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REVIEW

Safety of the PCSK9 inhibitor alirocumab: insights from 47 296 patient-years of observation

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The ODYSSEY OUTCOMES trial, comprising over 47 000 patient-years of placebo-controlled observation, demonstrated important reductions in the risk of recurrent ischaemic cardiovascular events with the monoclonal antibody to proprotein convertase subtilisin/kexin type 9 alirocumab, as well as lower all-cause death. These benefits were observed in the context of substantial and persistent lowering of low-density lipoprotein cholesterol with alirocumab compared with that achieved with placebo. The safety profile of alirocumab was indistinguishable from matching placebo except for a ∼1.7% absolute increase in local injection site reactions. Further, the safety of alirocumab compared with placebo was evident in vulnerable groups identified before randomization, such as the elderly and those with diabetes mellitus, previous ischaemic stroke, or chronic kidney disease. The frequency of adverse events and laboratory-based abnormalities was generally similar to that in placebo-treated patients. Thus, alirocumab appears to be a safe and effective lipid-modifying treatment over a duration of at least 5 years.

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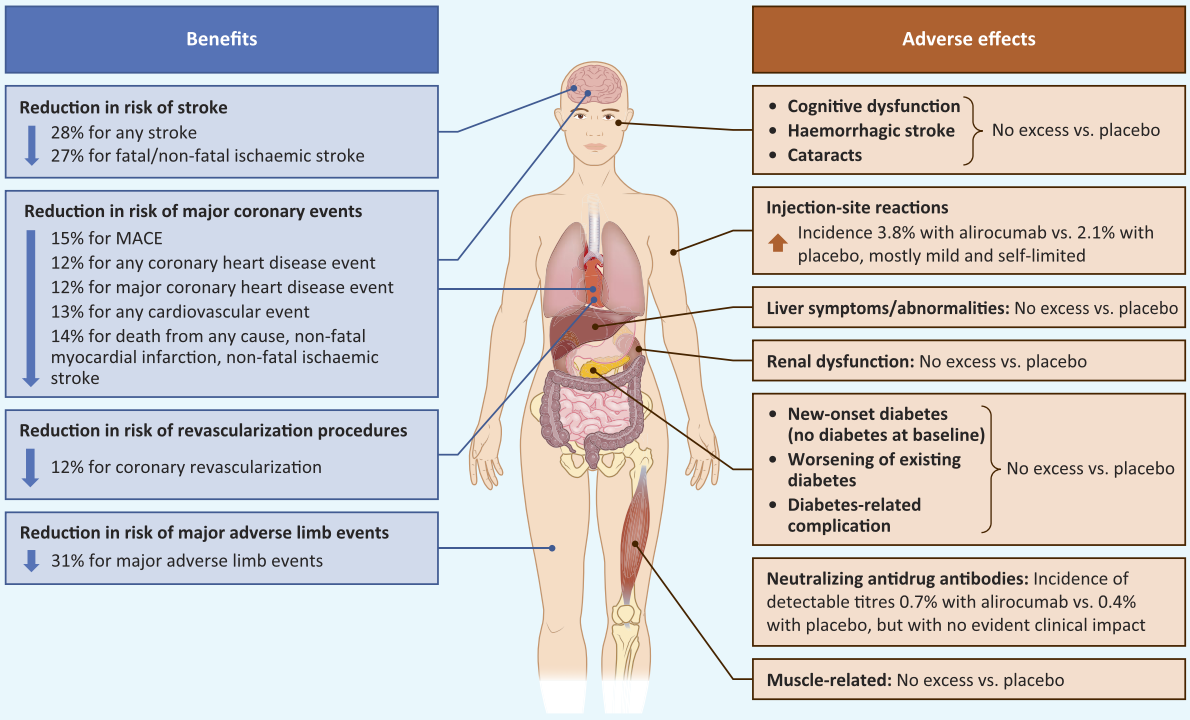
Graphical Abstract



Overview of the clinical efficacy and safety of alirocumab as observed in the ODYSSEY OUTCOMES clinical trial. MACE, major adverse cardiovascular event.

Keywords Safety • Alirocumab • PCSK9 • Cholesterol

Introduction

Alirocumab is a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9)[1] approved by most international regulatory agencies for the treatment of hypercholesterolaemia in individuals who require additional lowering of low-density lipoprotein cholesterol (LDL-C). The short- (e.g. 8 weeks) to medium-term (e.g. 52—104 weeks) lipid-lowering efficacy and safety of alirocumab compared with placebo or ezetimibe were established in 14 randomized, double-blind trials involving 5234 subjects.[2–20] The clinical efficacy of alirocumab over a median follow-up of 2.8 years and a maximum follow-up of 5 years was firmly established in the ODYSSEY OUTCOMES trial, which involved 18 924 patients with recent acute coronary syndrome (ACS) and elevated atherogenic lipoprotein levels despite high-intensity or maximum-tolerated statin treatment.[21]

