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Transiently achieved very low low-density lipoprotein cholesterol levels by statin and alirocumab after acute coronary syndrome are associated with cardiovascular risk reduction: the ODYSSEY OUTCOMES trial

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Abstract

Aims

Long-term, placebo-controlled cholesterol-lowering trials have demonstrated legacy effects (clinical benefits that persist or emerge after trial end). It is unknown whether legacy effects follow a short period of very low low-density lipoprotein cholesterol (LDL-C) levels achieved with statin plus proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor.

Methods and results

In 18 924 patients with recent acute coronary syndrome, the ODYSSEY OUTCOMES trial compared the PCSK9 inhibitor alirocumab with placebo, each added to high-intensity or maximum-tolerated statin therapy. Patients with two consecutive LDL-C levels <0.39 mmol/L (15 mg/dL) on alirocumab had blinded placebo substitution for the remainder of the trial with continued statin treatment. In *post hoc* analyses, major adverse cardiovascular events (MACE) in these patients were compared to MACE in propensity score-matched patients from the placebo group with similar baseline characteristics and study medication adherence. In the alirocumab group, 730 patients had blinded placebo substitution at a median of 8.3 months from randomization, after a median of 6.0 months with LDL-C <0.39 mmol/L. They were matched to 1460 placebo patients. Both groups had lower

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[†] A full list of the ODYSSEY OUTCOMES Committee Members and Investigators is provided in the Supplementary appendix.

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baseline LDL-C and lipoprotein(a) and better study medication adherence than those of the overall cohort. Over a median follow-up of 2.8 years, MACE occurred in 47 (6.4%) alirocumab patients with limited-duration, very low achieved LDL-C vs. 122 (8.4%) matched placebo patients (treatment hazard ratio 0.72; 95% confidence interval 0.51, 0.997; $P = 0.047$).

Conclusion

A short period of LDL-C levels <0.39 mmol/L achieved with statin and alirocumab, followed by statin monotherapy, was associated with a lower risk of MACE than statin monotherapy throughout the observation period. Clinical benefit persisted for several years.

Trial registration ClinicalTrials.gov NCT01663402

Structured Graphical Abstract

Key Question

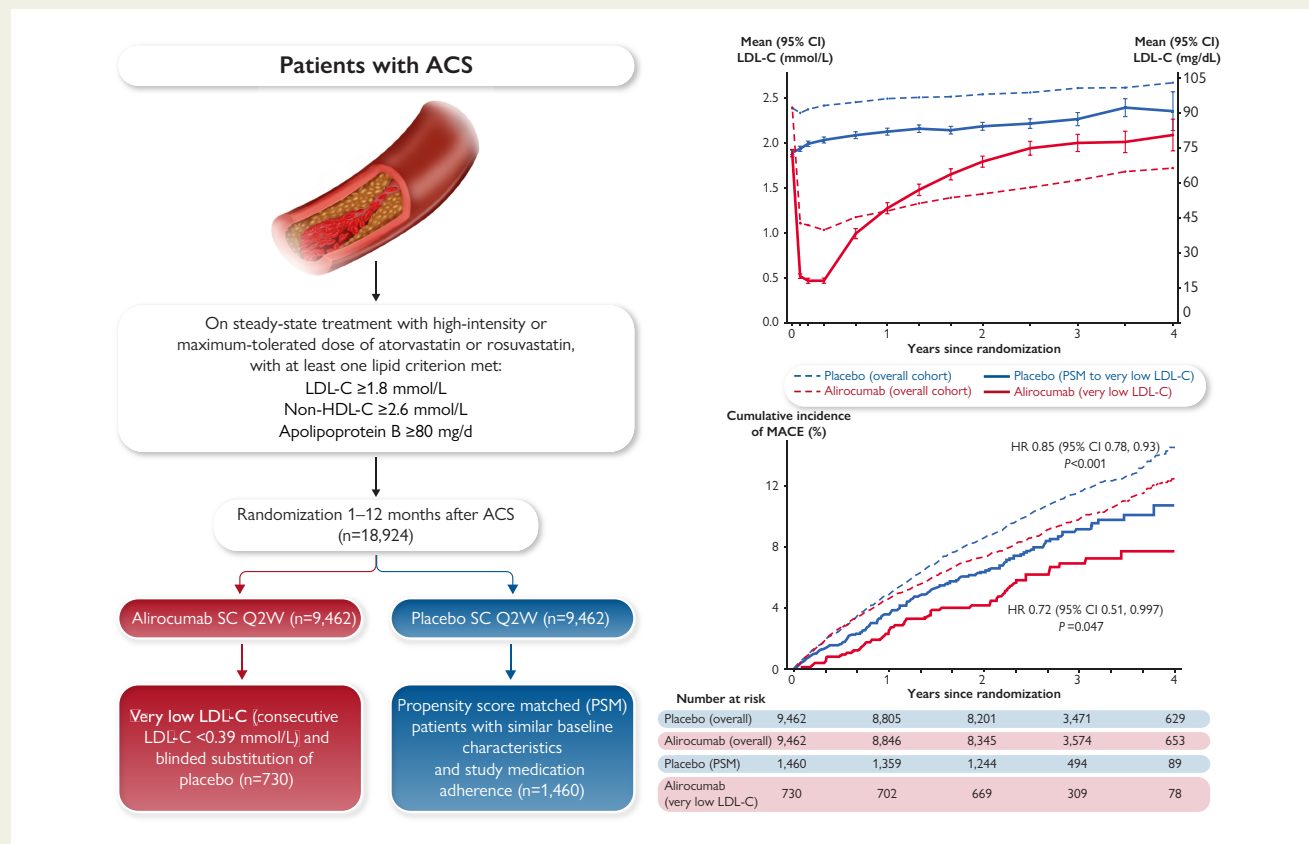
Does a short period of very low low-density lipoprotein cholesterol (LDL-C) achieved with statin and alirocumab result in prolonged cardiovascular risk reduction?

