

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



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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.

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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 MONO²⁵ study were at moderate CVD risk, according to SCORE.² Participants in the ALTERNATIVE study³⁰ 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](#).

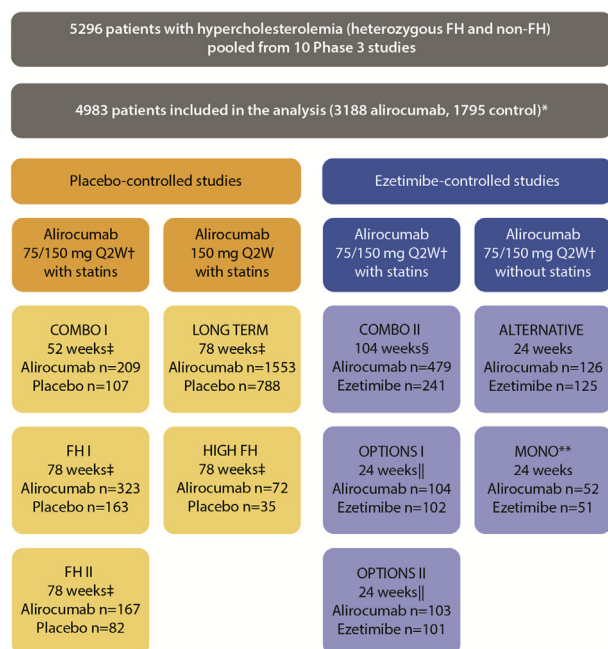


Figure 1 Summary of the studies included in the analysis (randomized population): FH I,²⁷ FH II,²⁷ HIGH FH,³¹ LONG TERM,²⁸ COMBO I,²⁰ COMBO II,²¹ OPTIONS I,²⁶ OPTIONS II,²⁹ ALTERNATIVE,³⁰ MONO.²⁵ *Statin-only control arms in OPTIONS III and ALTERNATIVE (N = 313) were excluded. †Alirocumab 75 mg Q2W was 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-based⁵ 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

