Journal of Clinical Lipidology (2019) ■, ■–■

Journal of Clinical Lipidology

Original Article

Treatment effect of alirocumab according to age group, smoking status, and hypertension: Pooled analysis from 10 randomized ODYSSEY studies

Frederick J. Raal, MBBCh, MMed, PhD*, Jaakko Tuomilehto, MD, PhD, Andrei C. Sposito, MD, PhD, Francisco A. Fonseca, MD, PhD, Maurizio Averna, MD, Michel Farnier, MD, PhD, Raul D. Santos, MD, PhD, MSc, Keith C. Ferdinand, MD, R. Scott Wright, MD, Eliano Pio Navarese, MD, PhD, Danielle M. Lerch, PharmD, RPh, Michael J. Louie, MD, MPH, MSc, L. Veronica Lee, MD, Alexia Letierce, PhD, Jennifer G. Robinson, MD, MPH

Division of Endocrinology and Metabolism, Department of Medicine, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa (Dr Raal); Department of Public Health Solutions, National Institute for Health and Welfare, Helsinki, Finland (Dr Tuomilehto); Diabetes Research Group, King Abdulaziz University, Jeddah, Saudi Arabia (Dr Tuomilehto); Cardiology Division, State University of Campinas School of Medicine (FCM Unicamp), Campinas, Brazil (Dr Sposito); Cardiology Division, Department of Medicine, Federal University of Sao Paulo, Sao Paulo, Brazil (Dr Fonseca); Department of Health Promotion Sciences Maternal and Infantile Care, Internal Medicine and Medical Specialties (PROMISE), School of Medicine, University of Palermo, Palermo, Italy (Dr Averna); Department of Cardiology, Lipid Clinic, Point Médical, CHU Dijon Bourgogne, Dijon, France (Dr Farnier); Lipid Clinic Heart Institute (InCor), University of Sao Paulo Medical School Hospital, Hospital Israelita Albert Einstein, Sao Paulo, Brazil (Dr Santos); Department of Medicine, Heart and Vascular Institute, Tulane University School of Medicine, New Orleans, LA, USA (Dr Ferdinand); Department of Cardiology, Mayo Clinic, Rochester, MN, USA (Dr Wright); Interventional Cardiology and Cardiovascular Medicine Research, Mater Dei Hospital, Bari, Italy (Dr Navarese); Cardiovascular Institute, Ludwik Rydygier Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland (Dr Navarese); SIRIO MEDICINE Network, VA, USA (Dr Navarese); Sanofi, Bridgewater, NJ, USA (Drs Lerch and Lee); Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA (Dr Louie); Sanofi, Biostatistics and Programming, Chilly–Mazarin, France (Dr Letierce); and University of Iowa, Iowa City, IA, USA (Dr Robinson)

Part of these data were presented at the American College of Cardiology 65th Annual Scientific Session, Chicago, IL, USA (April 3, 2016) and the World Heart Federation World Congress of Cardiology & Cardiovascular Health 2016 (June 4–7), Mexico City, Mexico.

Trial registration: ClinicalTrials.gov identifiers: NCT01507831, NCT01617655, NCT01644175, NCT01623115, NCT01709500, NCT01644188, NCT01730040, NCT01730053, NCT01709513, NCT01644474.

* Corresponding author. Faculty of Health Sciences, University of Witwatersrand, 29 Princess of Wales Terrace, Parktown, Johannesburg 2193, South Africa.

E-mail address: Frederick.raal@wits.ac.za

Submitted March 15, 2019. Accepted for publication June 24, 2019.

https://doi.org/10.1016/j.jacl.2019.06.006

KEYWORDS:
Hypercholesterolemia;
PCSK9;
Cholesterol;
Hypertension;
Smoking;
Age

BACKGROUND: Age, smoking, hypercholesterolemia, and hypertension are major risk factors for atherosclerotic cardiovascular disease.

OBJECTIVE: We examined whether the effects of alirocumab on low-density lipoprotein cholesterol (LDL-C) differed according to age, hypertension, or smoking status.

METHODS: Data were pooled from 10 Phase 3 ODYSSEY randomized trials (24–104 weeks' duration) in 4983 people with heterozygous familial hypercholesterolemia (FH) or non–familial hypercholesterolemia (3188 on alirocumab, 1795 on control [620 on ezetimibe and 1175 on placebo]). Most participants received concomitant maximum tolerated statin therapy. In 8 trials, the alirocumab dose was increased from 75 mg every 2 weeks (Q2W) to 150 mg Q2W at Week 12 if predefined risk-based LDL-C goals were not achieved at Week 8 (≥70 mg/dL in very high cardiovascular risk; ≥100 mg/dL in moderate or high cardiovascular risk). Two trials compared alirocumab 150 mg Q2W vs placebo. The efficacy and safety of alirocumab were assessed post hoc in subgroups stratified by age (<65, ≥65 to <75, ≥75 years) and baseline hypertension or smoking status.

RESULTS: Alirocumab reduced LDL-C by 23.7% (75/150 mg vs ezetimibe + statin) to 65.4% (150 mg vs placebo + statin) from baseline to Week 24 vs control. Subgroup analyses confirmed no significant interactions in response to alirocumab between age group, hypertension, or smoking status. Overall rates of treatment-emergent adverse events were similar between alirocumab and control groups.

