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FULL RESEARCH PAPER
Lipids & atherosclerosis

Achievement of ESC/EAS LDL-C treatment goals after an acute coronary syndrome with statin and alirocumab

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Aims European guidelines set low-density lipoprotein cholesterol (LDL-C) treatment goals <1.4 mmol/L after acute coronary syndrome (ACS), and <1.0 mmol/L for patients with recurrent cardiovascular events ≤2 years. Many ACS patients do not achieve these goals on statin alone. We examined actual goal achievement with alirocumab and projected achievement with ezetimibe, either added to optimized statin therapy.

Methods and results The ODYSSEY OUTCOMES trial (NCT01663402) compared alirocumab with placebo in 18 924 patients with recent ACS and hyperlipidaemia despite high-intensity or maximum-tolerated statin therapy. This subanalysis comprised 17 589 patients with LDL-C ≥1.4 mmol/L at baseline who did not receive ezetimibe treatment. High-intensity statin treatment was used in 88.8%. Median (interquartile range) baseline LDL-C was 2.3 (1.9−2.7) mmol/L. With alirocumab, 94.6% of patients achieved LDL-C <1.4 mmol/L at ≥1 post-baseline measurement vs. 17.3% with placebo. Among 2236 patients with a previous cardiovascular event within 2 years (before the qualifying ACS), 85.2% vs. 3.5%, respectively, achieved LDL-C <1.0 mmol/L. Among patients not treated with ezetimibe, we projected that its use would have achieved LDL-C <1.4 and <1.0 mmol/L in 10.6 and 0%, respectively, at baseline (assuming 18 ± 3% reduction of LDL-C).

Conclusion Among patients with recent ACS and LDL-C ≥1.4 mmol/L despite optimized statin therapy, the addition of alirocumab allowed 94.6% to achieve the 2019 European guideline LDL-C goal <1.4 mmol/L, and 85.2% of those with recurrent cardiovascular events to achieve <1.0 mmol/L. In contrast, the addition of ezetimibe to optimized statin therapy was projected to achieve LDL-C <1.4 mmol/L in only 10.6% of patients at baseline.

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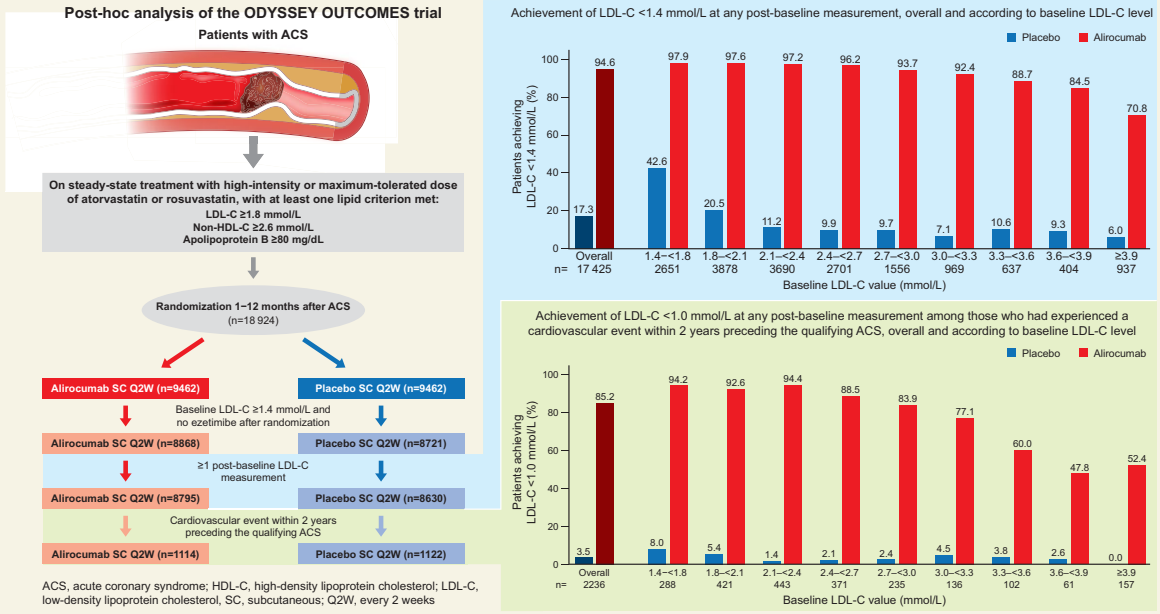
Graphical Abstract