Key Finding

In a post hoc subgroup analysis of a randomized trial, 730 patients treated with statin and alirocumab achieved LDL-C levels <0.39 mmol/L (15 mg/dL) for a median of 6 months before protocol-specified, blinded substitution with placebo for alirocumab. Over 2.8 years' median follow-up, they had a lower risk of cardiovascular events than 1,460 matched patients treated with statin and placebo throughout the observation period.

Take Home Message

A short period of very low LDL-C levels (<0.39 mmol/L) may result in prolonged cardiovascular risk reduction.



A short period of very low LDL-C levels achieved with statin and alirocumab is associated with a prolonged reduction of cardiovascular risk after ACS: a *post hoc* analysis of the ODYSSEY OUTCOMES randomized trial

Left: Patients with recent ACS and elevated atherogenic lipoproteins despite high-intensity or maximum-tolerated statin treatment were randomized to receive alirocumab or placebo. Per protocol, if consecutive LDL-C levels were <0.39 mmol/L (15 mg/dL) on alirocumab, it was blindly substituted with placebo for the remaining duration of the trial, with continuation of background statin. This occurred in 730 of 9462 patients assigned to alirocumab. They were compared to 1460 patients from the placebo group with similar baseline characteristics and study medication adherence, identified by propensity score matching. *Right:* LDL-C levels and incidence of MACE are shown for patients from the alirocumab group with very low LDL-C and substitution with

placebo (solid red), propensity score–matched patients from the placebo group (solid blue), and the overall alirocumab and placebo groups (dashed red and blue). ACS, acute coronary syndrome; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events as defined in the text; PSM, propensity score–matched; Q2W, every 2 weeks; SC, subcutaneous.

Keywords Low-density lipoprotein cholesterol • Statin • PCSK9 inhibitor • Acute coronary syndrome

Introduction

In most trials of cholesterol-lowering therapies, the clinical benefit evolves over time, with a smaller reduction in the risk of cardiovascular events during the first year of treatment than that in subsequent years.¹ Once fully established, the clinical benefit of lipid-lowering therapy may be long-lasting. For example, after the completion of several years of randomized treatment in placebo-controlled trials of statins, a persistent reduction in cardiovascular mortality was observed, in some cases for more than 10 years,^{2,3} and even when the majority of patients did not receive on-going statin treatment.⁴ This is known as a legacy effect.

When added to statins, inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9) have the potential to reduce low-density lipoprotein cholesterol (LDL-C) to levels not achievable with oral lipid-lowering therapies alone. Two large, placebo-controlled trials have demonstrated cardiovascular benefits of this approach.^{5,6} The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial demonstrated a reduction in non-fatal, but not fatal cardiovascular events with the PCSK9 inhibitor evolocumab, compared with placebo, over a median follow-up of 2.2 years.⁵ A legacy effect of randomized treatment with evolocumab was demonstrated when patients from both arms of the trial received open-label treatment with evolocumab for 5 additional years and fewer cardiovascular deaths occurred in the original evolocumab group.⁷

While evidence supports a persistent clinical benefit of cholesterol-lowering therapy after a prolonged period of treatment, it is uncertain whether clinical benefit ensues from a limited period of high-intensity cholesterol-lowering therapy. The placebo-controlled ODYSSEY OUTCOMES trial demonstrated a reduction in cardiovascular events and death with the PCSK9 inhibitor alirocumab over a median follow-up of 2.8 years in patients with recent acute coronary syndrome (ACS) who received high-intensity or maximum-tolerated statin treatment.^{6,8,9} The trial was designed to maximize the number of patients who achieved a target range of LDL-C 0.65–1.30 mmol/L (25–50 mg/dL) with alirocumab and to avoid sustained, very low levels of LDL-C (<0.39 mmol/L or 15 mg/dL), the safety of which was unknown at the time of trial design. Accordingly, patients with consecutive LDL-C measurements <0.39 mmol/L on alirocumab had blinded substitution with placebo for the remainder of the trial with continuation of background statin. Those patients therefore achieved very low LDL-C levels, but for a short period before being switched to placebo. The present *post hoc* analysis describes the cardiovascular outcomes of those patients in comparison to patients from the placebo group with similar baseline characteristics and study medication adherence, selected using a propensity score. We have previously reported that no safety concerns were identified in patients who achieved very low levels of LDL-C with alirocumab.¹⁰

Methods

The ODYSSEY OUTCOMES trial

The design and principal results of the ODYSSEY OUTCOMES trial have been reported.^{6,11} At each of 1315 sites in 57 countries, the trial was approved by the responsible institutional review committee, and patients gave informed consent. One to 12 months (median 2.6) after an ACS, 18 924 patients with elevated levels of atherogenic lipoproteins despite high-intensity or maximum-

tolerated statin treatment were randomly assigned in a 1:1 ratio to treatment with alirocumab 75 mg or placebo, administered subcutaneously every 2 weeks. Plasma lipids were measured at randomization, at 1, 2, 4, 8, 12, 16, 20, and 24 months after randomization, and at 6-month intervals thereafter. LDL-C was calculated with the Friedewald formula unless the calculated value was <0.39 mmol/L or the concurrent triglyceride level was ≥ 4.52 mmol/L. In those cases, LDL-C was measured directly by preparative ultracentrifugation and beta-quantitation. The alirocumab dose could be blindly increased to 150 mg if LDL-C remained >1.3 mmol/L (50 mg/dL) on the 75 mg dose. Conversely, if two consecutive measurements of LDL-C were <0.39 mmol/L on the 75 mg dose, alirocumab was blindly replaced by placebo at the next study visit, and placebo was continued for the remainder of the study. The protocol did not specify any adjustment of background statin or other oral lipid-lowering therapy based on achieved LDL-C levels. The primary endpoint of the trial was the composite of death from coronary heart disease, non-fatal myocardial infarction, hospitalization for unstable angina, or ischaemic stroke. All-cause death and ischaemia-driven coronary revascularization were among pre-specified secondary endpoints.