CONCLUSIONS: In this pooled analysis from 10 trials, alirocumab led to substantial LDL-C reductions vs control in every age group and regardless of hypertension or smoking status. Alirocumab was well tolerated in all subgroups.

Introduction

In addition to hypercholesterolemia, age, tobacco smoking, and hypertension are major risk factors for the development of cardiovascular disease (CVD).[1–5] These characteristics could also potentially influence the efficacy and safety of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibiting monoclonal antibodies, which are potent low-density lipoprotein cholesterol (LDL-C)-lowering drugs. PCSK9, a key regulator of cholesterol homeostasis, elevates LDL-C levels by binding to the low-density lipoprotein receptor, thereby enhancing its degradation.[6]

Advancing age increases the risk of atherosclerotic CVD,[1] is associated with a higher prevalence of comorbidities,[7–9] and raises the likelihood of polypharmacy and adverse drug reactions.[10,11] Aging is also associated with physiological changes affecting the pharmacokinetics and pharmacodynamics of medications, with the potential for modified efficacy and increased drug toxicity.[12]

In addition, exposure to cigarette smoke increases the risk of thrombosis via endothelial cell damage, platelet activation, and inflammatory, antifibrinolytic, and procoagulant effects.[13] Smoking alters plasma lipoprotein metabolism, raises LDL-C modestly, and reduces high-density lipoprotein cholesterol (HDL-C) levels.[14,15] One of the mechanisms through which smoking may promote atherosclerosis is by increasing inflammatory activity and oxidative stress, which mediate the generation of oxidized low-density lipoprotein.[16] PCSK9 may be upregulated in a dose-dependent manner via oxidized low-density lipoprotein stimulation in macrophages, lipopolysaccharide stimulation in the kidney, and inflammatory mediators in hepatocytes.[17] Hence, it is plausible to infer that smoking could affect PCSK9 bioavailability and potentially mitigate the efficacy of PCSK9 antibody therapy.

Hypertension commonly coexists with elevated LDL-C, and many hypertensive patients are eligible for lipid-lowering therapy (LLT) with statins to lower their cardiovascular risk.[18,19] Despite receiving maximally tolerated statin therapy, a substantial proportion of patients with high CVD risk require additional LDL-C reduction.[4,20,21] In parallel, the coexistence of hypertension and hypercholesterolemia seems to have a causal link through a mechanistic interaction, and a direct association has been reported between blood pressure and PCSK9 levels.[22]

Alirocumab is a highly specific, fully human monoclonal antibody to PCSK9. Alone, or in combination with other LLT, alirocumab reduced LDL-C levels by 43% to 73% at doses of 75 mg (with a possible dose increase to 150 mg) or 150 mg every 2 weeks (Q2W) in patients with hypercholesterolemia, including heterozygous familial hypercholesterolemia (FH).[20,21,23–31]

The objective of this analysis was to examine whether the effect of alirocumab on LDL-C differs according to participant age, hypertension, or smoking status.

Methods

In this analysis, data were pooled from 10 Phase 3 ODYSSEY randomized trials of 24 to 104 weeks' duration in people with hypercholesterolemia (heterozygous FH or non-FH): FH I (NCT01623115),[27] FH II (NCT01709500),[27]

HIGH FH (NCT01617655),[31] LONG TERM (NCT01507831),[28] COMBO I (NCT01644175),[20] COMBO II (NCT01644188),[21] OPTIONS I (NCT01730040),[26] OPTIONS II (NCT01730053),[29] ALTERNATIVE (NCT01709513),[30] and MONO (NCT01644474).[25] All participants received stable background statin with or without other LLT, except for those in ALTERNATIVE and MONO, which were conducted without background statin treatment. Details on the study designs are provided in Supplementary Table 1.

In 8 trials (COMBO I/II, FH I/II, OPTIONS I/II, ALTERNATIVE, and MONO, N = 1563 alirocumab, 972 control), the alirocumab dose was increased from 75 mg Q2W to 150 mg Q2W at Week 12 if predefined risk-based LDL-C goals were not achieved at Week 8 (≥70 mg/dL [1.8 mmol/L] in very high CVD risk patients [and in moderate-risk patients in MONO] or ≥100 mg/dL [2.6 mmol/L] in moderate or high CVD risk patients). The remaining 2 trials (LONG TERM and HIGH FH, N = 1625 alirocumab, 823 control) compared alirocumab 150 mg Q2W with placebo. In all studies, alirocumab 75 mg or 150 mg and placebo injections were administered subcutaneously using a 1 mL injection volume. Ezetimibe and its placebo were administered daily orally.

Age at entry in the trials was classified in 3 categories (<65, ≥65 to <75, ≥75 years). Hypertension status was determined by the investigator based on an assessment of the participant's medical history (eg, use of antihypertension medication). Smokers were defined as patients who smoked ≥1 cigarette during the past month, except for participants in MONO, OPTIONS I/II, and ALTERNATIVE, in which smokers were those who smoked ≥7 cigarettes weekly.