Keywords Alirocumab • LDL cholesterol • Acute coronary syndrome • Guidelines

Introduction

Robust evidence from clinical and genetic studies unequivocally demonstrates that low-density lipoproteins (LDLs) play a causal role in the development and progression of atherosclerotic cardiovascular disease, a leading cause of death and morbidity.[1,2] The efficacy of statin medications to reduce major adverse cardiovascular events (MACE) bears a consistent relationship with the absolute reduction in LDL cholesterol (LDL-C).[3] This evidence led to recommendations of the 2016 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS)[4] for an LDL-C treatment goal <1.8 mmol/L in patients at very high cardiovascular risk, a goal achievable with high-intensity statin treatment in a majority of patients with the acute coronary syndrome (ACS).[5–7] In recent clinical studies with non-statin therapies added to statins, greater reduction of LDL-C levels by either ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) antibody treatment has resulted in further reduction of MACE.[7–9] Based on this evolving evidence, the 2019 ESC/EAS dyslipidaemia guidelines lowered LDL-C treatment goals in patients considered very high risk (e.g. those with recent ACS).[10] An LDL-C goal of <1.4 mmol/L is now recommended together with >50% LDL-C reduction (I/A recommendation), and a lower LDL-C goal of <1.0 mmol/L may be considered for those with recurrent cardiovascular events within 2 years (IIb/B recommendation).[10] The recommendations for lower LDL-C goals have been reinforced by the 2021 ESC guidelines on cardiovascular disease prevention.[11]

Using data from the ODYSSEY OUTCOMES trial,[9] we examined how many patients not at goal with high-intensity or maximum-tolerated statin treatment achieved these new LDL-C treatment goals with alirocumab, a PCSK9 inhibitor, according to baseline LDL-C values and projected how many would have achieved the new treatment goals with the use of ezetimibe added to maximum-tolerated statin therapy.

Methods

Details of the ODYSSEY OUTCOMES (ClinicalTrials.gov: NCT01663402) study design[12] and primary efficacy and safety results[13] have been published. In brief, ODYSSEY OUTCOMES was a multicentre, double-blind, placebo-controlled trial in 18 924 patients at least 40 years of age who provided written informed consent and had been hospitalized with an ACS (defined as myocardial infarction or unstable angina) 1–12 months before randomization. Qualifying patients had a level of LDL-C ≥1.81 mmol/L, or non-high-density lipoprotein cholesterol (non-HDL-C) ≥2.59 mmol/L, or apolipoprotein B ≥0.80 mmol/L, measured after a minimum of 2 weeks of stable treatment with atorvastatin 40–80 mg daily, rosuvastatin 20–40 mg daily, or the maximum-tolerated dose of either statin (including no statin in case of documented intolerance). All sites obtained institutional

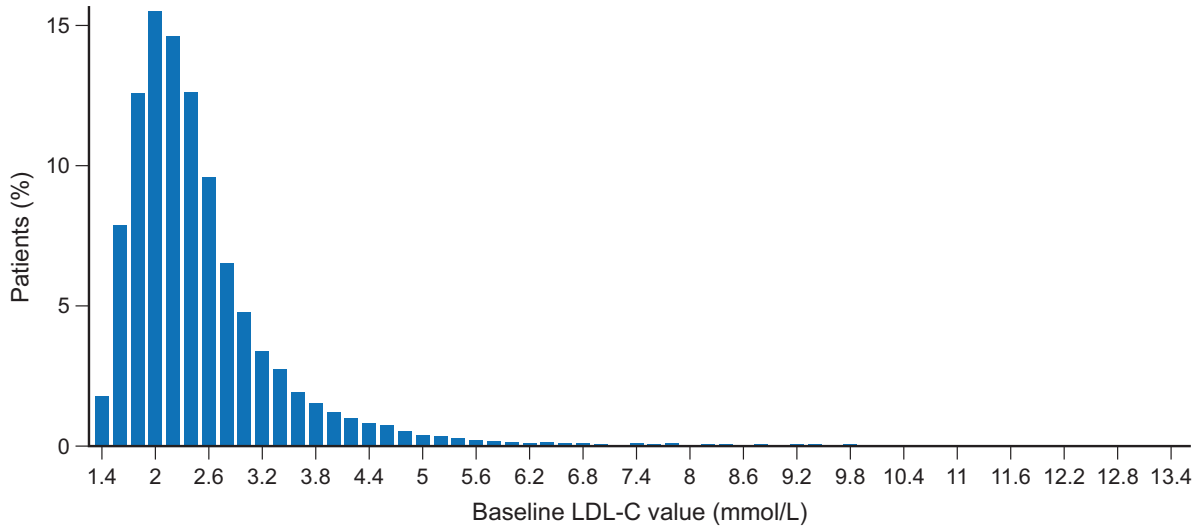


Figure 1 Baseline LDL-C levels among 17 423 patients with a valid post-baseline LDL-C value. Median baseline LDL-C value was 2.3 mmol/L. LDL-C, low-density lipoprotein cholesterol.

review board approval as per local and national guidelines and the study complied with the Declaration of Helsinki.