Concerns regarding intensive lowering of cholesterol have, however, been raised, given that cholesterol is the main component of cell membranes and intracellular structures, serves as a precursor in the biosynthesis of some vitamins, steroids, and sex hormones, and plays a key role in hepatic bile production.[22] Further, some studies have found an association between low cholesterol levels and an increased risk for dementia, intracranial haemorrhage, and death. The Further cardiovascular Outcomes Research with PCSK9 Inhibition in 27 564 subjects with Elevated Risk (FOURIER) trial demonstrated that the PCSK9 monoclonal antibody evolocumab could significantly lower LDL-C and the risk of cardiovascular events in patients with stable atherosclerotic cardiovascular disease followed for a median of 2.2 years without differences in major safety events or cognitive function testing when compared with placebo.[23–25] At the conclusion of randomized treatment, 6635 (24%) participants from both treatment arms continued in an open-label extension study and received evolocumab for a total observation time up to 8 years.[26] Extended treatment with evolocumab in the group initially randomized to evolocumab was safe, well-tolerated, and associated with fewer cardiovascular events and cardiovascular deaths compared with delayed treatment with evolocumab in those initially randomized to placebo who survived the parent study.[26,27] To review and extend the findings in the ODYSSEY OUTCOMES trial, this report provides safety data from 47 296 patient-years of observation after randomized assignment to treatment with alirocumab or placebo.

To date, reports from ODYSSEY OUTCOMES have focused on the clinical efficacy of alirocumab (reduction of cardiovascular events and association with numerically fewer deaths)[21,28–30] across prespecified subgroups.[21,31–35] Although, in aggregate, no safety concerns with alirocumab have emerged, specific categories of patients may be particularly vulnerable to adverse events and safety outcomes, such as the elderly and those with diabetes mellitus, previous ischaemic stroke, or chronic kidney disease (*Graphical abstract*). This report reviews the overall safety findings in the trial and then examines the safety and tolerability of alirocumab in the specific subgroups indicated above, as well as the effect of alirocumab on key laboratory tests.