Patients

All participants (aged ≥18 years) provided written informed consent. Participants randomized in the MONO[25] study were at moderate CVD risk, according to SCORE.[2] Participants in the ALTERNATIVE study[30] were statin intolerant and at moderate, high, or very high CVD risk.[32] The remaining 8 studies involved people at high or very high CVD risk (Supplementary Table 1).[32] Inclusion criteria for baseline LDL-C were ≥70 mg/dL (1.8 mmol/L) for participants with a history of CVD events and ≥100 mg/dL (2.6 mmol/L) in participants without previous CVD events, except for the HIGH FH and LONG TERM studies, in which LDL-C had to be ≥160 mg/dL (4.1 mmol/L) and ≥70 mg/dL (1.8 mmol/L), respectively, in all at baseline. Definitions for heterozygous FH, coronary heart disease, CVD, and diabetes are provided in Supplementary Table 2.

Statistical analysis

For efficacy analyses, data were pooled according to the initial alirocumab dose (75 mg or 150 mg) and control (placebo with statin or ezetimibe with/without statin). For safety analyses, data were pooled according to control group only (placebo or ezetimibe).

The efficacy and safety of alirocumab were assessed in participant subgroups stratified by age (<65, ≥65 to <75 [elderly], and ≥75 years [very elderly]), hypertension status at baseline, and smoking status at baseline.

Percent LDL-C reduction from baseline to Week 24 was analyzed using an intent-to-treat (ITT) approach (including all lipid data regardless of adherence to treatment). A mixed effects model with repeated measures was used to account for missing data. Treatment effect across subgroups was assessed using mixed effects model with repeated measures. The proportion of very high cardiovascular risk patients who reached a calculated LDL-C value <70 mg/dL or moderate to high cardiovascular risk patients who reached a calculated LDL-C <100 mg/dL at Week 24 was calculated in the on-treatment (modified ITT) population, defined as the randomized population who received the double-blind injection and had an evaluable primary efficacy endpoint during the efficacy double-blind treatment period.

The analysis was performed using SAS version 9.2 software (SAS Institute Inc, Cary, NC).

Results

A total of 4983 people (randomized population) were included in the placebo- or ezetimibe-controlled studies (Fig. 1), of which 3241 (65.0%) participants were aged <65 years, 1437 (28.8%) were aged ≥65 to <75 years, and 305 (6.1%) were aged ≥75 years. Hypertension was present in 3475 (69.7%) participants and 947 (19.0%) were smokers.

Baseline characteristics

The baseline characteristics for age, hypertension, and smoking subgroups, according to treatment, are detailed in Supplementary Table 3. The prevalence of heterozygous FH in the subgroup analyzed according to age ranged from 0% to 44.2%, CVD from 61.1% to 87.2%, and diabetes from 23.7% to 43.6% (Supplementary Table 3A).

Mean age of participants without hypertension ranged from 52.8 to 59.5 years, and those with hypertension ranged from 61.2 to 63.3 years (Supplementary Table 3B). The prevalence of heterozygous FH ranged from 2.8% to 22.9% in participants with hypertension, and from 9.9% to 65.1% in those without hypertension. The most common antihypertensive medication(s) taken by patients with hypertension were angiotensin-converting enzyme inhibitors (N = 1165; 52.6%) and angiotensin II receptor blockers (N = 604, 27.3%), alone or with calcium channel blockers and/or diuretics.

Mean age of participants who smoked ranged from 54.8 to 58.8 years, and mean age of nonsmokers ranged from 59.5 to 63.6 years (Supplementary Table 3C).

Baseline levels of PCSK9, LDL-C, lipoprotein(a), and high-sensitivity C-reactive protein (hsCRP) are detailed in Supplementary Table 3.

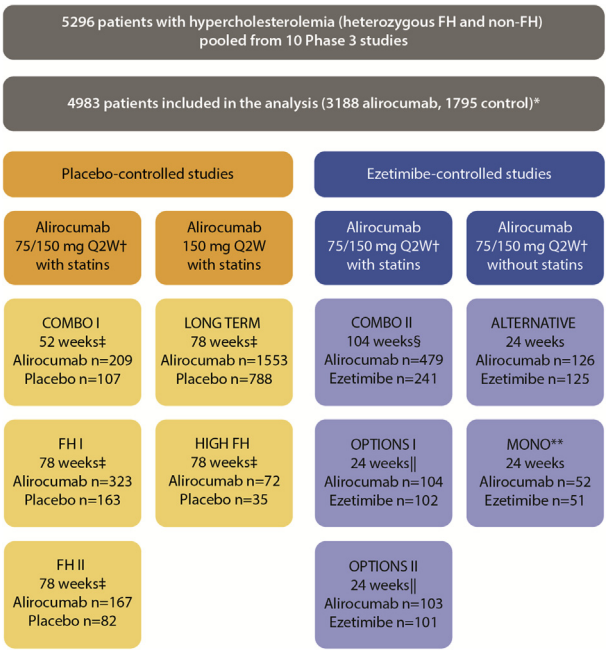


Figure 1 Summary of the studies included in the analysis (randomized population): FH I,[27] FH II,[27] HIGH FH,[31] LONG TERM,[28] COMBO I,[20] COMBO II,[21] OPTIONS I,[26] OPTIONS II,[29] ALTERNATIVE,[30] MONO.[25] *Statin-only control arms in OPTIONS I/II and ALTERNATIVE (N = 313) were excluded. †Alirocumab 75 mg Q2W was increased to 150 mg Q2W at Week 12 depending on LDL-C at Week 8. ‡Maximally tolerated statin (atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg or lower doses with an investigator-approved reason) ± LLT. §Maximally tolerated statin, no other LLT. ‖Fixed doses of atorvastatin 20 to 40 mg or rosuvastatin 10 to 20 mg ± non-statin LLT. **No statins or other LLT. FH, familial hypercholesterolemia; LDL, low-density lipoprotein; LLT, lipid-lowering therapy; Q2W, every 2 weeks.