Patients were randomly assigned in a 1:1 ratio stratified by country to receive treatment with alirocumab 75 mg subcutaneously every 2 weeks or matching placebo. Lipid levels were subsequently monitored in blinded fashion. In case of a persistent LDL-C ≥1.29 mmol/L on treatment, the dose of alirocumab was up-titrated to 150 mg. When two consecutive measurements of LDL-C <0.65 mmol/L were identified on the 150-mg dose, the alirocumab dose was reduced to 75 mg, and safety was monitored by an independent physician blinded to treatment allocation. In case of two consecutive measurements of LDL-C <0.39 mmol/L on alirocumab 75 mg, alirocumab was discontinued with blinded substitution of placebo for the remainder of the trial. All dose adjustments were done while maintaining the blind. The protocol did not specify any change to the background statin dose.

Outcomes for the current analysis

Among patients with LDL-C ≥1.4 mmol/L at baseline who did not receive ezetimibe after randomization (to avoid confounding), we determined the number of patients in the alirocumab and placebo groups who achieved LDL-C <1.4 mmol/L at any post-randomization time point. Among the subset of patients with at least one other cardiovascular event in a 2-year period preceding the qualifying ACS, we determined the number of patients who achieved LDL-C <1.0 mmol/L at any post-randomization time point. A cardiovascular event was defined as myocardial infarction or unstable angina, coronary revascularization (percutaneous coronary intervention, coronary artery bypass grafting, and other arterial revascularization procedures), stroke, transient ischaemic attack, and a peripheral artery disease event (critical limb ischaemia, limb revascularization, or amputation for ischaemia).

Among patients who were not treated with ezetimibe at baseline or after randomization and who had LDL-C ≥1.4 mmol/L at baseline, we performed a simulation analysis to project how many would have met new guideline targets if ezetimibe had been added to their treatment, assuming an 18 ± 3% reduction of LDL-C values. We determined the number of patients who would have met the guideline targets at baseline or at least once after randomization.

Statistical analysis

Efficacy analyses were performed on an intention-to-treat basis. Descriptive statistics of the numbers and percentages of patients meeting target LDL-C values were evaluated, in composite and according to nine strata of baseline LDL-C concentration ranging from ≥1.4 to ≥3.9 mmol/L. Analyses were performed in SAS version 9.4.

Results

Of 18 924 randomized patients, 9462 were assigned to the alirocumab group and 9462 to the placebo group, with a median follow-up of 2.8 years (interquartile range 2.3–3.4). Of these, 17 589 patients (8868 alirocumab, 8721 placebo) were considered in the current analysis (i.e. baseline LDL-C ≥1.4 mmol/L and no ezetimibe after randomization). Of these, 17 425 patients had at least one post-baseline measurement of LDL-C.

At baseline, the median LDL-C was 2.3 mmol/L (interquartile range 1.9–2.7) (*Figure 1*), with 15 619 of 17 589 (88.8%) patients receiving high-intensity statin (atorvastatin 40–80 mg/day or rosuvastatin 20–40 mg/day) treatment (*Table 1*). Among the patients treated with alirocumab, 94.6% achieved LDL-C <1.4 mmol/L on ≥1 post-baseline measurement compared with 17.3% in the placebo group (*Figure 2*); these ranged from 70.8 to 97.9% for alirocumab and 6.0 to 42.6% for placebo, depending on baseline LDL-C. Of the 8868 patients in the alirocumab on-treatment group, 8304 (95.0%) achieved the LDL-C goal of <1.4 mmol/L at least once after randomization.