Statistical analysis

For this *post hoc* analysis, the risks of a primary endpoint, all-cause death, and ischaemia-driven coronary revascularization were compared in patients who achieved LDL-C levels <0.39 mmol/L on alirocumab followed by blinded substitution with placebo and in patients from the placebo group with similar baseline characteristics and study medication adherence using propensity score matching in a 1:2 ratio. A threshold of $P < 0.1$ with forward selection in a logistic regression model was used to determine the baseline characteristics that differed between patients in the alirocumab subgroup who had blinded substitution with placebo for alirocumab and all placebo patients. Baseline characteristics considered for matching were age, sex, and geographic region; history of diabetes, current smoking, prior coronary artery bypass grafting, prior percutaneous coronary intervention, peripheral artery disease, cerebrovascular disease, heart failure, chronic obstructive pulmonary disease, and malignancy; and type of index ACS (non-ST-segment elevation myocardial infarction, ST-segment elevation myocardial infarction, or unstable angina), revascularization for the index ACS, intensity of statin therapy at randomization (high intensity vs. other), body mass index, systolic blood pressure, estimated glomerular filtration rate dichotomized at 60 mL/min/1.73 m², and baseline concentrations of LDL-C and lipoprotein(a). Adherence was assessed by the number of doses of study medication injected during the 61 days preceding the Month 4 study visit, as reported in patient diaries. There was no imputation of missing adherence data. Greedy matching on propensity scores¹² was performed with calliper of 0.25.

Treatment hazard ratios (HR) and associated 95% confidence intervals (CI) were estimated by Cox proportional hazards models for major adverse cardiovascular events (MACE), its components, and all-cause death; P values were determined by logrank tests. Time-averaged LDL-C was calculated using baseline and post-randomization LDL-C values prior to a MACE event or right censoring for MACE at last follow-up.

All presented P values are two-sided; $P < 0.05$ was considered statistically significant, with no adjustment for multiple testing. Analyses were performed in SAS version 9.4 (IBM, Armonk, New York).

Results

For the overall trial cohort, the median [quartile (Q) 1, Q3] follow-up was 2.8 (2.3, 3.4) years. Background treatment with high-dose

atorvastatin or rosuvastatin was employed in 88.8%, with a median (Q1, Q3) baseline LDL-C of 2.25 (1.89, 2.69) mmol/L [87 (73, 104) mg/dL]. Alirocumab reduced the risk of a primary MACE endpoint (HR 0.85; 95% CI 0.78, 0.93; $P < 0.001$) and was associated with a lower risk of death (HR 0.85; 95% CI 0.73, 0.98; $P = 0.03$) and ischaemia-driven coronary revascularization (HR 0.88; 95% CI 0.79–0.97; $P = 0.01$).

Characteristics of patients who achieved consecutive LDL-C levels <0.39 mmol/L on alirocumab followed by blinded placebo substitution and of propensity score-matched patients from the placebo group

In the alirocumab group, 730 (7.7%) patients had consecutive LDL-C levels <0.39 mmol/L and underwent blinded substitution with placebo. They were matched to 1460 patients from the placebo group. Eight characteristics were used to determine the propensity score for matching. These were baseline LDL-C, lipoprotein(a), body mass index, systolic blood pressure, geographic region, sex, high-intensity statin treatment (vs. other), and study medication adherence (number of self-reported doses administered during the 61-day period prior to the Month 4 LDL-C assessment; full adherence corresponded to an average of 4.3 doses).

Table 1 shows the characteristics of the aggregate alirocumab and placebo groups, the 730 patients from the alirocumab group who achieved very low LDL-C levels and had blinded substitution with placebo, and the 1460 propensity score-matched patients from the placebo group. As expected, patients in the alirocumab group who achieved consecutive LDL-C levels <0.39 mmol/L on alirocumab had lower baseline LDL-C and lipoprotein(a) levels than those in the entire study cohort. In addition, patients who achieved very low LDL-C on alirocumab were more likely to be male, to have diabetes, to receive high-intensity statin treatment, to have better study medication adherence, and to be enrolled in Asia or South America, but less likely to be enrolled in Europe. The table also shows that propensity score-matched patients among those randomized to placebo had characteristics that were well-aligned with their comparator group.

The median (Q1, Q3) follow-up for the primary MACE endpoint of the patients who achieved consecutive LDL-C levels <0.39 mmol/L on alirocumab followed by blinded substitution with placebo and of the propensity score-matched comparison patients from the placebo group was 2.8 (2.2, 3.5) and 2.6 (2.2, 3.3) years, respectively. Figure 1 provides a histogram of the time to substitution with placebo for alirocumab in the former group. The median (Q1, Q3) time to substitution was 8.3 (4.2, 15.7) months after randomization. Prior to substitution, these patients spent a median (Q1, Q3) of 6.0 (3.3, 8.3) months with LDL-C <0.39 mmol/L. The median (Q1, Q3) LDL-C at month 4 was 0.41 (0.26, 0.62) mmol/L [16 (10, 24) mg/dL], and the minimum achieved LDL-C among these patients during follow-up was 0.18 (0.10, 0.26) mmol/L [7 (4, 10) mg/dL].