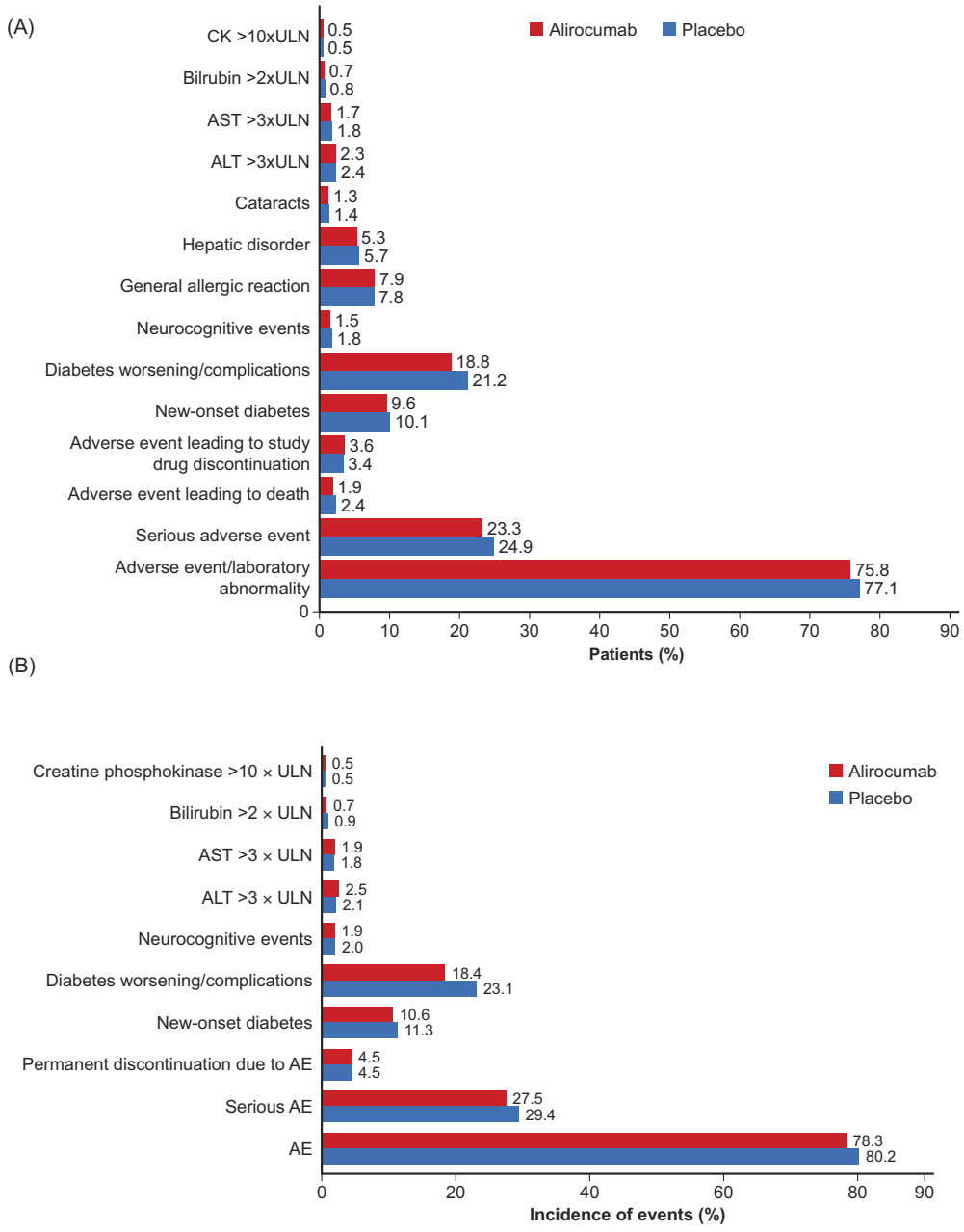


Figure 1 Frequency of laboratory abnormalities and adverse events in the (*A*) overall patient population and (*B*) subgroup of 8228 patients (43.5%) eligible for 3–5 years of treatment (modified with permission) in the ODYSSEY OUTCOMES trial.[21,36] ALN, alanine transaminase; AST, aspartate aminotransferase; CK, creatine kinase; ULN, upper limit of normal.

Summary of overall safety findings from the ODYSSEY OUTCOMES trial

Adverse events and laboratory abnormalities

In the ODYSSEY OUTCOMES trial over a median (quartile [Q]1, Q3) follow-up of 2.8 (2.3–3.4) years, alirocumab was essentially indistinguishable from placebo with respect to the frequency of adverse events, serious adverse events, adverse events leading to death, adverse events leading to study drug discontinuation, general allergic reaction, hepatic disorder, and cataracts (*Figure 1A*).[21] The only exception was patient-reported local injection site reactions, which occurred more frequently in the alirocumab group (3.8% vs. 2.1%; $P < 0.001$). However, these injection site reactions (e.g. itching, erythema, or swelling) were usually mild, self-limited, and led to study drug discontinuation in only 26 (of 9462) alirocumab-treated patients at a median of 8.3 months after randomization vs. 3 patients in the placebo group.[21] Further, among 8242 patients (43.5%) eligible for

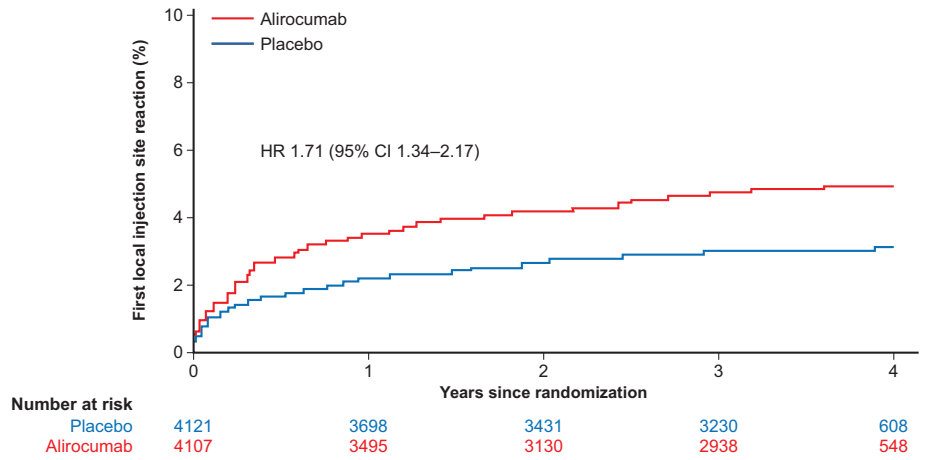


Figure 2 Kaplan–Meier cumulative incidence for time to first local injection site reaction in the subgroup of 8228 patients (43.5%) eligible for 3–5 years of treatment over ~4 years.[36] CI, confidence interval; HR, hazard ratio. (Reproduced with permission).

3–5 years of follow-up (i.e. randomized ≥3 years before the common study end date),[29] 8228 received one or more doses of study medication, comprising 24 610 patient-years of observation, with a median follow-up of 3.3 years.[36] The Kaplan–Meier cumulative incidence for time to first local injection site reaction in this subgroup was <5% over ~4 years, with most occurring within the first 6 months (*Figure 2*).[36] Treatment-emergent adverse events occurred in 78.3% of alirocumab- and 80.2% of placebo-treated patients in this subgroup, including 27.5% and 29.4% of serious adverse events, respectively; treatment-emergent adverse events leading to death occurred in 2.7% and 3.3% in the alirocumab and placebo groups, respectively (*Figure 1B*).

Recognizing that the ODYSSEY OUTCOMES trial employed a single-blind placebo run-in period (2–16 weeks) for eligible patients to be instructed in the technique of self-injection of study drug using a 1 mL prefilled pen,[37] which could lead to a more adherent population, premature discontinuation of the assigned alirocumab or placebo for reasons other than death occurred in 1343 patients (14.2%) in the alirocumab group and 1496 patients (15.8%) in the placebo group over the median follow-up of 2.8 years. In the subgroup eligible for 3–5 years of follow-up, rates of permanent treatment discontinuation due to adverse events were similar in both treatment groups (*Figure 1B*).