Of the 17 589 patients, 2236 had experienced a cardiovascular event within 2 years preceding the qualifying ACS and had a post-baseline measurement of LDL-C. Among this subgroup, 940/1103 (85.2%) of those assigned to alirocumab achieved LDL-C <1.0 mmol/L at ≥1 post-baseline measurement, compared with 39/

Table 1 Baseline characteristics according to randomized treatment

	All patients ($n = 17\,589$)		Prior cardiovascular event ($n = 2236$)	
	Alirocumab ($n = 8868$)	Placebo ($n = 8721$)	Alirocumab ($n = 1114$)	Placebo ($n = 1122$)
Age (years), mean (SD)	58.6 (9.3)	58.8 (9.4)	60.4 (9.0)	60.3 (9.7)
Male sex	6596 (74.4)	6492 (74.4)	822 (73.8)	836 (74.5)
Medical history, *n* (%)				
Hypertension[a]	5810 (65.5)	5594 (64.1)	890 (79.9)	865 (77.1)
Family history of CAD[a]	3198 (36.1)	3099 (35.5)	451 (40.5)	463 (41.3)
Diabetes mellitus	2475 (27.9)	2503 (28.7)	402 (36.1)	405 (36.1)
Current smoker	2157 (24.3)	2119 (24.3)	256 (23.0)	269 (24.0)
Myocardial infarction[b]	1688 (19.0)	1712 (19.6)	664 (59.6)	705 (62.8)
Congestive heart failure[a]	1279 (14.4)	1367 (15.7)[c]	258 (23.2)	264 (23.5)
PCI (for index event)	5959 (67.2)	5884 (67.5)	711 (63.8)	692 (61.7)
CABG[b]	485 (5.5)	489 (5.6)	156 (14.0)	182 (16.2)
Cerebrovascular disease[a]	439 (5.0)	428 (4.9)	200 (18.0)	184 (16.4)
Peripheral artery disease[a]	356 (4.0)	363 (4.2)	215 (19.3)	242 (21.6)
Stroke	281 (3.2)	279 (3.2)	135 (12.1)	123 (11.0)
Index ACS, *n* (%)				
NSTEMI	4310 (48.6)	4247 (48.7)	604 (54.2)	594 (52.9)
STEMI	3094 (34.9)	2982 (34.2)	281 (25.2)	306 (27.3)
Unstable angina	1447 (16.3)	1482 (17.0)	225 (20.2)	221 (19.7)
Missing	17 (0.2)	10 (0.1)	4 (0.4)	1 (0.1)
Lipid-lowering therapy at randomization, *n* (%)				
High-intensity atorvastatin or rosuvastatin[d]	7844 (88.5)	7775 (89.2)	945 (84.8)	959 (85.5)
Other lipid-lowering therapy	801 (9.0)	742 (8.5)	124 (11.1)	106 (9.4)
None	223 (2.5)	204 (2.3)	45 (4.0)	57 (5.1)

ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CAD, coronary artery disease; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction.
[a]Before the run-in period.
[b]Before the index ACS event.
[c]$P = 0.020$. All other comparisons were not significant.
[d]Atorvastatin 40–80 mg/day or rosuvastatin 20–40 mg/day.

1109 (3.5%) of those assigned to placebo (*Figure 3*); the likelihood of achieving LDL-C <1.0 mmol/L depended on the baseline LDL-C level. For example, among those with baseline LDL-C <1.8 mmol/L, the goal was achieved by 130/138 (94.2%) of those assigned to alirocumab and 12/150 (8.0%) of those assigned to placebo. Among patients with baseline LDL-C ≥3.9 mmol/L, the goal was achieved by 43/82 (52.4%) of those assigned to alirocumab and 0/75 (0%) of those assigned to placebo (*Figure 3*).

In a simulation analysis in patients not treated with ezetimibe that assumed ezetimibe would produce an 18 ± 3% reduction of LDL-C with a symmetrical distribution, 10.6% ($n = 1815$) of patients were projected to meet the LDL-C goal of <1.4 mmol/L and 0% the goal of <1.0 mmol/L at baseline (i.e. with high-intensity or maximum-tolerated statin therapy and hypothetical ezetimibe treatment). Projecting the effect of ezetimibe on achieved LDL-C levels after randomization in the alirocumab group, 96.6% (8260/8548) would have met the LDL-C goal of <1.4 mmol/L at least once (i.e. patients assigned to alirocumab receiving high-intensity or maximum-tolerated statin therapy and hypothetical ezetimibe treatment). In comparison, 41.9% (3507/8372) would have met this goal at least once in the placebo group (i.e. patients assigned to placebo with high-intensity or maximum-tolerated statin therapy and hypothetical ezetimibe treatment) (*Figure 4A*).

Of the 2236 patients indicated above with a cardiovascular event within 2 years preceding the qualifying ACS, 2099 received no ezetimibe treatment and had at least one post-baseline measurement of LDL-C. In this subgroup, projected achievement of LDL-C <1.0 mmol/L at any post-randomization measurement was 91.0% with alirocumab, high-intensity or maximum-tolerated statin, and hypothetical ezetimibe vs. 8.3% with placebo, high-intensity or maximum-tolerated statin, and hypothetical ezetimibe (*Figure 4B*). Of 312 patients assigned to placebo who actually received ezetimibe post-randomization, 49 (15.9%) achieved the LDL-C goal of <1.4 mmol/L at least once after randomization.

