen, Kowa, Merck, Novartis, Sanofi, Regeneron Pharmaceuticals, Inc., and Pfizer. **Michael H Davidson:** speaker's bureau fees from Sanofi, Regeneron Pharmaceuticals, Inc., and Amgen; significant honoraria from Sanofi, Regeneron Pharmaceuticals, Inc., and Amgen; and consultant/advisory board fees from Sanofi, Regeneron Pharmaceuticals, Inc., and Amgen. **Robert H Eckel:** research grants from Ionis and UniQure; modest consultant/advisory board fees from Merck; and significant consultant/advisory board fees from Regeneron Pharmaceuticals, Inc. and Sanofi. **L Veronica Lee:** employee/stockholder of Sanofi. **Laurence Bessac:** employee/stockholder, Sanofi. **Robert Pordy:** employee/stockholder, Regeneron Pharmaceuticals, Inc. **Alexia Letierce:** employee/stockholder, Sanofi. **Christopher P Cannon:** research grants from Arisaph, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Merck, and Takeda; modest consultant/advisory board fees from Alnylam, Amgen, Arisaph, Boehringer Ingelheim, Boehringer Ingelheim/Eli Lilly, Bristol Myers Squibb, GlaxoSmithKline, Kowa, Merck, Takeda, and Pfizer; and significant consultant/advisory board fees from Lipimedix, Regeneron Pharmaceuticals, Inc., and Sanofi.

Poster presented at the American College of Cardiology 66th Annual Scientific Session, March 17–19, 2017, Washington, DC, USA.