The incidence of laboratory abnormalities was similar in the alirocumab and placebo groups (*Figure 1A*). Alanine (ALT) and aspartate (AST) aminotransferases, total bilirubin, and creatine kinase (CK) were monitored serially in the setting of 89% of patients receiving high-intensity atorvastatin (80 or 40 mg in 27%) or rosuvastatin (40 or 20 mg in 62%) as background lipid-lowering treatment. There were infrequent and similar incidences of elevations of these laboratory tests [ALT and AST >3 times upper limit of normal (ULN), bilirubin >2 times ULN, CK >10 times ULN] during follow-up in the alirocumab and placebo groups.[21] Similarly, among a prespecified subgroup of 8228 patients eligible for 3–5 years of follow-up, elevations of ALT >3 (2.5% vs. 2.1%), AST >3 (1.9% vs. 1.8%), bilirubin >2 (0.7% vs. 0.9%), and CK >10 (0.5% vs. 0.5%) times ULN were similar in the alirocumab and placebo groups, respectively (*Figure 1B*). The low incidence of transaminase and CK elevations is also notable in this population where ~83–87% of patients remained on high-intensity statin treatment at 1 and 3 years post-randomization.[21]

Alirocumab in vulnerable populations in the ODYSSEY OUTCOMES trial

Alirocumab was not associated with an excess of laboratory abnormalities or adverse events compared with placebo in any patient subgroup including the elderly and those with diabetes or chronic kidney disease.

Older patients

The mean age at entry into the ODYSSEY OUTCOMES trial (58 years) was somewhat younger than in most cardiovascular outcome trials because of the selection of patients with ACS based upon elevated levels of atherogenic lipoproteins, reflecting a lifetime risk factor and thus a younger age at presentation with disease. Nonetheless, ODYSSEY OUTCOMES enrolled 5084 (26.9%) patients ≥65 years of age, of whom 1007 (5.3%) were ≥75 years of age and 42 (0.2%) were ≥85 years of age. Prespecified subgroup analyses comparing the efficacy and safety of alirocumab vs. placebo were undertaken, stratified according to younger (40–64 years) and older (≥65 years) age.[21,34] Older patients were more often female and more likely to have a history of hypertension, diabetes, myocardial infarction, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), stroke, peripheral artery disease, and heart failure (HF).[34] Older patients were also more likely to have presented with non-ST-segment elevation myocardial infarction (vs. ST-segment elevation myocardial infarction or unstable angina) and less likely to have undergone coronary revascularization (PCI or CABG) for their index ACS event. Adherence to assigned study treatment decreased over time in both age categories (e.g. ~88% in patients <65 years of age vs. ~86% in patients ≥65 years of age at 2 years) but was similar in the alirocumab and placebo groups. The relative benefit of alirocumab over placebo on the primary (and key secondary) outcome was consistent across the entire age range, with estimated absolute benefit increasing with advancing age due to higher absolute risk. Consistent with the safety findings we observed in those ≥65 years of age,[21] although adverse events were observed more frequently in patients aged ≥75 years compared with the younger cohort, there were no differences between alirocumab and placebo

Table 1 Adverse events by randomized treatment and age group (≥75 vs. <75 years old).

Adverse event	Randomized treatment: Alirocumab, *n*/*N* (%)	Randomized treatment: Placebo, *n*/*N* (%)	Relative risk (95% CI) (alirocumab vs. placebo)
Any adverse events			
≥75 years old	391/492 (79.5)	439/513 (85.6)	0.93 (0.88–0.98)
<75 years old	6774/8959 (75.6)	6843/8930 (76.6)	0.99 (0.97–1.00)
Serious adverse events			
≥75 years old	163/492 (33.1)	194/513 (37.8)	0.88 (0.74–1.04)
<75 years old	2039/8959 (22.8)	2156/8930 (24.1)	0.94 (0.89–0.99)
Adverse event that led to discontinuation of the trial regimen			
≥75 years old	22/492 (4.5)	36/513 (7.0)	0.64 (0.38–1.07)
<75 years old	321/8959 (3.6)	288/8930 (3.2)	1.11 (0.95–1.30)
Neurocognitive disorder			
≥75 years old	12/492 (2.4)	24/513 (4.7)	0.52 (0.26–1.03)
<75 years old	131/8959 (1.5)	143/8930 (1.6)	0.91 (0.72–1.16)
New-onset diabetes among patients without diabetes at baseline			
≥75 years old	26/330 (7.9)	37/346 (10.7)	0.74 (0.46–1.19)
<75 years old	622/6433 (9.7)	639/6350 (10.1)	0.96 (0.87–1.07)
Haemorrhagic stroke—adjudicated			
≥75 years old	0/492 (0.0)	2/513 (0.4)	–
<75 years old	9/8959 (0.1)	14/8930 (0.2)	0.64 (0.28–1.48)
Alanine transaminase >3 ULN			
≥75 years old	11/486 (2.3)	15/507 (3.0)	0.77 (0.35–1.65)
<75 years old	201/8883 (2.3)	213/8834 (2.4)	0.94 (0.78–1.14)
Aspartate aminotransferase >3 ULN			
≥75 years old	9/486 (1.9)	10/507 (2.0)	0.94 (0.38–2.29)
<75 years old	151/8881 (1.7)	156/8831 (1.8)	0.96 (0.77–1.20)