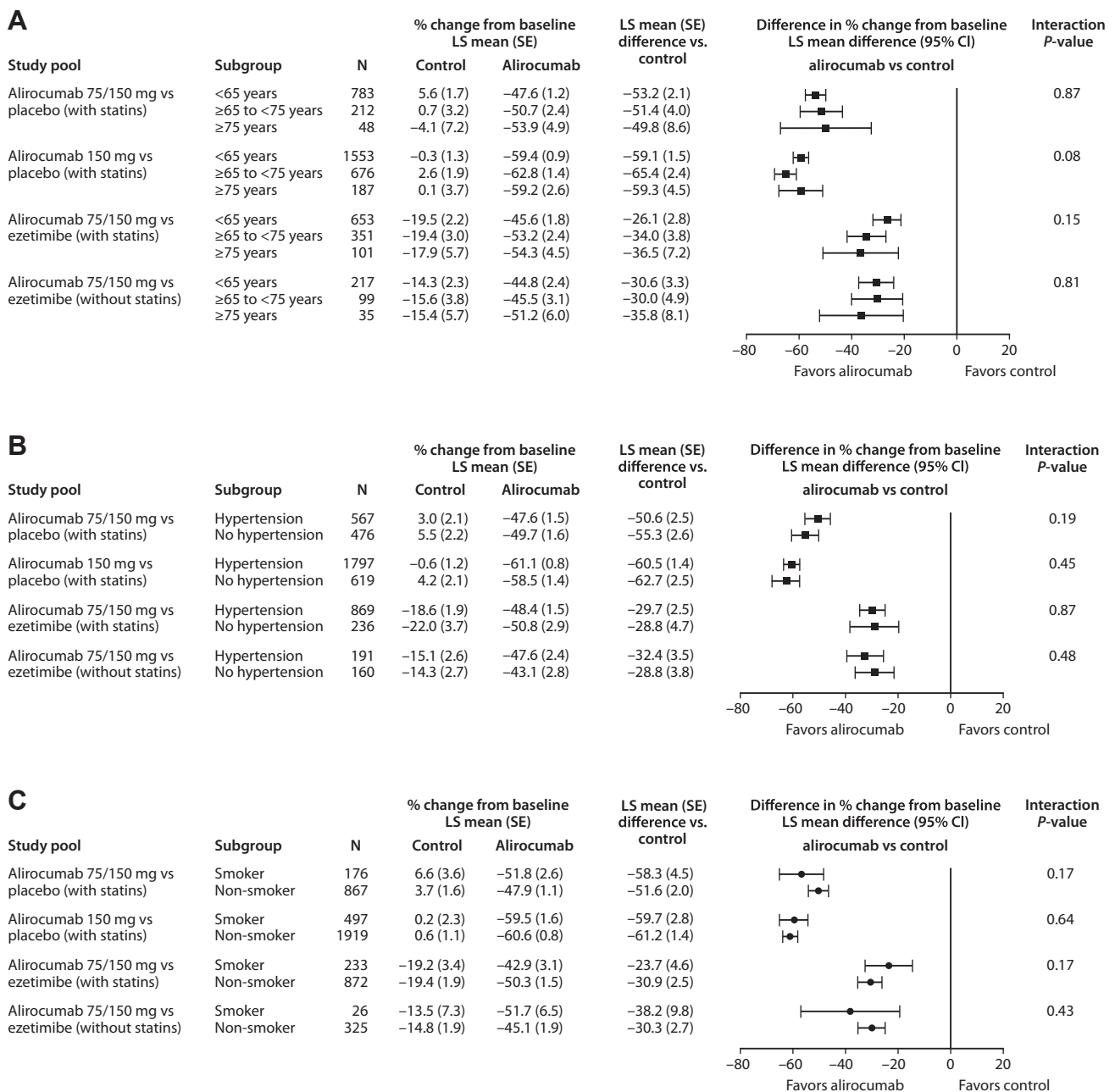


Figure 2 Percent change in LDL-C at Week 24 according to (A) age group, (B) hypertension, and (C) smoking status (ITT analysis). CI, confidence interval; ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol; LS, least square; SE, standard error.

<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 al²² 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 non-smokers,³⁸ as illustrated in our study in which smokers were younger than nonsmokers. Smoking alters plasma lipoprotein metabolism, raising LDL-C and, in particular,

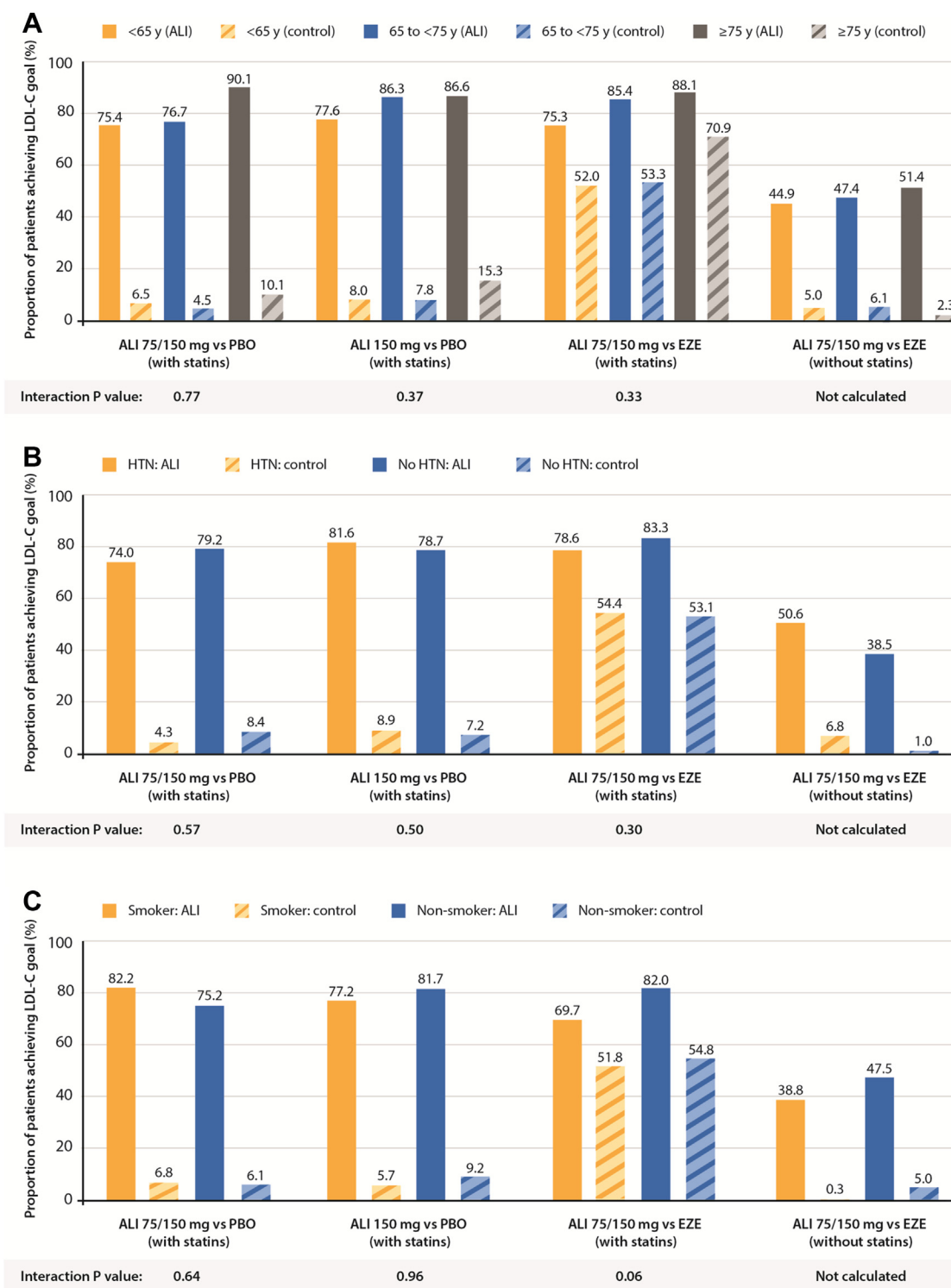


Figure 3 Proportion of very high cardiovascular risk patients reaching calculated LDL-C <70 mg/dL or moderate to high cardiovascular risk patients reaching calculated LDL-C <100 mg/dL at Week 24 according to (A) age group, (B) hypertension, and (C) smoking status (on-treatment [modified ITT] analysis). 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 trial³⁹ 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 study⁴⁰ 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.

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Supplementary data

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

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