Figure 2 (top panel) shows mean LDL-C levels over time. In patients from the alirocumab group who had blinded substitution with placebo and in propensity score-matched patients from the placebo group, mean (95% CI) time-averaged LDL-C levels were 1.31 (1.27, 1.34) mmol/L [51 (49, 52) mg/dL] and 2.11 (2.08, 2.15) mmol/L [82 (80, 83) mg/dL], respectively ($P < 0.001$). As expected, LDL-C rose after substitution with placebo for alirocumab and by the end of the observation period reached a level not significantly different from propensity score-matched patients from the placebo group ($P > 0.05$). The mean

time-averaged difference in LDL-C between these two subgroups was 0.81 mmol/L (31 mg/dL).

In the overall alirocumab and placebo groups, mean (95% CI) time-averaged LDL-C levels were 1.29 (1.27, 1.30) mmol/L [50 (49, 50) mg/dL] and 2.48 (2.46, 2.49) mmol/L [96 (95, 96) mg/dL], with a corresponding mean time-averaged difference of 1.19 mmol/L (46 mg/dL).

Cardiovascular outcomes and death

A primary MACE endpoint event occurred in 47/730 (6.4%) patients who achieved consecutive LDL-C levels <0.39 mmol/L on alirocumab followed by blinded substitution with placebo, compared with 122/1460 (8.4%) of matched patients from the placebo group. The 47 events among the patients initially treated with alirocumab represented 5.2% of the 903 MACE endpoint events observed in the aggregate alirocumab group. Figure 2 (bottom panel) shows the cumulative incidence of MACE in the 730 patients from the alirocumab group who underwent blinded substitution with placebo, in the 1460 propensity score-matched patients from the placebo group, and in the entire alirocumab and placebo groups. The propensity score-matched patients from the placebo group had a substantially lower risk of MACE than that of the entire placebo group, with 4-year Kaplan–Meier estimates of 10.7% and 14.5%, respectively. Notwithstanding a relatively brief period of alirocumab treatment and lower risk of their comparator group (propensity score-matched placebo patients), patients in the alirocumab group who achieved consecutive LDL-C levels <0.39 mmol/L followed by blinded substitution with placebo had a numerically lower estimated treatment HR for MACE (0.72; 95% CI 0.51, 0.997; $P = 0.047$) than that in the entire alirocumab vs. placebo groups (HR 0.85; 95% CI 0.78, 0.93; $P < 0.001$). There were non-significant treatment HRs for each component of the primary endpoint, all-cause death, and ischaemia-driven coronary revascularization (Table 2).

Discussion

The ODYSSEY OUTCOMES trial incorporated blinded substitution with placebo in patients who had consecutive levels of LDL-C <0.39 mmol/L on alirocumab. The original intent of this design was to avoid sustained, very low levels of LDL-C because of theoretical safety concerns at the time the study was designed and conducted.^{13,14} However, the design also provided a unique opportunity to assess the clinical efficacy of achieving a very low level of LDL-C for a limited period. The present analysis shows that patients treated with alirocumab plus high-intensity or maximum-tolerated statin for a median of 8.3 months, resulting in LDL-C levels <0.39 mmol/L for a median of 6.0 months, had a significantly lower risk of MACE over a median follow-up of 2.8 years compared with that of propensity score-matched, statin-treated patients from the placebo group whose mean LDL-C levels remained between approximately 1.9 and 2.3 mmol/L (Structured Graphical Abstract). Qualitatively, the Kaplan–Meier curves depicting the cumulative incidence of MACE continued to diverge through the observation period. These findings indicate that a short period of very high-intensity cholesterol-lowering therapy resulting in very low LDL-C levels may be associated with prolonged cardiovascular risk reduction that extends well beyond the period of treatment. We have previously reported that no safety concerns were observed in this subgroup.¹⁰

Since patients who had blinded substitution with placebo represented a small fraction of patients while experiencing an even smaller fraction of the primary MACE endpoint events within the alirocumab group, their impact on the overall study results was limited. Notwithstanding this point, the estimated treatment HR for patients in the alirocumab group with blinded placebo substitution (0.72) was lower than that in the overall study cohort

Table 1 Characteristics of patients who achieved consecutive low-density lipoprotein cholesterol levels <0.39 mmol/L on alirocumab and had blinded substitution with placebo, compared to propensity score–matched patients from the placebo group