Efficacy

Alirocumab significantly reduced LDL-C from baseline to Week 24, ranging from 23.7% with the 75/150 mg alirocumab dose vs ezetimibe plus statin to 65.4% with the 150 mg alirocumab dose vs placebo plus statin; reductions were observed in all study pools (Fig. 2A–C). Subgroup analysis confirmed that there were no significant interactions in LDL-C response to alirocumab between age group, hypertension, or smoking status. There was also no effect on the proportion of participants with very high CVD risk reaching calculated LDL-C <70 mg/dL (1.8 mmol/L) or participants with high CVD risk reaching calculated LDL-C <100 mg/dL (2.6 mmol/L) (modified ITT analysis; Fig. 3).

Safety

The overall rates of treatment-emergent adverse events (TEAEs) were similar between the alirocumab and control (placebo or ezetimibe) patients (Supplementary Table 4). The incidence of injection site reactions for the overall placebo-controlled pool was 7.2% for alirocumab and 5.3% for placebo. Corresponding data for the overall ezetimibe-controlled pool are 2.9% for alirocumab and 2.1% for ezetimibe.

The rates of TEAEs according to age, hypertension status, and smoking status are detailed in Supplementary Table 5. The rates of TEAEs, treatment-emergent serious adverse events, and TEAEs leading to treatment discontinuation appeared to increase with advancing age in both the alirocumab and the placebo groups. In the ezetimibe-controlled studies, TEAEs leading to treatment discontinuation were highest among very elderly participants treated with ezetimibe. The rates of treatment-emergent serious adverse events were higher among the hypertensive vs non-hypertensive participants in the alirocumab, ezetimibe, and placebo groups. No differences were apparent in the rates of overall TEAEs in smokers vs nonsmokers.

Discussion

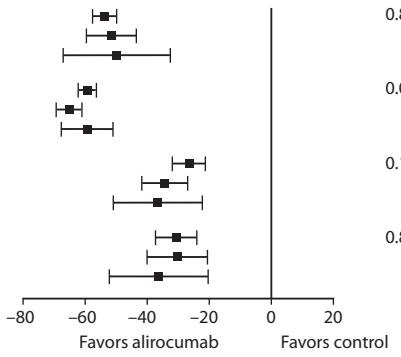
The present pooled analysis of 10 randomized trials from the ODYSSEY program confirms that alirocumab substantially reduces LDL-C levels by between 49.8% and 65.4% vs placebo and by 23.7% and 38.2% vs ezetimibe in moderate to very high CVD risk people with hypercholesterolemia with or without other LLT, including patients with heterozygous FH. This large-scale analysis extends the previous findings[20,21,24–30,33] in that it shows a consistent treatment effect by alirocumab in providing a robust reduction in LDL-C levels across a wide range of ages and independently of hypertension or smoking status. Alirocumab treatment, compared with control therapy (placebo plus statin or ezetimibe), enabled a higher percentage of patients in all subgroups to reach the risk-based[5] LDL-C treatment target. Alirocumab was well tolerated at any age and in participants with or without hypertension and current or nonsmokers.

This analysis—based on individual participant data—affirms the efficacy of alirocumab in significantly reducing LDL-C levels, which is largely unaffected by wide variations in age, hypertension, or smoking status. Thus, it is central to providing additional insights into the LDL-lowering potential of alirocumab when there is a variable coexistence of these clinical risk factors in the same individual. The robust reductions observed were accompanied by the parallel safety of the administered drug, with similar rates of adverse events across the spectrum of participant subsets treated with alirocumab vs controls with various age ranges, hypertension, or smoking status.

Aging is associated with an increased risk of atherosclerotic CVD and other comorbid conditions,[1,7–9] leading to polypharmacy and potential for adverse drug reactions.[10,11] In our population, the number of medications being taken in addition to alirocumab ranged from 6 to 9 by age (Supplementary Table 3A). Aging is also associated with physiological changes that can increase drug toxicity.[12] In this pooled population, participants aged