Discussion

In recent years, evidence from clinical and genetic studies has accumulated to support the notion that LDL is a causal factor for the development and progression of atherosclerotic cardiovascular disease.[1,2]

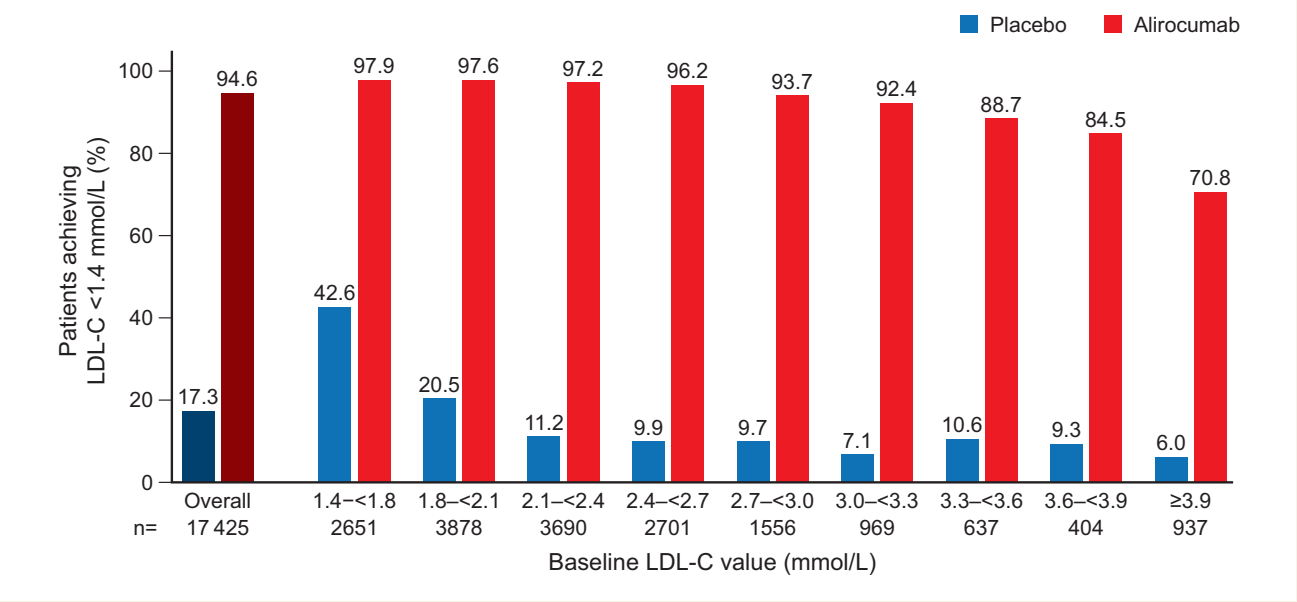


Figure 2 Percentages of patients who achieved LDL-C <1.4 mmol/L on at least one post-baseline measurement, overall and according to baseline LDL-C stratum (17 425 patients had a valid post-baseline LDL-C value; 2 patients had missing data at baseline). LDL-C, low-density lipoprotein cholesterol.