Characteristic	Alirocumab group, all patients (n = 9462)	Placebo group, all patients (n = 9462)	Alirocumab group, consecutive LDL-C <0.39 mmol/L and blinded substitution with placebo (n = 730)	Placebo group, propensity score–matched to patients with consecutive LDL-C <0.39 mmol/L on alirocumab (n = 1460)
Demographics				
Age, years	58 (52, 65)	58 (52, 65)	58 (51, 65)	58 (52, 65)
Female sex ^a , n %	2390 (25.2)	2372 (25.1)	114 (15.6)	230 (15.8)
Geographic region^a, n %				
Western Europe	2084 (22.0)	2091 (22.1)	88 (12.1)	173 (11.8)
Eastern Europe	2719 (28.7)	2718 (28.7)	127 (17.4)	258 (17.7)
North America	1435 (15.2)	1436 (15.2)	92 (12.6)	194 (13.3)
South America	1293 (13.7)	1295 (13.7)	188 (25.8)	365 (25.0)
Asia	1150 (12.2)	1143 (12.1)	195 (26.7)	389 (26.6)
Rest of world	781 (8.3)	779 (8.2)	40 (5.5)	81 (5.5)
Medical history, n (%)				
Hypertension	6205 (65.6)	6044 (63.9)	457 (62.6)	877 (60.1)
Diabetes	2693 (28.5)	2751 (29.1)	255 (34.9)	480 (32.9)
Current smoking	2282 (24.1)	2278 (24.1)	162 (22.2)	333 (22.8)
CABG	521 (5.5)	526 (5.6)	31 (4.2)	55 (3.8)
PCI	1626 (17.2)	1615 (17.1)	111 (15.2)	197 (13.5)
Heart failure	1366 (14.4)	1449 (15.3)	88 (12.1)	170 (11.6)
Peripheral artery disease	373 (3.9)	386 (4.1)	14 (1.9)	46 (3.2)
Stroke	306 (3.2)	305 (3.2)	18 (2.5)	48 (3.3)
High-intensity statin treatment at randomization ^a	8380 (88.6)	8431 (89.1)	669 (91.6)	1346 (92.2)
Index ACS				
NSTEMI	4574 (48.3)	4601 (48.6)	330 (45.2)	638 (43.7)
STEMI	3301 (34.9)	3235 (34.2)	235 (32.2)	513 (35.1)
Unstable angina	1568 (16.6)	1614 (17.1)	162 (22.2)	305 (20.9)
Missing	19 (<0.1)	12 (<0.1)	3 (0.4)	4 (0.3)
Time from index ACS to randomization, months	2.6 (1.7, 4.4)	2.6 (1.7, 4.3)	2.6 (1.7, 3.8)	2.7 (1.8, 4.3)
PCI or CABG for index ACS, n (%)	6799 (71.9)	6878 (72.7)	510 (69.9)	1051 (72.0)
Baseline lipids and lipoproteins				
LDL-C ^a , mmol/L	2.23 (1.89, 2.69)	2.23 (1.89, 2.69)	1.84 (1.50, 2.15)	1.86 (1.61, 2.18)
Lipoprotein(a) ^a , mg/dL	20.8 (6.8, 59.1)	21.6 (6.6, 60.1)	9.9 (2.0, 24.8)	9.4 (2.0, 22.6)
Triglycerides, mmol/L	1.46 (1.06, 2.05)	1.46 (1.07, 2.07)	1.77 (1.30, 2.41)	1.53 (1.06, 2.20)
HDL-C, mmol/L	1.11 (0.96, 1.30)	1.09 (0.93, 1.30)	1.04 (0.88, 1.22)	1.06 (0.88, 1.22)
Other baseline biometric and laboratory data				
BMI ^a , kg/m ²	28 (25, 31)	28 (25, 31)	27 (24, 30)	27 (24, 30)
eGFR, mL/min/1.73 m ²	78 (67, 90)	78 (68, 90)	78 (67, 90)	79 (68, 92)

Continued

Table 1 Continued

Characteristic	Alirocumab group, all patients (n = 9462)	Placebo group, all patients (n = 9462)	Alirocumab group, consecutive LDL-C <0.39 mmol/L and blinded substitution with placebo (n = 730)	Placebo group, propensity score-matched to patients with consecutive LDL-C <0.39 mmol/L on alirocumab (n = 1460)
HbA1c, %	5.8 (5.5, 6.3)	5.8 (5.5, 6.3)	5.9 (5.5, 6.6)	5.9 (5.6, 6.5)
Systolic blood pressure ^a , mm Hg	127 (118, 138)	126 (117, 138)	125 (117, 137)	127 (116, 140)
Post-randomization characteristics				
Minimum LDL-C, mmol/L	0.47 (0.34, 0.70)	1.71 (1.40, 2.07)	0.18 (0.10, 0.26)	1.50 (1.17, 1.76)
Time-averaged LDL-C, mmol/L	1.06 (0.78, 1.58)	2.33 (1.97, 2.82)	1.27 (0.96, 1.58)	2.05 (1.71, 2.41)
Adherence ^b : ≥ 4 doses of study medication during the 61 days preceding Month 4 assessment, n (%)	8606 (91.0)	8628 (91.2)	704 (96.4)	1404 (96.2)

Continuous variables are reported as median (Q1, Q3). Dichotomous variables are reported as percentage with the characteristic.

ACS, acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

^aCharacteristics used in propensity score matching.

^bStudy medication adherence is measured by the number of self-reported injections over the 2-month period between Month 2 and Month 4. Full adherence was approximately 4.3 injections.