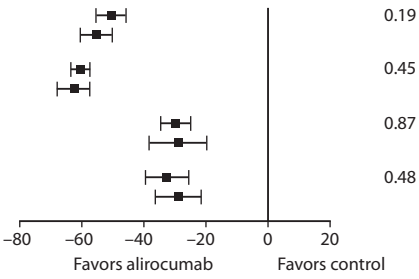
A

Study pool	Subgroup	N	% change from baseline LS mean (SE) Control	% change from baseline LS mean (SE) Alirocumab	LS mean (SE) difference vs. control	Difference in % change from baseline LS mean difference (95% CI) alirocumab vs control	Interaction *P*-value
Alirocumab 75/150 mg vs placebo (with statins)	<65 years	783	5.6 (1.7)	−47.6 (1.2)	−53.2 (2.1)		0.87
	≥65 to <75 years	212	0.7 (3.2)	−50.7 (2.4)	−51.4 (4.0)		
	≥75 years	48	−4.1 (7.2)	−53.9 (4.9)	−49.8 (8.6)		
Alirocumab 150 mg vs placebo (with statins)	<65 years	1553	−0.3 (1.3)	−59.4 (0.9)	−59.1 (1.5)		0.08
	≥65 to <75 years	676	2.6 (1.9)	−62.8 (1.4)	−65.4 (2.4)		
	≥75 years	187	0.1 (3.7)	−59.2 (2.6)	−59.3 (4.5)		
Alirocumab 75/150 mg vs ezetimibe (with statins)	<65 years	653	−19.5 (2.2)	−45.6 (1.8)	−26.1 (2.8)		0.15
	≥65 to <75 years	351	−19.4 (3.0)	−53.2 (2.4)	−34.0 (3.8)		
	≥75 years	101	−17.9 (5.7)	−54.3 (4.5)	−36.5 (7.2)		
Alirocumab 75/150 mg vs ezetimibe (without statins)	<65 years	217	−14.3 (2.3)	−44.8 (2.4)	−30.6 (3.3)		0.81
	≥65 to <75 years	99	−15.6 (3.8)	−45.5 (3.1)	−30.0 (4.9)		
	≥75 years	35	−15.4 (5.7)	−51.2 (6.0)	−35.8 (8.1)		



B

Study pool	Subgroup	N	% change from baseline LS mean (SE) Control	% change from baseline LS mean (SE) Alirocumab	LS mean (SE) difference vs. control	Difference in % change from baseline LS mean difference (95% CI) alirocumab vs control	Interaction *P*-value
Alirocumab 75/150 mg vs placebo (with statins)	Hypertension	567	3.0 (2.1)	−47.6 (1.5)	−50.6 (2.5)		0.19
	No hypertension	476	5.5 (2.2)	−49.7 (1.6)	−55.3 (2.6)		
Alirocumab 150 mg vs placebo (with statins)	Hypertension	1797	−0.6 (1.2)	−61.1 (0.8)	−60.5 (1.4)		0.45
	No hypertension	619	4.2 (2.1)	−58.5 (1.4)	−62.7 (2.5)		
Alirocumab 75/150 mg vs ezetimibe (with statins)	Hypertension	869	−18.6 (1.9)	−48.4 (1.5)	−29.7 (2.5)		0.87
	No hypertension	236	−22.0 (3.7)	−50.8 (2.9)	−28.8 (4.7)		
Alirocumab 75/150 mg vs ezetimibe (without statins)	Hypertension	191	−15.1 (2.6)	−47.6 (2.4)	−32.4 (3.5)		0.48
	No hypertension	160	−14.3 (2.7)	−43.1 (2.8)	−28.8 (3.8)		



C

Study pool	Subgroup	N	% change from baseline LS mean (SE) Control	% change from baseline LS mean (SE) Alirocumab	LS mean (SE) difference vs. control	Difference in % change from baseline LS mean difference (95% CI) alirocumab vs control	Interaction *P*-value
Alirocumab 75/150 mg vs placebo (with statins)	Smoker	176	6.6 (3.6)	−51.8 (2.6)	−58.3 (4.5)		0.17
	Non-smoker	867	3.7 (1.6)	−47.9 (1.1)	−51.6 (2.0)		
Alirocumab 150 mg vs placebo (with statins)	Smoker	497	0.2 (2.3)	−59.5 (1.6)	−59.7 (2.8)		0.64
	Non-smoker	1919	0.6 (1.1)	−60.6 (0.8)	−61.2 (1.4)		
Alirocumab 75/150 mg vs ezetimibe (with statins)	Smoker	233	−19.2 (3.4)	−42.9 (3.1)	−23.7 (4.6)		0.17
	Non-smoker	872	−19.4 (1.9)	−50.3 (1.5)	−30.9 (2.5)		
Alirocumab 75/150 mg vs ezetimibe (without statins)	Smoker	26	−13.5 (7.3)	−51.7 (6.5)	−38.2 (9.8)		0.43
	Non-smoker	325	−14.8 (1.9)	−45.1 (1.9)	−30.3 (2.7)		

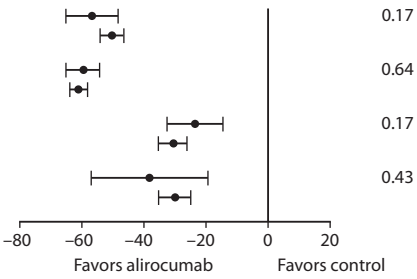


Figure 2 Percent change in LDL-C at Week 24 according to (A) age group, (B) hypertension, and (C) smoking status (ITT analysis). CI, confidence interval; ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol; LS, least square; SE, standard error.

<65 years were more likely than older patients to receive nonstatin LLT in addition to statins (placebo-controlled population). They also had higher baseline LDL-C levels, most likely reflecting the higher prevalence of heterozygous FH among the participants aged <65 years. Our results show a consistent effect across all age and treatment groups, as demonstrated by Ginsberg et al.[34] The overall rates of TEAEs increased slightly with age, but these increases were apparent in both the alirocumab and the placebo groups.

Hypertension and hypercholesterolemia frequently coexist, are strongly related from a pathophysiological perspective,[35] and may lead to a higher rate of CVD events than expected in individuals with only one of these conditions.[36] Lakoski et al[22] reported an association between blood pressure and PCSK9 levels, but the correlation was weak ($r = 0.02–0.08$). In our analysis, there was no suggestion of higher levels of PCSK9 among participants with vs without hypertension.