CI, confidence interval; ULN, upper limit of normal.

in older or younger patients (*Table 1*). Similarly, serious adverse events or adverse events that led to discontinuation of the trial regimen were more frequent in older patients, but without differences between the randomized treatment arms. Patient/site-reported neurocognitive disorders were infrequent (<2% overall), and although numerically more common among patients ≥75 years of age, the incidence did not differ between the alirocumab and placebo groups in this age stratum [age ≥65 years: 2.4% vs. 4.7%; hazard ratio (HR): 0.52, 95% confidence interval (CI): 0.26–1.03; age <75 years: 1.5% vs. 1.6%; HR: 0.91, 95% CI: 0.72–1.16)]. Thus, in the ODYSSEY OUTCOMES trial, adding alirocumab to maximum-tolerated high-intensity statins significantly improved outcomes in patients after an ACS irrespective of age, without any age-related safety issues.[34]

Diabetes mellitus

In the ODYSSEY OUTCOMES trial at baseline, 5444 (28.8%) patients had a history of diabetes, 8246 (43.6%) prediabetes, and 5234 (27.7%) normoglycaemia.[31] While patients with diabetes had the highest incidence of the primary outcome over a median of 2.8 years (16.4% vs. 9.2% prediabetes vs. 8.5% normoglycaemia), the relative benefit of alirocumab was consistent across each glycaemic category and the absolute benefit was greatest in those with previous diabetes (i.e. number needed to treat for 3 years, ∼44 vs. 83 vs. 83, respectively).

A blinded independent expert committee was prospectively established to review and adjudicate potential cases of incident diabetes among patients without diabetes at baseline. This was an important objective, given previous observations that statins increase the risk of incident diabetes,[38,39] and findings in Mendelian randomization analyses that genes encoding variants in PCSK9 associated with lower LDL-C levels are also associated with greater incident diabetes.[40] In fact, alirocumab did not increase the risk of new-onset diabetes (*Figure 1A*) among patients without diabetes at baseline (including those with prediabetes). Likewise, among the patients eligible for ≥3 years of follow-up, new-onset diabetes occurred with similar frequency among the alirocumab and placebo groups: 10.6% vs. 11.3% with prediabetes and 3.8% vs. 3.0% with normoglycaemia at baseline (*Figure 1B*). Despite achieving a median LDL-C of 0.80 mmol/L at 4 months post-randomization, alirocumab had no effect on plasma glucose concentrations or haemoglobin A_{1c}. In addition, no increase in diabetes worsening or diabetes complications was observed with alirocumab compared with placebo (*Figure 1A*) among patients with diabetes at baseline.[31] Finally, in 2281 patients with diabetes at baseline who were eligible for ≥3 years of follow-up, 18.4% of alirocumab- and 23.1% of placebo-treated patients experienced diabetes worsening or complications, including diabetes-related serious adverse events (but no deaths) in 3.3% of alirocumab- and 3.0% of placebo-treated patients (*Figure 1B*).[36]

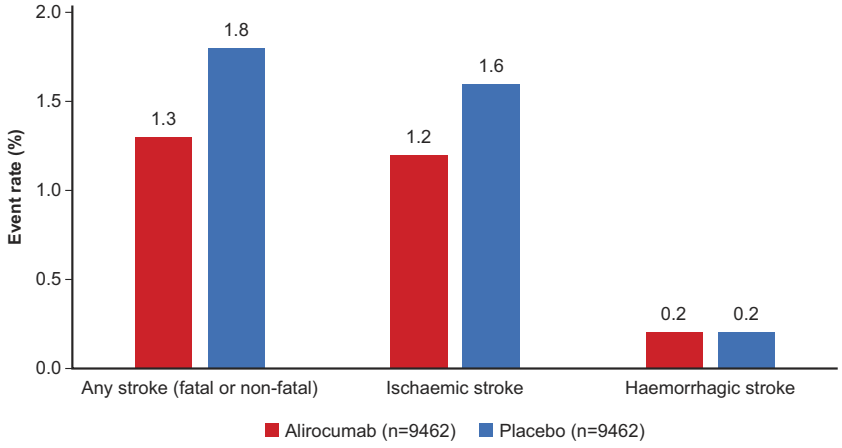


Figure 3 Risk of any fatal or non-fatal stroke, ischaemic stroke, and haemorrhagic stroke in the ODYSSEY OUTCOMES trial.[21,48]

The abovementioned LDL-C and non-high-density lipoprotein cholesterol lowering and safety findings in the subgroup of patients in ODYSSEY OUTCOMES with diabetes mellitus are consistent with those from the ODYSSEY DM-INSULIN[41] and ODYSSEY DM-DYSLIPIDEMIA[42] trials comparing alirocumab with placebo both in patients on maximum-tolerated statin and in patients with diabetes on insulin (both type 1 and type 2) and type 2 diabetes, respectively.

