Effect of alirocumab on major adverse cardiovascular events according to renal function in patients with a recent acute coronary syndrome: prespecified analysis from the ODYSSEY OUTCOMES randomized clinical trial

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Aims
Statins reduce cardiovascular risk in patients with acute coronary syndrome (ACS) and normal-to-moderately impaired renal function. It is not known whether proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors provide similar benefit across a range of renal function. We determined whether effects of the PCSK9 inhibitor alirocumab to reduce cardiovascular events and death after ACS are influenced by renal function.

Methods and results
ODYSSEY OUTCOMES compared alirocumab with placebo in patients with recent ACS and dyslipidaemia despite intensive statin treatment. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m² was exclusionary. In 18 918 patients, baseline eGFR was 82.8 ± 17.6 mL/min/1.73 m², and low-density lipoprotein cholesterol (LDL-C) was 92 ± 31 mg/dL. At 36 months, alirocumab decreased LDL-C by 48.5% vs. placebo but did not affect eGFR (P = 0.65). Overall, alirocumab reduced risk of the primary outcome (coronary heart disease death, non-fatal myocardial infarction, ischaemic stroke, or unstable angina requiring hospitalization) with fewer deaths. There was no interaction...
between continuous eGFR and treatment on the primary outcome or death \((P=0.14\) and 0.59, respectively). Alirocumab reduced primary outcomes in patients with eGFR \(\geq 90\,\text{mL/min/1.73 m}^2\) \((n=7470;\) hazard ratio 0.784, 95% confidence interval 0.670–0.919; \(P=0.003\) ) and 60 to <90 \((n=9326;\) 0.833, 0.731–0.949; \(P=0.006\)), but not in those with eGFR < 60 \((n=2122;\) 0.974, 0.805–1.178; \(P=0.784\)). Adverse events other than local injection-site reactions were similar in both groups across all categories of eGFR.

**Conclusions** In patients with recent ACS, alirocumab was associated with fewer cardiovascular events and deaths across the range of renal function studied, with larger relative risk reductions in those with eGFR > 60 mL/min/1.73 m\(^2\).

**Graphical Abstract**

**Keywords** PCSK9 inhibition • Acute coronary syndrome • Low-density lipoprotein cholesterol • Chronic kidney disease • Glomerular filtration rate • Major adverse cardiovascular events

**Introduction**

Patients with chronic kidney disease (CKD) are at high risk for major adverse cardiovascular events (MACE). Several factors may account for this high risk. First, CKD is associated with other established risk factors, including age, hypertension, and diabetes. Second, lipoprotein abnormalities frequently accompany CKD, including increased triglycerides, decreased high-density lipoproteins, and an excess of small, dense low-density lipoprotein particles. Third, CKD is associated with elevated inflammatory biomarkers, abnormal platelet function, and extensive vascular calcifications.

Statins decrease the incidence of cardiovascular events in patients with moderate-to-severe CKD, but not in those on dialysis. Although some guidelines suggest the use of moderate-dose statins in patients with moderate-to-severe CKD, the recent US guidelines on the management of blood cholesterol consider CKD stages 3 or 4 to be one of the ‘very high risk’ conditions that warrant the use of high-intensity or maximum-tolerated statin treatment for secondary prevention, and the addition of ezetimibe or an inhibitor of proprotein convertase subtilisin-kexin type 9 (PCSK9) if low-density lipoprotein cholesterol (LDL-C) remains above 70 mg/dL. Similarly, recent European guidelines indicate that a goal of treatment in patients with moderate-to-severe CKD is to ‘achieve the largest possible absolute reduction in LDL-C safely.’

The PCSK9 inhibitors alirocumab and evolocumab decrease the incidence of cardiovascular events in patients with acute coronary syndromes (ACS) and chronic atherosclerotic cardiovascular disease, respectively. Alirocumab reduces LDL-C levels without
significant safety concerns in patients with CKD. Likewise, evolocumab therapy was associated with reduced MACE in patients with CKD and chronic atherosclerosis treated with statins.

Patients with CKD and ACS are at particularly high risk for recurrent MACE. The efficacy and safety of PCSK9 inhibition in such patients has not previously been investigated. In this prespecified analysis of the ODYSSEY OUTCOMES trial, we examined whether the reduction of MACE with alirocumab, added to intensive or maximum-tolerated statin therapy after ACS, depends upon the level of estimated glomerular filtration rate (eGFR).