Tobacco smoking is related to increased CVD risk and remains an important risk factor despite substantial improvements in the prevention and treatment of CVD.[37,38] Smokers experience CVD events much earlier than nonsmokers,[38] as illustrated in our study in which smokers were younger than nonsmokers. Smoking alters plasma lipoprotein metabolism, raising LDL-C and, in particular,

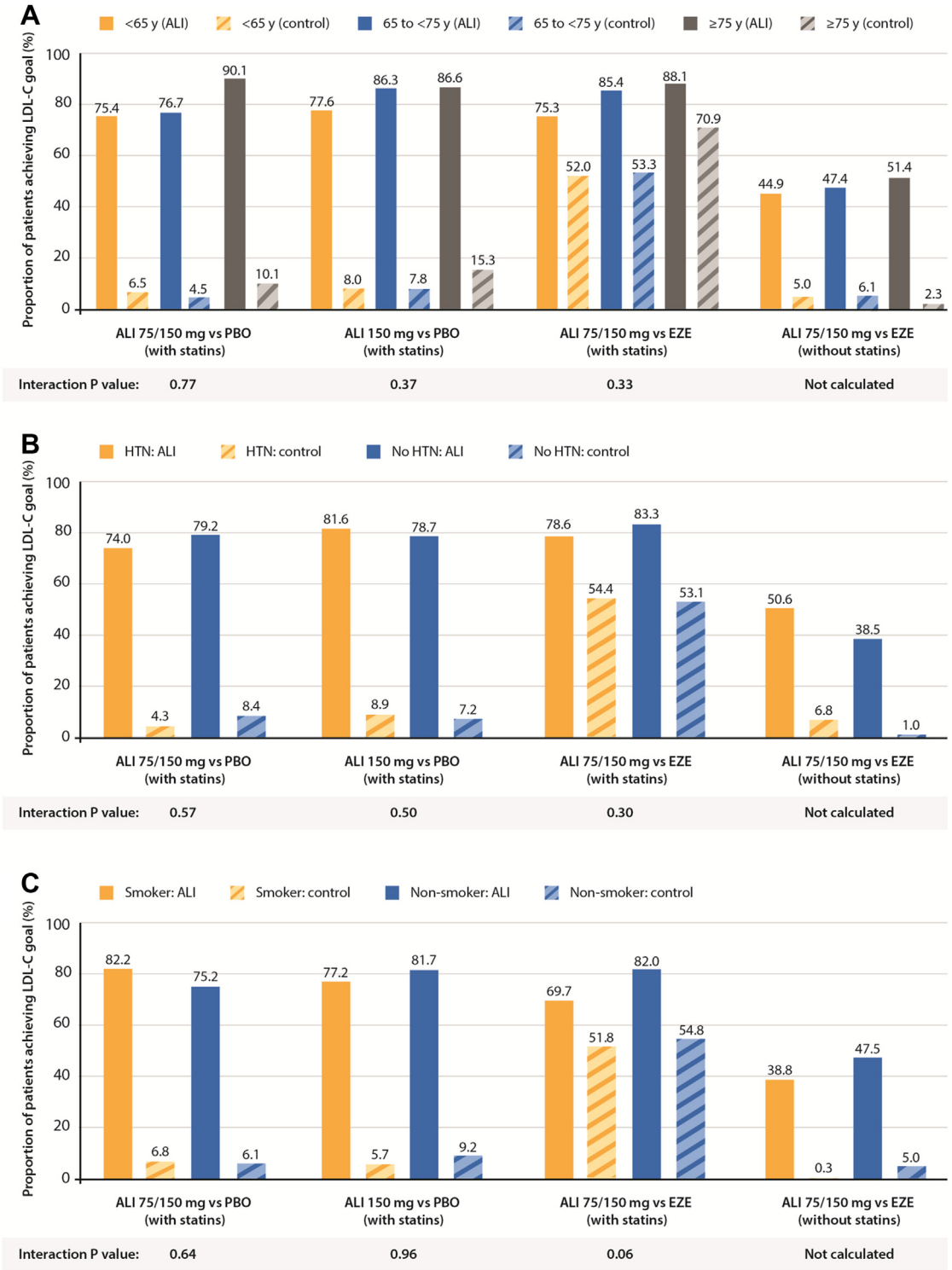


Figure 3 Proportion of very high cardiovascular risk patients reaching calculated LDL-C <70 mg/dL or moderate to high cardiovascular risk patients reaching calculated LDL-C <100 mg/dL at Week 24 according to (A) age group, (B) hypertension, and (C) smoking status (on-treatment [modified ITT] analysis). ALI, alirocumab; EZE, ezetimibe; ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol; PBO, placebo; y, years.

reducing HDL-C levels,[14,15] and may also upregulate PCSK9 levels.[17] In the present study, however, baseline PCSK9 levels were similar between smokers and non-smokers. In addition, baseline levels of LDL-C and the inflammatory marker hsCRP were similar among the treatment groups regardless of smoking status, whereas smokers demonstrated slightly lower levels of HDL-C.