Because low levels of lipoprotein(a) have been associated with an increased risk of incident diabetes, and because PCSK9 inhibitors lower levels of lipoprotein(a), the effect of alirocumab vs. placebo on incident diabetes as a function of baseline lipoprotein(a) was evaluated in an additional exploratory analysis of ODYSSEY OUTCOMES.[43] While there was no overall effect of alirocumab on incident diabetes, patients with low baseline levels of lipoprotein(a) had a lower incidence with alirocumab than with placebo and patients with high baseline lipoprotein(a) levels (~1.29 mmol/L or greater) tended to have an increased risk of incident diabetes. Nonetheless, the cardiovascular benefits of alirocumab in patients with high lipoprotein(a) in ODYSSEY OUTCOMES[44,45] appear to outweigh any possible small increase in the risk of incident diabetes in that subset.[43]

Stroke

While lowering of atherogenic lipoproteins with statins reduces the risk of ischaemic stroke,[46] concerns have been raised about the association of spontaneously very low LDL-C levels and the higher risk for haemorrhagic stroke, as well as a potential increase in intracranial haemorrhage in patients receiving intensive statin therapy after ischaemic stroke.[39,47] In the overall population in the ODYSSEY OUTCOMES trial, with blinded adjudication of all stroke events, alirocumab significantly reduced the risk of any stroke and ischaemic stroke without any increase in haemorrhagic stroke (*Figure 3*).[21,48] The benefit of alirocumab for reducing the risk of stroke was similar among 944 patients (5.0%) with a history of cerebrovascular disease and among those without a history of cerebrovascular disease ($P_{interaction} = 0.37$).[48] Furthermore, there was no relation between lower achieved LDL-C (at 4 months post-randomization) and the incidence of haemorrhagic stroke in the alirocumab group.[21,48] An important caveat is that a history of haemorrhagic stroke was an exclusion criterion in ODYSSEY OUTCOMES and the safety of alirocumab in patients with previous haemorrhagic stroke therefore remains undetermined.

Chronic kidney disease

In the ODYSSEY OUTCOMES trial, the aggregate baseline estimated glomerular filtration rate (eGFR) was 83 ± 18 mL/min/1.73 m^2, including 2122 patients (11.2%) with an eGFR <60 mL/min/1.73 m^2.[35] While an eGFR <30 mL/min/1.73 m^2 was a screening exclusion criterion, 69 patients (0.4%) had an eGFR <30 mL/min/1.73 m^2 at randomization. The annualized incidence rates for the primary outcome and death increased progressively as eGFR decreased, with patients receiving alirocumab having fewer events than those on placebo across all values of eGFR, with larger relative risk reductions in those with eGFR >60 mL/min/1.73 m^2. Alirocumab had no effect on eGFR over the duration of the trial. The percentages of patients having a decrease in eGFR from baseline of ≥30% (1.8% alirocumab vs. 2.1% placebo; $P = 0.09$), 40% (0.8% vs. 0.9%; $P = 0.48$), or 50% (0.3% vs. 0.4%; $P = 0.62$) were similar in both treatment groups. Further, this subgroup analysis found no excess of any adverse event (other than local injection site reactions) with alirocumab compared with placebo in any category of eGFR.[35] Therefore, both the efficacy and safety of alirocumab appeared consistent across the eGFR categories enrolled in ODYSSEY OUTCOMES. This finding is consistent with the fact that alirocumab is an immunoglobulin G (IgG) monoclonal antibody; renal elimination is relatively unimportant for IgG, as its large size prevents efficient filtration through the glomerulus. Thus, IgG elimination occurs primarily via intracellular catabolism following receptor-mediated endocytosis; based on non-renal elimination of alirocumab, renal impairment would not be expected to significantly affect the pharmacokinetic/pharmacodynamic profile of alirocumab.

Nevertheless, an important caveat is that the number of patients with advanced chronic kidney disease in ODYSSEY OUTCOMES was too low to allow for meaningful conclusions for patients with an eGFR <30 mL/min/1.73 m^2, and patients on dialysis were excluded from the trial.

Neurocognitive events

In 2012, the US Food and Drug Administration (FDA) issued a warning regarding potential adverse effects of statins on neurocognition (e.g. memory loss, confusion) based on the Adverse Events Reporting