**Methods**

**Trial design**

The design and primary efficacy and safety results of the ODYSSEY OUTCOMES trial (clinicaltrials.gov: NCT01663402) have been published. Ethics committee approval was obtained at all participating centres. All participants provided written informed consent. The trial was a randomized, double-blind, placebo-controlled comparison of alirocumab or placebo in 18 924 patients with an ACS (myocardial infarction or unstable angina) 1–12 months before randomization. Qualifying patients had persistent dyslipidaemia [LDL-C >70 mg/dL (1.81 mmol/L), non-high-density lipoprotein cholesterol (non-HDL-C) >100 mg/dL (2.59 mmol/L), or apolipoprotein B >80 mg/dL (0.0016 mmol/L)] despite treatment with atorvastatin 40–80 mg daily, rosuvastatin 20–40 mg daily, or the maximum-tolerated dose of one of these statins (including no statin treatment).

The primary outcome was a composite of MACE, including death due to coronary heart disease, non-fatal myocardial infarction, ischaemic stroke, or unstable angina requiring hospitalization. Death from any cause was a secondary outcome. All outcomes were blindly adjudicated.

In this prespecified analysis, we investigated whether the effect of alirocumab on MACE and death varied across the range of baseline renal function, gauged by eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. We also analysed the incidence of adverse effects as a function of eGFR, and looked for potential effects of alirocumab on eGFR.

**Statistical analysis**

Details on the sample size calculation are included in the Supplementary material online. The comparisons of baseline differences among eGFR subgroups were tested using the $\chi^2$ test for categorical variables and analysis of variance for continuous variables, except for triglycerides and lipoprotein(a), which were tested using median regression due to their skewed distributions. Efficacy analyses were performed on an intention-to-treat basis. Incidence rates per 100 patient-years for MACE and all-cause death were estimated by treatment groups in each decile of baseline eGFR, and smoothed curves were fit to estimations based on each eGFR decile subgroup using local regression. Interactions between study treatment and baseline eGFR for MACE and death were tested using proportional hazard models, using either eGFR subgroups or a continuous value of eGFR. Differences in eGFR at Month 36 between treatment groups were assessed using the Student’s t-test. Differences between treatment groups in the proportion of adverse events were evaluated using the $\chi^2$ test. This test was also used to compare treatment differences in the percentages of patients whose eGFR at the end of treatment was reduced by 30%, 40%, or 50% from baseline. Statistical significance was set at $P<0.05$ (two-sided) without multiplicity adjustment. Analyses were performed in SAS version 9.4.

**Results**

A total of 18 924 patients underwent randomization at 1315 sites in 57 countries (Supplementary material online, Table S1). Of these, 9462 were assigned to alirocumab and 9462 to placebo (Figure 1). Outside of China, patients were randomized between November 2012 and November 2015. In China, 613 patients were randomized between May 2016 and February 2017. In this analysis, 6 of the patients (4 in the placebo group and 2 in the alirocumab group) were excluded because their baseline serum creatinine values were not available, leaving 18 918 patients for the analysis (9460 in the alirocumab group and 9458 in the placebo group). Median follow-up was 2.8 (interquartile range 2.3–3.4) years.

In the aggregate trial cohort, baseline eGFR was 82.8 ± 17.6 mL/min/1.73 m². There were 7470 (39.5%) patients with eGFR >90 [98.6 (94.3, 103.5)] mL/min/1.73 m², 9326 (49.3%) with eGFR 60 to <90 [77.8 (70.6, 84.2)] mL/min/1.73 m², and 2122 (11.2%) with eGFR <60 [51.4 (44.2, 56.1)] mL/min/1.73 m². While eGFR <30 mL/min/1.73 m² was a screening exclusion criterion, 69 patients (0.4%) had eGFR <30 mL/min/1.73 m² at randomization and were included in the analysis. Supplementary material online, Table S2 shows the distribution of the population according to eGFR range and study treatment. Of patients receiving alirocumab, 7.8% were switched to placebo, primarily due to two consecutive LDL-C values <15 mg/dL (0.39 mmol/L) in the subgroups with eGFR <60 and 60 to <90 mL/min/1.73 m², and 7.6% in the subgroup with eGFR >90 mL/min/1.73 m².

Baseline characteristics of the population across eGFR subgroups are shown in Supplementary material online, Table S3. Overall, patients with lower eGFR were older; more likely to have a history of hypertension, diabetes, myocardial infarction, coronary revascularization, stroke, peripheral artery disease, and heart failure; and had higher levels of triglycerides and lipoprotein(a). In addition, patients with lower eGFR were less likely to receive intensive statin treatment and dual antiplatelet therapy but were more likely to receive inhibitors of the renin–angiotensin system and oral anticoagulants.