The FOURIER trial[39] reported that evolocumab reduced the rate of CVD events in patients with atherosclerotic CVD and LDL-C levels ≥70 mg/dL (1.8 mmol/L) on a

background of statin therapy. The ODYSSEY OUTCOMES study[40] reported that alirocumab reduced the rate of major adverse cardiovascular events in nearly 19,000 patients with an acute coronary syndrome and elevated levels of atherogenic lipoproteins despite high-intensity or maximum tolerated statin treatment. Alirocumab was also associated with a lower rate of all-cause death and was safe and well tolerated over the trial, in which many patients were treated for ≥3 years. The results from these clinical trials offer evidence for the putative role of the PCSK9 inhibitors in addition to or as an alternative to statins in routine clinical practice.

Limitations

This was a pooled subgroup analysis of 10 randomized trials. Consequently, participants were not stratified at randomization according to age group, hypertension, or smoking status, leading to minor variations in baseline characteristics in the various subgroups and treatment groups of the participants. The population aged ≥75 years was relatively small, and only a single marker of inflammation was analyzed. The participants in these 10 studies were mainly white and male, and it would be necessary to carry out external validation in women and other ethnic groups. As only baseline measures of baseline systolic and diastolic blood pressure were available, the definition of hypertension was based on investigator-reported history of hypertension.

Conclusions

Alirocumab treatment resulted in significant LDL-C reductions compared with either ezetimibe or placebo at Week 24, with reductions seen in the age groups studied and regardless of hypertension or smoking status. Alirocumab was well tolerated by all participants at any age and regardless of hypertension or smoking status.

Acknowledgments

The authors thank the patients, their families, and all investigators involved in the ODYSSEY studies included in this analysis. The following people from the study sponsors provided editorial comments on the article: Michael Howard, MBA (Sanofi), Carol Hudson, MS, and Eva-Lynne Greene, MS (Regeneron Pharmaceuticals, Inc). The statistical analysis was performed by Desmond Thompson (Regeneron Pharmaceuticals, Inc). Medical writing support under the direction of the authors was provided by Sophie K. Rushton-Smith, PhD (MedLink Healthcare Communications), funded by Regeneron Pharmaceuticals, Inc, according to the Good Publication Practice guidelines (https://www.ismpp.org/gpp3). The sponsors were involved in the study design, collection, analysis, and interpretation of data, as well as data checking of information provided in the article. The authors were responsible for all content and editorial decisions and received no honoraria related to the development of this publication.

Funding: This study was funded by Sanofi, United States and Regeneron Pharmaceuticals, Inc, United States.

Disclosure

F.J.R. received research grants from Amgen, Sanofi, Regeneron Pharmaceuticals, Inc, and the Medicines Company and honoraria for speaker's bureau and consultancy/advisory boards for Amgen, Sanofi, Regeneron Pharmaceuticals, Inc, and the Medicines Company. J.T. received research grants from Bayer, Boehringer Ingelheim, Merck, Pfizer, and Sanofi and honoraria for speaker's bureau and consultancy/advisory boards for Merck, Sanofi, Bayer, and Novo Nordisk. A.C.S. received honoraria for speaker's bureau and consultancy/advisory boards for Sanofi, AstraZeneca, Amgen, and Novo Nordisk. F.A.F. received honoraria for advisory boards/speaker for Sanofi, Abbott, Amgen, Bayer, Biolab, Novo Nordisk, Novartis, Merck, and AstraZeneca. M.A. received consultant/advisory board fees from Abbot/Mylan, Amgen, AstraZeneca, Kowa, Merck, Sanofi, and Regeneron Pharmaceuticals Inc. M.F. received research support from Amgen, Merck, and Sanofi; speaker's bureau fees from Amgen, Sanofi, Regeneron Pharmaceuticals Inc, and Merck; honoraria from Abbott, Akcea/Ionis, Eli Lilly, Mylan, and Pfizer; and consultant/advisory board fees from Abbot, Akcea/Ionis, Amgen, AstraZeneca, Eli Lilly, Kowa, Merck, Mylan, Pfizer, Roche, Sanofi, Regeneron Pharmaceuticals Inc, and Servier. R.D.S. received honoraria for consulting, speaker, and research activities from Amgen, AstraZeneca, Akcea, Biolab, Esperion, Kowa, Merck, Pfizer, Sanofi, and Regeneron Pharmaceuticals Inc. K.C.F. was a consultant of Boehringer Ingelheim, Quantum genomics, Sanofi, Regeneron Pharmaceuticals, Inc, Amgen, Novartis, and Eli Lilly. R.S.W. was a consultant of Sanofi, Regeneron Pharmaceuticals Inc, AstraZeneca, The Medicines Company, Pfizer, Boehringer Ingelheim, and Eli Lilly. E.P.N. received honoraria for speaker activities: Sanofi, Regeneron Pharmaceuticals, Inc, Amgen, AstraZeneca. Research grants: Amgen. D.M.L. is an employee of Sanofi. A.L. and L.V.L., are employees of and stockholders in Sanofi. M.J.L. was an employee of and stockholder in Regeneron Pharmaceuticals, Inc. J.G.R. received research grants to her institution from Acasti, Amarin, Amgen, Astra-Zeneca, Esai, Espiron, Merck, Novartis, Novo-Nordisk, Regeneron, Sanofi, and Takeda and has served as a consultant for Amgen, The Medicines Company, Merck, Novartis, Novo-Nordisk, Pfizer, Regeneron Pharmaceuticals Inc., and Sanofi.

Supplementary data

Supplementary data to this article can be found online at https://dx.doi.org/10.1016/j.jacl.2019.06.006.