System and a review of the medical literature. However, a subsequent Mendelian randomization study showed that low LDL-C levels due to 3-hydroxy-3-methylglutaryl-CoA reductase (and PCSK9) genetic variants had no causal effects on the increased risk of Alzheimer's disease, vascular dementia, any dementia, or Parkinson's disease.[49] Further, evidence (including frequency of adverse cognitive events reported or measurements using standard neuropsychological cognitive test scores) from placebo-controlled randomized clinical trials of statins failed to support any association between cognitive impairment and statin therapy in cognitively normal or impaired subjects.[50] In the context of this uncertainty, in 2014, the FDA directed pharmaceutical companies conducting clinical trials of PCSK9 inhibitors to carefully monitor cognitive adverse effects. Two meta-analyses of Phase 2 and 3 trials concluded that PCSK9 inhibitors were not associated with an increased risk of severe adverse events, musculoskeletal effects, or stroke,[51] and potentially reduced all-cause death,[52] but suggested an increased incidence of adverse neurocognitive effects.[51,52] Subsequent pooled analyses of 10−14 trials reported no safety concerns with alirocumab treatment over an 8- to 104-week follow-up, even with very low levels of achieved LDL-C,[15,17,20] including incidence of neurocognitive adverse events.[18] However, the median and maximum exposure times in these trials were relatively brief. Therefore, a longer-term safety assessment, such as that recently reported,[36] was deemed desirable.[53]

In the ODYSSEY OUTCOMES trial, with median and maximum observation times of 2.8 and 5.0 years, neurocognitive disorders were reported in 1.5% of alirocumab- and 1.8% of placebo-treated patients (*Figure 1A*).[21] In the subgroup of 8228 patients eligible for ≥3 years of follow-up, neurocognitive disorders were reported in 80 (1.9%) patients in the alirocumab group and 83 (2.0%) patients in the placebo group (*Figure 1B*). While serial neurocognitive testing was not employed in ODYSSEY OUTCOMES, a dedicated neurocognitive study (double-blind, placebo-controlled) of alirocumab in 2176 patients with heterozygous familial hypercholesterolaemia or non-familial hypercholesterolaemia at high/very high cardiovascular risk demonstrated no effect of alirocumab on neurocognitive function assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB) over 96 weeks of treatment.[54] These findings are consistent with those from the prospective cognitive function substudy of the FOURIER trial[23] with evolocumab and the Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects (EBBINGHAUS) study.[25]

Antidrug antibodies

In the ODYSSEY OUTCOMES trial, 5.5% of patients treated with alirocumab compared with 1.6% of patients treated with placebo had antidrug antibodies detected after initiating treatment, with most of these being transient responses. Persistent antidrug antibody responses (defined by the presence of positive responses detected after the start of study drug administration in two or more consecutive post-baseline serum samples and separated by a ≥16-week period) were observed in 0.7% of patients treated with alirocumab and 0.4% of patients treated with placebo. Neutralizing antibody responses were observed in 0.5% of patients treated with alirocumab and in <0.1% of patients treated with placebo.[21] Similarly, among patients eligible for ≥3 years of follow-up, antidrug antibodies were observed more frequently in the alirocumab vs. placebo group (0.9% vs. 0.5%); neutralizing antibodies on two or more occasions were observed in only one patient in each group. However, the clinical importance of these findings, particularly in the context of a fully human monoclonal antibody therapy, remains unclear. An analysis of 10 trials involving 4747 patients concluded 'antidrug antibodies developed in few patients who were treated with alirocumab, and even those patients had substantial and durable evidence of LDL-cholesterol lowering'.[55] Further, the development—albeit infrequent—of antidrug and neutralizing antibodies in 32 and 6 placebo-treated patients raises uncertainty about the specificity of the anti-alirocumab test itself. Most importantly, there were no discernible safety concerns associated with detection of antidrug antibodies.

Efficacy and safety of alirocumab according to the achieved level of LDL-C in the ODYSSEY OUTCOMES trial

The optimal LDL-C concentration achieved with lipid-lowering therapies for reducing cardiovascular events with acceptable safety remains uncertain. For example, in a *post hoc* analysis of the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, patients achieving LDL-C <0.78 mmol/L experienced significant increases in diabetes, haematuria, hepatobiliary disorders, and insomnia.[56] In contrast, a prespecified analysis of the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) found that post-ACS patients achieving an LDL-C <0.78 mmol/L at 1 month after randomization (to either simvastatin or simvastatin plus ezetimibe) had a similar safety profile (and numerically the lowest rate of cardiovascular events) over a 6-year period compared with patients achieving higher LDL-C concentrations.[22] A prespecified regression analysis of the FOURIER trial with the PCSK9 inhibitor evolocumab showed a monotonic relationship between achieved (at 4 weeks) LDL-C and major cardiovascular outcomes down to an LDL-C concentration of <0.2 mmol/L, without association of achieved LDL-C with any safety outcome.[24] Inference from this regression analysis regarding clinical efficacy as a function of achieved LDL-C should be considered with the caveats that patients in both the placebo and evolocumab groups were included, patients who achieved the lowest LDL-C levels were likely to have started with low baseline LCL-C levels, and that concurrent levels of lipoprotein(a) and study medication adherence were not considered.