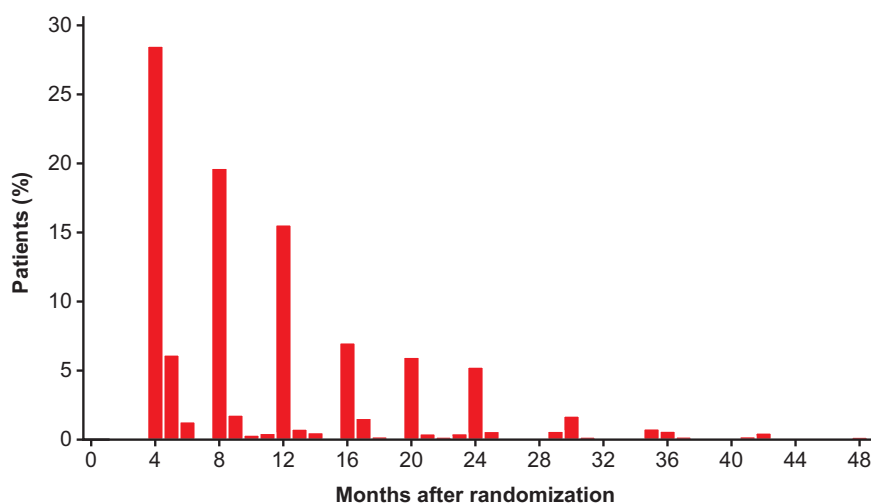


Figure 1 Histogram of time to blinded substitution with placebo for alirocumab in 730 patients. Substitution with placebo for alirocumab occurred at the study visit following the second consecutive low-density lipoprotein cholesterol level <0.39 mmol/L. Nominal times of post-randomization study visits were Months 1, 2, 4, 8, 12, 16, 20, 24, 30, 36, 42, and 48.

(0.85), indicating that the former subgroup more likely strengthened than diluted the overall clinical treatment effect in the trial. This is despite the fact that the time-averaged difference in LDL-C between former subgroup and propensity score-matched placebo patients was smaller than the time-averaged difference in LDL-C between the overall alirocumab and placebo groups. It is unknown whether patients assigned to alirocumab who had blinded substitution with placebo would have derived even greater benefit had alirocumab been continued in the face of very low achieved LDL-C.

It is important to note that the patients who achieved consecutive LDL-C levels <0.39 mmol/L on alirocumab comprised an inherently

lower-risk group than the overall ODYSSEY OUTCOMES trial population. This is illustrated in [Figure 2](#) by the fact that the comparison propensity score-matched patients from the placebo group had substantially lower LDL-C levels and risk of MACE than the overall placebo group. Nonetheless, despite their lower risk, patients who achieved very low LDL-C for a short time derived significant clinical benefit from alirocumab treatment.

As depicted in [Figure 2](#), although mean LDL-C levels were nearly identical at baseline in patients who achieved consecutive LDL-C levels <0.39 mmol/L with alirocumab and in propensity score-matched patients from the placebo group, mean LDL-C levels in the former