References

1. D'Agostino RB Sr., Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:743–753.
2. Conroy RM, Pyorala K, Fitzgerald AP, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24:987–1003.
3. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016;37:2315–2381.
4. Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1–full report. *J Clin Lipidol*. 2015;9:129–169.
5. Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Eur Heart J*. 2016;37:2999–3058.
6. Seidah NG, Awan Z, Chretien M, Mbikay M. PCSK9: a key modulator of cardiovascular health. *Circ Res*. 2014;114:1022–1036.
7. Violan C, Foguet-Boreu Q, Flores-Mateo G, et al. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. *PLoS One*. 2014;9:e102149.
8. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet*. 2012;380:37–43.
9. Zhang QL, Rothenbacher D. Prevalence of chronic kidney disease in population-based studies: systematic review. *BMC Public Health*. 2008;8:117.
10. Field TS, Gurwitz JH, Harrold LR, et al. Risk factors for adverse drug events among older adults in the ambulatory setting. *J Am Geriatr Soc*. 2004;52:1349–1354.
11. Obreli Neto PR, Nobili A, de Lyra DP Jr., et al Incidence and predictors of adverse drug reactions caused by drug-drug interactions in elderly outpatients: a prospective cohort study. *J Pharm Pharm Sci*. 2012;15:332–343.
12. Shi S, Klotz U. Age-related changes in pharmacokinetics. *Curr Drug Metab*. 2011;12:601–610.
13. Barua RS, Ambrose JA. Mechanisms of coronary thrombosis in cigarette smoke exposure. *Arterioscler Thromb Vasc Biol*. 2013;33:1460–1467.
14. Slagter SN, van Vliet-Ostaptchouk JV, Vonk JM, et al. Associations between smoking, components of metabolic syndrome and lipoprotein particle size. *BMC Med*. 2013;11:195.
15. Freeman DJ, Griffin BA, Murray E, et al. Smoking and plasma lipoproteins in man: effects on low density lipoprotein cholesterol levels and high density lipoprotein subfraction distribution. *Eur J Clin Invest*. 1993;23:630–640.
16. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. *J Am Coll Cardiol*. 2004;43:1731–1737.
17. Feingold KR, Moser AH, Shigenaga JK, Patzek SM, Grunfeld C. Inflammation stimulates the expression of PCSK9. *Biochem Biophys Res Commun*. 2008;374:341–344.
18. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003;361:1149–1158.
19. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA*. 2002;288:2998–3007.
20. Kereiakes DJ, Robinson JG, Cannon CP, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: the ODYSSEY COMBO I study. *Am Heart J*. 2015;169:906–915.e913.
21. Cannon CP, Cariou B, Blom D, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. *Eur Heart J*. 2015;36:1186–1194.
22. Lakoski SG, Lagace TA, Cohen JC, Horton JD, Hobbs HH. Genetic and metabolic determinants of plasma PCSK9 levels. *J Clin Endocrinol Metab*. 2009;94:2537–2543.
23. McKenney JM, Koren MJ, Kereiakes DJ, Hanotin C, Ferrand AC, Stein EA. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/-REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. *J Am Coll Cardiol*. 2012;59:2344–2353.
24. Stein EA, Gipe D, Bergeron J, et al. Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial. *Lancet*. 2012;380:29–36.
25. Roth EM, Taskinen MR, Ginsberg HN, et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24 week, double-blind, randomized Phase 3 trial. *Int J Cardiol*. 2014;176:55–61.
26. Bays H, Gaudet D, Weiss R, et al. Alirocumab as add-on to atorvastatin versus other lipid treatment strategies: ODYSSEY OPTIONS I randomized trial. *J Clin Endocrinol Metab*. 2015;100:3140–3148.
27. Kastelein JJ, Ginsberg HN, Langslet G, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. *Eur Heart J*. 2015;36:2996–3003.
28. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372:1489–1499.
29. Farnier M, Jones P, Severance R, et al. Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular-risk patients: The ODYSSEY OPTIONS II randomized trial. *Atherosclerosis*. 2016;244:138–146.
30. Moriarty PM, Thompson PD, Cannon CP, et al. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol*. 2015;9:758–769.
31. Ginsberg HN, Rader DJ, Raal FJ, et al. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia and LDL-C of 160 mg/dL or higher. *Cardiovasc Drugs Ther*. 2016;30:473–483.
32. Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS guidelines for the management of dyslipidaemias: the Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J*. 2011;32:1769–1818.
33. Roth EM, McKenney JM, Hanotin C, Asset G, Stein EA. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. *N Engl J Med*. 2012;367:1891–1900.
34. Ginsberg HN, Tuomilehto J, Hovingh GK, et al. Impact of age on the efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia. *Cardiovasc Drugs Ther*. 2019;33:69–76.
35. Borghi C, Urso R, Cicero AF. Renin-angiotensin system at the crossroad of hypertension and hypercholesterolemia. *Nutr Metab Cardiovasc Dis*. 2017;27:115–120.

36. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial Research Group. *Arch Intern Med*. 1992; 152:56–64.
37. Burke GM, Genuardi M, Shappell H, D'Agostino RB Sr., Magnani JW. Temporal associations between smoking and cardiovascular disease, 1971 to 2006 (from the Framingham Heart Study). *Am J Cardiol*. 2017;120:1787–1791.
38. Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation*. 2006;113:791–798.
39. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017; 376:1713–1722.
40. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379: 2097–2107.