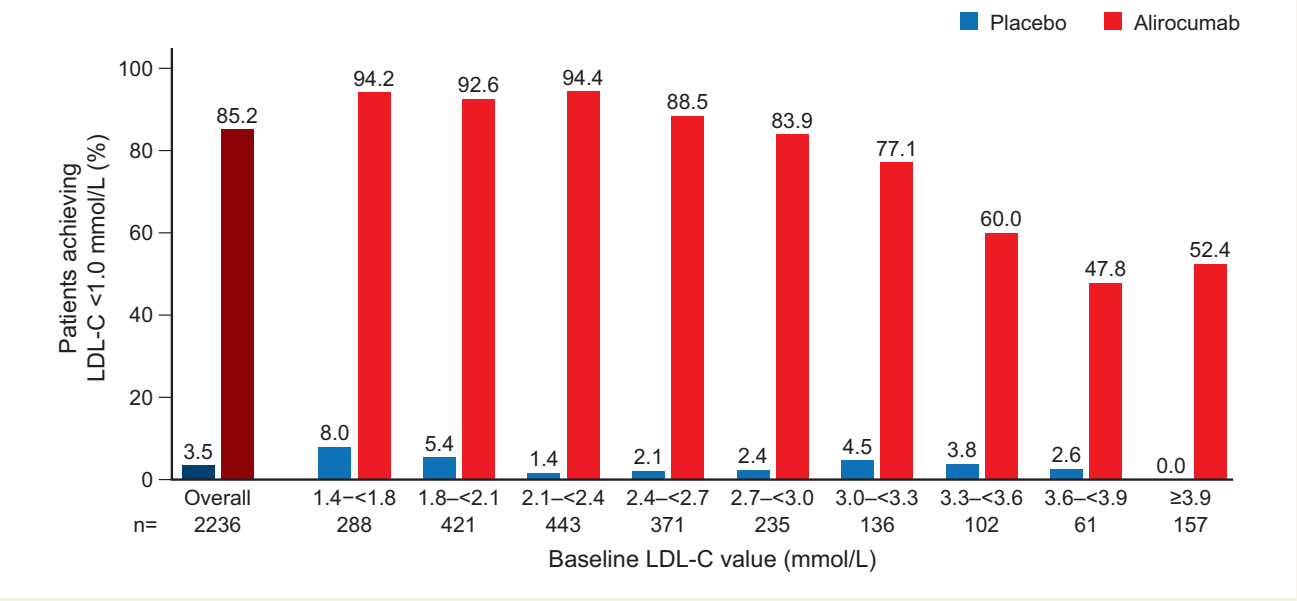


Figure 3 Percentages of patients with a previous cardiovascular event within 2 years preceding the qualifying ACS who achieved LDL-C <1.0 mmol/L on at least one post-baseline measurement in the ODYSSEY OUTCOMES study, overall and according to baseline LDL-C level. ACS, acute coronary syndrome; LDL-C, low-density lipoprotein cholesterol.

The 2016 ESC/EAS dyslipidaemia guidelines recommended statin therapy for all patients with atherosclerotic cardiovascular disease, to achieve a reduction of LDL-C by at least 50% to a level <1.8 mmol/L.[4] Since these guidelines were published, clinical trials have shown that further LDL-C lowering by PCSK9 inhibition in addition to maximum-tolerated statin therapy not only substantially lowers LDL-C but also further reduces the risk of cardiovascular events in patients with atherosclerotic cardiovascular disease.[7–9] The 2019 ESC/EAS guidelines therefore recommended lower LDL-C treatment goals in patients