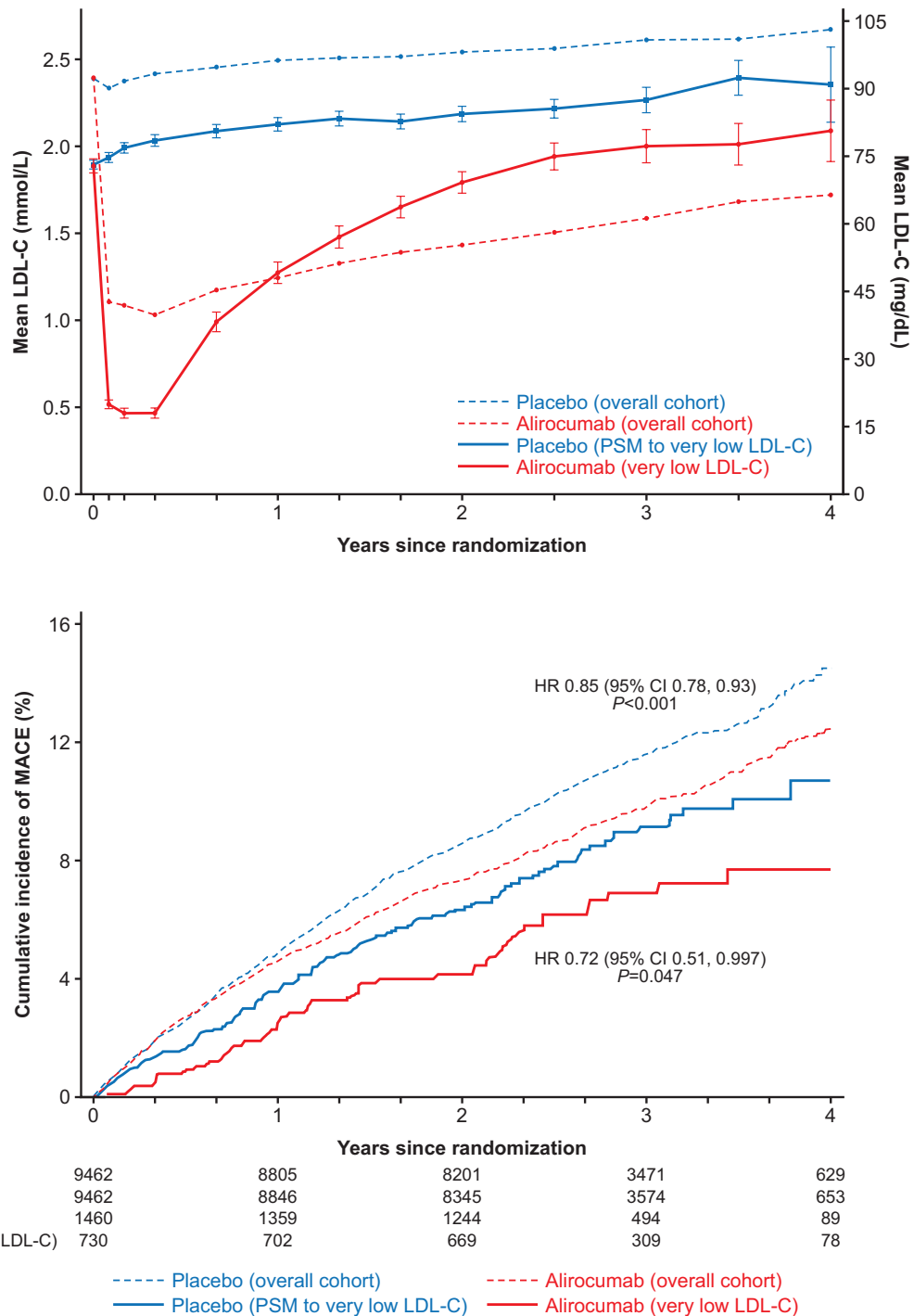


Figure 2 Mean LDL-C levels and cumulative incidence of MACE among patients in the alirocumab group who achieved consecutive LDL-C levels <0.39 mmol/L and had blinded substitution with placebo, in propensity score–matched patients from the placebo group, and in the entire alirocumab and placebo groups. In 730 patients assigned to alirocumab who had consecutive levels LDL-C < 0.39 mmol/L (solid red), alirocumab was blindly substituted with placebo for the remainder of the study. The comparator group comprised 1460 patients assigned to placebo with similar baseline characteristics and study medication adherence, selected by propensity score matching (solid blue). These patients are compared to all patients in the ODYSSEY OUTCOMES trial assigned to alirocumab (dashed red) or placebo (dashed blue). Upper panel: mean (95% CI) LDL-C levels over time. Bottom panel: cumulative incidence of MACE, comprising death from coronary heart disease, non-fatal myocardial infarction, ischaemic stroke, and hospitalization for unstable angina. CI, confidence interval; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events as defined in the text; PSM, propensity score–matched; SD, standard deviation.

Table 2 Endpoint events in patients, who achieved consecutive low-density lipoprotein cholesterol levels <0.39 mmol/L on alirocumab and had blinded substitution with placebo, and in propensity score-matched patients from the placebo group

Outcome	Alirocumab group, consecutive LDL-C < 0.39 mmol/L and blinded substitution with placebo (n = 730)	Placebo group, propensity score-matched patients with consecutive LDL-C < 0.39 mmol/L on alirocumab (n = 1460)	Hazard ratio (95% confidence interval)	P value
	n (events per 100 person-years)			
MACE composite (primary)	47 (2.3)	122 (3.2)	0.72 (0.51, 0.997)	0.047
Coronary heart disease death	11 (0.5)	25 (0.6)	0.83 (0.41, 1.68)	0.59
Non-fatal myocardial infarction	31 (1.5)	81 (2.1)	0.72 (0.48, 1.09)	0.11
Fatal or non-fatal ischaemic stroke	7 (0.3)	21 (0.5)	0.62 (0.26, 1.45)	0.25
Hospitalization for unstable angina	2 (0.1)	10 (0.3)	0.36 (0.08, 1.64)	0.14
All-cause death	15 (0.7)	48 (1.2)	0.58 (0.33, 1.04)	0.06
Ischaemia-driven coronary revascularization procedure	57 (2.8)	89 (2.3)	1.24 (0.89, 1.73)	0.21

LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events.

subgroup remained somewhat lower than that in the latter subgroup until 4 years from randomization. There are several potential explanations for this. A few patients achieved very low LDL-C levels on alirocumab and had placebo substitution as late as 3.5 years after randomization. Two patients in the alirocumab group who had substitution of placebo for alirocumab were subsequently treated with an open-label PCSK9 inhibitor. Finally, although patients were instructed to return unused study medication at each visit, we cannot exclude the possibility that some doses of alirocumab were retained and self-administered after the intended substitution of placebo.

Prior evidence indicates that high-intensity statin treatment provides an early clinical benefit after ACS. In the placebo-controlled Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial, atorvastatin 80 mg reduced the mean LDL-C from a baseline of 124 to 62 mg/dL (3.21–1.61 mmol/L) at 6 weeks. The incidence of MACE at 16 weeks was significantly reduced with atorvastatin (14.8%) compared with placebo (17.4%).¹⁵ The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial suggested that a clinical benefit of atorvastatin 80 mg vs. pravastatin 40 mg daily could be identified within a similar time frame.¹⁶

The placebo-controlled Studies of PCSK9 Inhibition and the Reduction of Vascular Events (SPIRE) trials¹⁷ with the PCSK9 inhibitor bococizumab were conducted in patients with established atherosclerotic cardiovascular disease or high cardiovascular risk, 93% of whom were treated with statins. The trials were prematurely terminated due to greater than expected development of anti-drug antibodies and attenuation of lipid-lowering efficacy over time. In SPIRE-1, reduction of mean LDL-C levels with bococizumab from a baseline of 93.8 mg/dL (2.42 mmol/L) to 38.2 mg/dL (0.99 mmol/L) at 1 month and 41.8 mg/dL (1.08 mmol/L) at 6 months did not reduce the risk of MACE over a median follow-up of 7 months. In contrast, in SPIRE-2,

reduction of mean LDL-C levels with bococizumab from a baseline of 133.9 mg/dL (3.46 mmol/L) to 58.2 mg/dL (1.50 mmol/L) at 1 month and 77.3 mg/dL (2.00 mmol/L) at 12 months reduced the cumulative incidence of MACE compared with placebo (3.32% vs. 4.19%) over a median follow-up of 12 months. In sum, the evidence from MIRACL, PROVE IT, and SPIRE indicate that early clinical benefit of intensive LDL-C reduction, either with statin monotherapy or with addition of a PCSK9 inhibitor to statin therapy, may depend upon a combination of high baseline LDL-C levels, low achieved LDL-C levels, and a sufficiently long observation period. However, none of these studies determined if brief exposure to very low LDL-C levels provides clinical benefit that persists beyond the period of lipid-lowering treatment.