An analysis of ODYSSEY OUTCOMES attempted to overcome these limitations by categorizing alirocumab-assigned patients according to three strata of LDL-C achieved at month 4 (<0.65, 0.65–1.29, or >1.29 mmol/L).[57] Each of these categories was matched in a 1:1 ratio to patients from the placebo group with similar baseline characteristics [including LDL-C and lipoprotein(a)] and study medication adherence, using a propensity score. Treatment HR and the absolute reduction in the risk of major adverse cardiovascular events (MACE) with alirocumab were examined in each category. In the placebo group, there was a gradient in the risk of MACE, with the greatest incidence among those matched to patients with achieved LDL-C >1.29 mmol/L with alirocumab and the lowest incidence among those matched to patients with achieved LDL-C <0.65 mmol/L with alirocumab. Treatment HR and absolute risk reduction were similar for the achieved LDL-C categories of 0.65−1.29 mmol/L and <0.65 mmol/L. For those with achieved LDL-C >1.29 mmol/L with alirocumab, treatment HR was higher and absolute risk reduction lower than for the other categories. The conclusion of this analysis was that an achieved LDL-C of 0.65−1.29 mmol/L may be a reasonable goal after ACS.

Regarding safety according to achieved levels of LDL-C, a pooled analysis of 14 Phase 2 and 3 trials in the ODYSSEY programme, with follow-up as long as 104 weeks, found similar rates of adverse events in alirocumab-treated patients achieving two consecutive LDL-C values <0.65 and <0.39 mmol/L compared with those who did not achieve LDL-C <0.65 mmol/L, including neurological and neurocognitive events.[20] However, in a propensity score analysis, the rate of cataracts was 0.8% higher in patients achieving an LDL-C level

<0.65 mmol/L. No difference in cataract incidence was observed between the pooled alirocumab and control (placebo or ezetimibe) groups.[20] The incidence of cataracts was similar in the alirocumab and placebo groups in the ODYSSEY OUTCOMES trial (1.3% vs. 1.4%).[58] Further, in patients treated with alirocumab with two or more LDL-C values of <0.65 mmol/L, the incidence of cataracts was 1.6% vs. 1.4% in propensity score-matched patients from the placebo group.[58]

The ODYSSEY OUTCOMES trial was designed with a treat-to-target approach, with blinded adjustment of the alirocumab dose to maximize the number of patients who achieved LDL-C values of 0.65–1.29 mmol/L and minimize prolonged exposure to levels <0.39 mmol/L.[21,37] With this caveat, no safety concerns were associated with the relatively limited period of LDL-C <0.39 mmol/L (an average of 6.8 months spent below this level before blinded substitution of placebo at a median 8.3 months from randomization in 730 patients).[57] This included similar rates of neurocognitive events and haemorrhagic stroke in alirocumab-treated patients achieving these very low LDL-C levels compared with the aggregate placebo group or propensity score-matched patients in the placebo group. The 525 of 6769 (7.8%) patients in the alirocumab group without diabetes at baseline who achieved consecutive LDL-C levels <0.39 mmol/L were at a greater risk of new-onset diabetes than those in the aggregate placebo group (15.1% vs. 10.1%; HR: 1.46, 95% CI: 1.16−1.85; $P = 0.001$). However, this difference in the risk of new-onset diabetes was attenuated and no longer statistically significant compared with the propensity score-matched placebo subgroup without diabetes at baseline (15.1% vs. 13.0%; HR: 1.10, 95% CI: 0.85−1.43; $P = 0.46$).[57]

The overall safety profile of alirocumab in the ODYSSEY OUTCOMES trial appears excellent: the only side effect that occurred more frequently than in the placebo group was mild injection site reactions. However, despite the present analysis representing more than 47 000 patient-years of follow-up, the longest follow-up was 5 years and the mean age of the participating patients at the time of randomization was 59 years. Therefore, it is not possible to exclude the remote possibility that more serious safety signals could emerge over longer periods of treatment and in older more fragile populations. Thus, as with any newer class of drugs, continued pharmacovigilance efforts are warranted. It is reassuring that, since alirocumab has been on the market for approximately 8 years, no serious adverse event has emerged and has been reported in a pharmacovigilance report to various health authorities (e.g. the European Medicines Agency (EMA)) that regularly monitor drug safety.

Conclusions

The ODYSSEY OUTCOMES trial comprised over 47 000 patient-years of placebo-controlled observation, including observation in 8228 patients eligible for at least 3, and up to 5, years of follow-up and received at least one dose of study medication. The trial demonstrated important reductions in the risk of recurrent ischaemic cardiovascular events with alirocumab, as well as fewer deaths compared with placebo. These benefits were observed in the context of substantial and persistent lowering of LDL-C compared with placebo. The safety profile of alirocumab was indistinguishable from matching placebo except for a ~1.7% absolute increase in local injection site reactions ~3 years. No safety concerns with alirocumab emerged in the patients eligible for 3−5 years of follow-up. Further, the safety of alirocumab compared with placebo was evident in vulnerable groups identified before randomization, such as the elderly and those with diabetes mellitus, previous ischaemic stroke, or chronic kidney disease. The frequency of adverse events and laboratory-based abnormalities was generally similar when compared with placebo. Thus, alirocumab appears to be both a safe and effective lipid-modifying treatment over a duration of at least 5 years.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Data availability

The dataset(s) supporting the conclusions of this article is(are) included within the article.

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