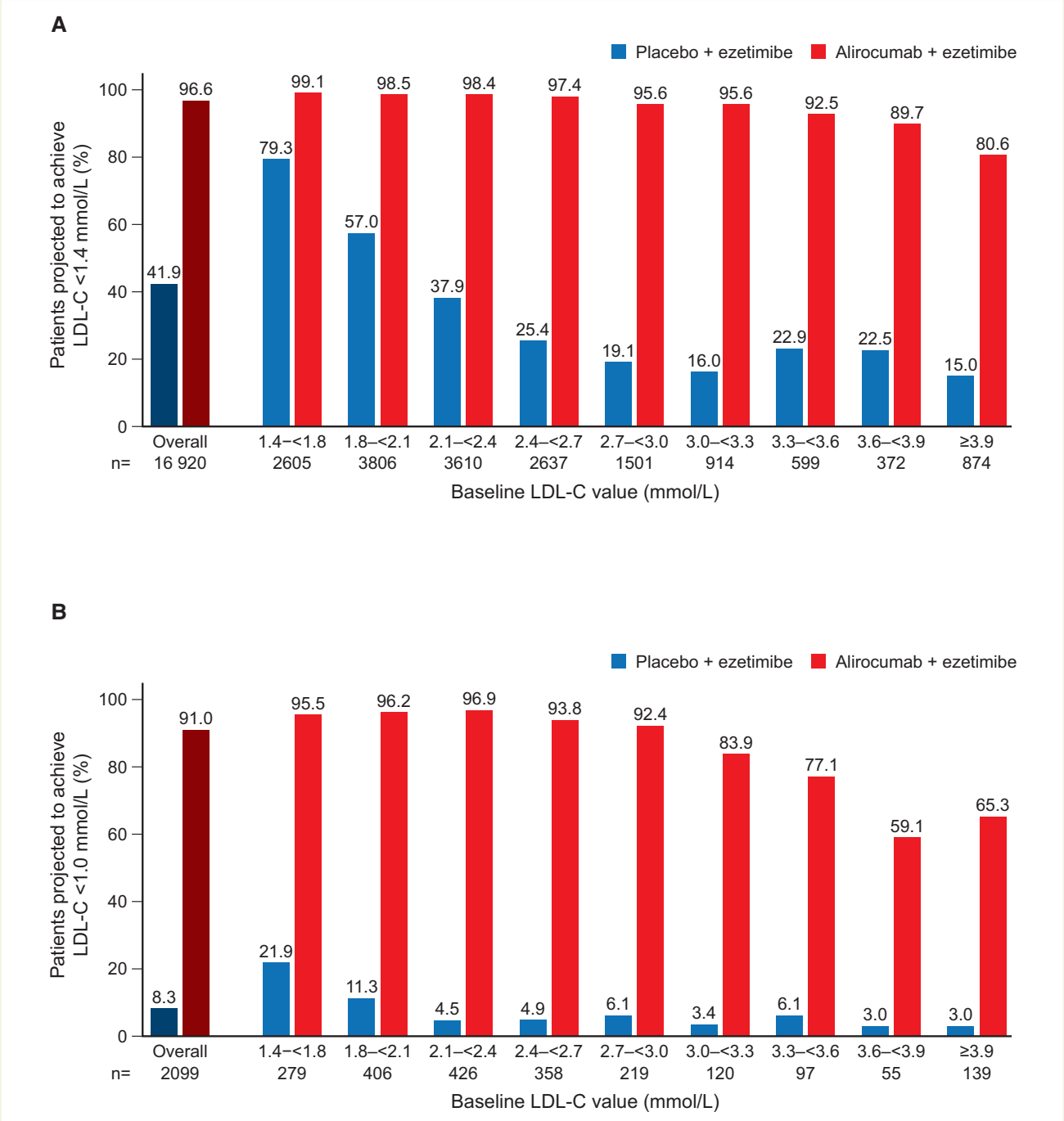


Figure 4 Projected effect of ezetimibe, added to assigned study treatment and optimized statin treatment, on achievement of LDL-C goals. Modelled analysis projecting achievement of LDL-C goals at any post-baseline time point by assuming an 18 ± 3% reduction in LDL-C had ezetimibe been added to assigned, randomized study treatment and optimized background statin treatment. Patients who received ezetimibe at baseline are excluded. Results are shown overall and by baseline LDL-C stratum. (A) Projected achievement of LDL-C <1.4 mmol/L among the full analysis cohort; (B) projected achievement of LDL-C <1.0 mmol/L among patients with a previous cardiovascular event within 2 years preceding the qualifying acute coronary syndrome. LDL-C, low-density lipoprotein cholesterol.

at very high cardiovascular risk,[10] such as those with recent ACS, and recommend a combination treatment for LDL-C lowering if these new treatment targets are not reached with optimized statin therapy alone.

The current analysis, using data from the ODYSSEY OUTCOMES trial in patients with recent ACS and elevated atherogenic lipoproteins despite high-intensity or maximum-tolerated statin therapy, indicates that the standard LDL-C goal defined in the 2019 ESC/EAS

guidelines[10] (<1.4 mmol/L) was achieved by few patients (17.3%). In contrast, the addition of alirocumab allowed 94.6% of patients to achieve the standard goal and 85.2% to achieve the lower goal (<1.0 mmol/L). Based on LDL-C reduction expected with the addition of ezetimibe to high-intensity statin treatment, simulations predicted that far fewer patients would achieve these goals with ezetimibe, whereas almost all patients would achieve both goals if treated with the triple combination of statin, alirocumab, and ezetimibe. Achieving treatment goals in a carefully selected and closely followed clinical trial cohort as analysed in the present study may, however, be easier than achieving and maintaining those goals over the long-term in clinical practice.

Patients, healthcare providers, and healthcare systems are concerned about the efficacy, complexity, and cost of lipid-lowering therapy after ACS. In that context, it is important to consider the clinical implications of the current findings. Statins remain foundational in lipid-lowering, and their use should be optimized within the bounds of safety and tolerability in all patients. Some patients will require triple therapy with statin, ezetimibe, and a PCSK9 inhibitor to achieve the more stringent LDL-C goals. A substantial number of patients will achieve the recommended LDL-C goal with statin and ezetimibe. For example, in the IMPROVE-IT trial, approximately half of all patients treated with simvastatin and ezetimibe achieved LDL-C levels <1.4 mmol/L,[7] with the caveat that median LDL-C levels on statin monotherapy were substantially lower in IMPROVE-IT than in ODYSSEY OUTCOMES (1.8 mmol/L vs. 2.3 mmol/L), reflecting selection of patients with elevated LDL-C on high-intensity or maximum-tolerated statin therapy in the latter. The cost of a statin/ezetimibe approach is substantially lower than a statin/PCSK9 inhibitor approach. However, a substantial number of patients will not achieve the standard LDL-C goal of <1.4 mmol/L with statin and ezetimibe alone, and very few will reach levels <1.0 mmol/L. For these patients, treatment with statin and a PCSK9 inhibitor will allow goal achievement in most cases and has been shown to further reduce the risk of MACE in patients with chronic atherosclerotic cardiovascular disease and the risk of MACE and death after ACS.[8,9] There are several possible hurdles for implementation of PCSK9 inhibition to reach guideline goals into clinical practice, including cost-related factors. Cost-effective solutions need to be further pursued in different healthcare systems. For example, the National Health Service (NHS) in the UK has recently made an agreement on a population health management approach to address increased LDL-C in eligible patients with ASCVD using the PCSK9 small interfering RNA drug inclisiran.