Intravascular imaging studies indicate the potential for rapid and favourable coronary plaque remodelling with intensive cholesterol-lowering therapy. The Reduction in Yellow Plaque by Aggressive Lipid Lowering Therapy (YELLOW) trial showed that 7 weeks of high-intensity statin treatment (rosuvastatin 40 mg) reduced the lipid core of obstructive coronary plaques compared to usual care, with corresponding average LDL-C levels of 58 vs. 82 mg/dL (1.50 vs. 2.12 mmol/L).¹⁸ Early, favourable changes in coronary plaque morphology after ACS are particularly pronounced in patients who initiate statin treatment at the time of ACS, compared with chronically treated patients.¹⁹ Recently, the Effects of the PCSK9 Antibody Alirocumab on Coronary Atherosclerosis in Patients with Acute Myocardial Infarction (PACMAN-AMI) trial compared the effects of alirocumab 150 mg vs. placebo, both added to high-intensity statin treatment, on coronary plaque morphology using multimodal intravascular imaging in 300 patients with ACS.²⁰ Between baseline (during hospitalization for ACS) and 1 year of assigned treatment, the changes in atheroma volume, lipid core burden, and fibrous cap thickness were more favourable with alirocumab than placebo. However, these studies did not determine

whether the effects of this lipid-lowering strategy on plaque characteristics were evident at time points earlier than 1 year, persisted beyond the period of alirocumab treatment, or predicted the risk of MACE.

Clinical legacy effects of statins² and evolocumab⁷ have been demonstrated after extended treatment periods. For example, in the Scandinavian Simvastatin Survival Study (4S), total and coronary mortality were reduced by simvastatin vs. placebo during 5 years of randomized treatment, and that benefit was maintained during 5 additional years of observation when most patients from both groups received open-label simvastatin.²¹ In the West of Scotland Coronary Prevention Study (WOSCOPS), total and coronary mortality was reduced by pravastatin compared with placebo during 5 years of randomized treatment, and the benefit remained evident for up to 15 years of extended follow-up even though statin treatment was employed in fewer than 40% of patients from either original treatment group.⁴ In a 5-year open-label extension of the FOURIER trial, which comprised approximately 24% of its initial cohort, those originally assigned to receive evolocumab demonstrated sustained, very low levels of LDL-C and a lower long-term risk of MACE and cardiovascular death than that of those initially assigned to placebo.⁷ However, none of these analyses define whether a legacy effect ensues after a short period of very high-intensity cholesterol-lowering therapy resulting in very low LDL-C levels.

The present analysis begins to address that question. It shows that a limited period of combination treatment with high-intensity or maximum-tolerated atorvastatin or rosuvastatin plus the PCSK9 inhibitor alirocumab resulting in temporary, very low LDL-C levels, followed by on-going treatment with statin and placebo, is associated with a prolonged reduction in the risk of MACE compared with statin and placebo treatment during the entire observation period. However, several limitations of the present analysis should be considered. The analysis is *post hoc* and uses post-randomization data to define the subgroup with very low achieved LDL-C and thus should be considered exploratory. Although, the latter limitation was mitigated by comparing this subgroup with propensity score-matched patients from the placebo group with similar baseline characteristics and study medication adherence, the possibility of residual confounding cannot be excluded. Another limitation is that the subgroup with very low LDL-C on alirocumab and blinded substitution with placebo comprised a small proportion of all of those treated assigned to alirocumab treatment and contributed an even smaller proportion of MACE in the entire alirocumab group. The propensity score-matched patients from the placebo group also had a notably lower incidence of MACE than the aggregate placebo group. Due to these factors, the CI around the estimated treatment HR was wide, although it did not cross 1. There was a non-uniform time with LDL-C < 0.39 mmol/L and for substitution with placebo for alirocumab; thus, an optimal duration of very low LDL-C to reduce subsequent MACE cannot be determined from these data. Patients in ODYSSEY OUTCOMES were randomized at a median of 2.4 months and a minimum of 1 month after an index ACS. Therefore, the potential benefit of achieving very low LDL-C levels immediately following ACS cannot be determined. The Evolocumab for Early Reduction of Low-Density Lipoprotein Cholesterol Levels in Patients with Acute Coronary Syndromes (EVOPACS) and PACMAN-AMI trials demonstrated the lipid-lowering efficacy and safety of this approach.^{20,22}

Cholesterol lowering is generally considered a chronic therapy with no defined time for attenuation of treatment intensity. Recognizing the limitations above, the current findings raise the possibility that a short period of very high-intensity cholesterol lowering with a PCSK9 inhibitor and statin resulting in very low LDL-C levels, followed by long-term

statin monotherapy (i.e. an induction and maintenance regimen), may provide clinical efficacy with lower cost and complexity of care than indefinite dual-agent therapy. Future prospective randomized clinical trials could be designed to compare clinical outcomes with these two approaches.

Author contributions

G.G.S., M.S., and P.G.S had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: G.G.S., M.S., and P.G.S. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: G.G.S. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: M.S. Obtained funding: G.G.S., P.G.S. Study supervision: G.G.S., M.S., and P.G.S.

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Pre-registered Clinical Trial Number

clinicaltrials.gov NCT01663402.

Ethical Approval

The trial was approved by the responsible institutional review committee at each of the 1315 participating sites.

Data availability

Requests from qualified investigators for data from the ODYSSEY OUTCOMES trial will be considered by its Executive Steering Committee at odysseyoutcomesESC@gmail.com.

Conflict of interest

All authors have completed and submitted the International Committee of Medical Journal Editors Form for Disclosure of Potential Conflicts of Interest.

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