At baseline, mean LDL-C was 92 ± 31 mg/dL in both treatment groups. Alirocumab decreased LDL-C by 62.2% and 48.5% vs. placebo at 4 and 36 months, respectively. The effect of alirocumab on LDL-C was consistent across eGFR subgroups at 4 months: the LDL-C values of patients on alirocumab were 40 ± 30 mg/dL in the eGFR <60 mL/min/1.73 m² subgroup, 38 ± 30 mg/dL in the 60 to <90 mL/min/1.73 m² subgroup, and 38 ± 28 mg/dL in the >90 mL/min/1.73 m² subgroup. At 36 months, these values were 52 ± 36, 56 ± 40, and
The most common reasons for screen failures during the run-in period were related to lipid criteria (34.1% of patients) or withdrawal of patient consent (6.1% of patients). From Schwartz et al. Copyright © (2018) Massachusetts Medical Society. Reprinted with permission.
$60 \pm 42$ mg/dL, respectively (Figure 2 and Supplementary material online, Table S4). Supplementary material online, Figures S1–S4 show the effect of alirocumab on apolipoprotein B, triglycerides, HDL-C, and non-HDL-C, respectively, across the three categories of eGFR. Alirocumab decreased apolipoprotein B and non-HDL-C and increased HDL-C homogeneously across eGFR categories. At baseline, triglyceride levels were higher in patients with eGFR <60 mL/min/1.73 m² than in the other two subgroups and the decrease in triglycerides with alirocumab was greatest in that eGFR category.

Overall, alirocumab reduced incident MACE [9.5% vs. 11.1%; hazard ratio (HR) 0.85, 95% confidence interval (CI) 0.78–0.93] and was
associated with fewer deaths (3.5% vs. 4.1%; HR 0.85, 95% CI 0.73–0.98). The incidences of MACE and death over the range of baseline eGFR are presented in the alirocumab and placebo groups in the Take home figure. The annualized incidence rates for MACE and death increased progressively as eGFR decreased, beginning at eGFR values <80 mL/min/1.73 m². Patients receiving alirocumab had fewer MACE and deaths than those on placebo across all values of eGFR. There were no significant interactions of assigned treatment (alirocumab or placebo) and eGFR on the incidence rates for MACE and death (P = 0.14 and P = 0.59, respectively).

When the population was divided in subgroups according to CKD stage, alirocumab was associated with a significant reduction in the incidence of MACE in patients with eGFR ≥90 mL/min/1.73 m² and between 60 and <90 mL/min/1.73 m² (Table 1), but not in patients with eGFR <60 mL/min/1.73 m². In all three subgroups, there were numerically fewer deaths in patients receiving alirocumab, without statistical significance in any individual category. The interaction P-value between eGFR and alirocumab was 0.21 for MACE and 0.83 for death.

When the population was divided into quintiles according to eGFR, patients on alirocumab had a lower incidence of MACE in all the quintiles (Supplementary material online, Figure S5A). Similar findings were observed for the incidence of death, with the exception of quintile 2, where it was similar in both groups (Supplementary material online, Figure S5B).

At baseline, eGFR was 82.7 ± 17.7 mL/min/1.73 m² in the alirocumab group and 82.9 ± 17.6 mL/min/1.73 m² in the placebo group. Alirocumab had no effect on eGFR over the duration of the trial; for example, at 36 months, these values were 83.9 ± 18.0 and 84.1 ± 17.6 mL/min/1.73 m², respectively (P = 0.65) (Supplementary material online, Figure S6). The percentages of patients having a decrease in eGFR from baseline of at least 30% [1.8% (n = 170) vs. 2.1% (n = 202); P = 0.09], 40% [0.8% (n = 78) vs. 0.9% (n = 87); P = 0.48], or 50% [0.3% (n = 30) vs. 0.4% (n = 34); P = 0.62, for alirocumab and placebo, respectively] were similar in both treatment groups.

In the overall trial population and in each category of baseline eGFR, compared with patients on placebo, patients in the alirocumab group had a higher incidence of local injection-site reactions, without any excess of all treatment-emergent adverse events, serious adverse events, adverse events leading to death, rhabdomyolysis, or increases in liver enzymes or creatine kinase (Table 2).