Notably, no safety issues other than an excess of injection site reactions, usually mild to moderate, have been observed in clinical trials of PCSK9 inhibitors completed to date (including alirocumab, evolocumab, and inclisiran). Longer-term safety data will become available from several analyses, such as the long-term extension programmes from clinical studies with PCSK9 inhibition. Ongoing clinical outcome trials are currently investigating whether treatment with newer drugs such as inclisiran or bempedoic acid, added to statin and ezetimibe, will reduce MACE while achieving the LDL-C goals defined in the 2019 ESC/EAS guidelines.

Limitations

ODYSSEY OUTCOMES enrolled a population of ACS patients with elevated atherogenic lipoproteins despite high-intensity or maximum-tolerated statin treatment and may therefore overestimate the proportion of patients not at goal compared with a population-based analysis of ACS patients. Our modelling assumed an 18 ± 3% reduction of LDL-C if ezetimibe were added to high-intensity statin treatment.[14] Other reports suggest that the effect of ezetimibe may be smaller (e.g. mean 14% LDL-C reduction[15]). In that context, our model may overestimate the potential achievement of LDL-C goals with ezetimibe. This is an exploratory analysis and assumptions about the efficacy of ezetimibe cannot be translated with precision into clinical practice.

In the 2019 ESC/EAS guidelines,[10] it is recommended that patients considered to be at very high risk (e.g. after an ACS) achieve an LDL-C reduction of >50% as well as an absolute LDL-C level <55 mg/dL. In the present study, we report and focus on the percentage of patients reaching the LDL-C goal of <55 mg/dL or the optional goal of <40 mg/dL. Since we do not have untreated (natural) LDL-C levels, we cannot determine the percentage of patients who achieved a >50% LDL-C reduction from that baseline. In the ODYSSEY OUTCOMES trial, 89% of patients were treated with a high-intensity statin regimen that has the potential to provide a mean LDL-C reduction of approximately 50%.[16] Mean LDL-C reductions achieved in clinical practice may be less than those observed in research studies, although the mean per cent reduction tends to be higher when untreated LDL cholesterol levels are higher.[17] Therefore, a substantial, albeit undetermined, proportion of ODYSSEY OUTCOMES participants is expected to have achieved at least a 50% LDL-C reduction before randomization to alirocumab or placebo and a large majority to have achieved that reduction after the addition of alirocumab. Few patients in ODYSSEY OUTCOMES were treated with ezetimibe. However, modelling based on ODYSSEY OUTCOMES data suggests that even if ezetimibe had been added to high-intensity or maximum-tolerated statin treatment in all patients, only a small percentage of the placebo group would have reached the guideline goal of <55 mg/dL while a large majority of those assigned to alirocumab would have done so.

Conclusions

The observations of the present study indicate that 94.6% of patients with a recent ACS and elevated atherogenic lipoproteins despite maximum-tolerated statin therapy can achieve the 2019 ESC/EAS guideline treatment goal for LDL-C (<1.4 mmol/L) and 85.2% of those with recurrent cardiovascular events can achieve the lower goal (<1.0 mmol/L) with the addition of the PCSK9 inhibitor alirocumab.

Supplementary material

Supplementary material is available at the *European Journal of Preventive Cardiology*.

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Authorship

U.L., P.G.S., and G.G.S. contributed to the conception or design of the work. U.L., P.G.S., D.L.B., V.A.B., R.D., M.D., S.G.G., J.W.W., M.L., I.P., R.P., S.H.P., M.S., and H.D.W. contributed to the acquisition, analysis, or interpretation of data for the work. U.L., P.G.S., and G.G.S. drafted the manuscript. J.M. performed the statistical analyses. All critically revised the manuscript and gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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