### Discussion

This is the first analysis of the effects of a PSCK9 inhibitor on clinical outcomes according to renal function in post-ACS patients. In this prespecified analysis, we found that alirocumab had a consistent effect on plasma LDL-C and on the incidence of MACE across the range of baseline renal function of patients in the study. Subgroup analysis showed a significant decrease in the incidence of MACE among patients with eGFR 60 to <90 or >90 mL/min/1.73 m². The decrease was not significant in patients with eGFR <60 mL/min/1.73 m². There was no excess of any adverse event other than local injection-site reactions with alirocumab compared with placebo in any category of eGFR. Alirocumab or placebo treatment did not influence the level of eGFR at 36 months after randomization.

Patients with CKD are at high risk of developing cardiovascular events.1–3 Statins with or without ezetimibe decrease cardiovascular risk in patients with moderate-to-severe CKD.7,18,21 However, part of the benefit of statins in this setting may be counterbalanced by an increased risk of adverse events.18 Furthermore, this benefit seems to decrease as eGFR declines, with little or no benefit in patients on dialysis.8,9,19 Given this background, it cannot be assumed that the balance of efficacy and safety with a lipid-lowering drug in a broad population applies similarly to patients with CKD.

Proprotein convertase subtilisin-kexin type 9 inhibitors are powerful lipid-lowering drugs, decreasing LDL-C, apolipoprotein B, triglycerides, and lipoprotein(a), without evidence to date of any serious safety concerns.13,20 A subanalysis of the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk) trial in patients with chronic atherosclerotic cardiovascular disease demonstrated that evolocumab reduced the incidence of cardiovascular events across CKD subgroups.15 Here, we present the first evidence of the effects of a PCSK9 inhibitor according to renal function in patients 1–12 months post-ACS.

### Table 1: Effect of alirocumab on the incidence of MACE and death in different subgroups according to eGFR

| eGFR subgroup | n   | Incidence per 100 patient-years at risk | Hazard ratio (95% CI) | P     | Pinteraction |
|---------------|-----|--------------------------------------|-----------------------|-------|--------------|
|               |     | MACE                                 |                       |       |              |
| eGFR (mL/min/1.73 m²) |     |                                      |                       |       |              |
| <60           | 2122| 7.9                                  | 8.1                   | 0.2   | 0.97 (0.81–1.18) | 0.78  |
| 60 to <90     | 9326| 3.2                                  | 3.9                   | 0.7   | 0.83 (0.73–0.95) | 0.006 |
| ≥90           | 7470| 2.7                                  | 3.5                   | 0.8   | 0.78 (0.67–0.92) | 0.0026|
| All-cause death |     |                                      |                       |       |              |
| eGFR (mL/min/1.73 m²) |     |                                      |                       |       |              |
| <60           | 2122| 3.4                                  | 3.8                   | 0.4   | 0.90 (0.69–1.18) | 0.46  |
| 60 to <90     | 9326| 1.2                                  | 1.4                   | 0.2   | 0.82 (0.66–1.01) | 0.07  |
| ≥90           | 7470| 0.7                                  | 0.9                   | 0.2   | 0.81 (0.60–1.10) | 0.18  |

ARR, absolute risk reduction; CI, confidence interval; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular event.
Overall in the ODYSSEY OUTCOMES trial, treatment with alirocumab decreased the incidence of MACE and was associated with fewer total deaths.12 Of the patients in the trial, 60% had an eGFR <90 mL/min/1.73 m², reflecting at least mild CKD, and 10.9% (n = 2053) had an eGFR of 30 to <60 mL/min/1.73 m², indicating moderate CKD. The low number of patients in the latter category limited power to determine an effect of alirocumab on MACE or death. The FOURIER trial was larger than ODYSSEY OUTCOMES, included more than twice the number of patients with eGFR <60 mL/min/1.73 m² (n = 4443), and had a different primary MACE endpoint of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization. Notwithstanding these differences, the qualitative findings in both trials are similar. In both, there was no difference in treatment effects of PCSK9 inhibition on LDL-C, apolipoprotein B, non-HDL-C or HDL-C across categories of eGFR, and a larger absolute decrease in triglycerides in patients with eGFR <60 mL/min/1.73 m². In both trials, the point estimate of the treatment HR for the primary Endpoint was

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**Table 2  Incidence of TEAEs according to baseline eGFR category**

|                          | Alirocumab | Placebo | P value |
|--------------------------|------------|---------|---------|
| All patients (n=9460)    |            |         |         |
| Any TEAE, n (%)          | 7164 (75.7)| 7278 (77.0) | 0.0481 |
| Any serious TEAE, n (%)  | 2201 (23.3)| 2350 (24.8) | 0.011  |
| TEAE leading to death, n (%) | 181 (1.9) | 222 (2.3) | 0.0388 |
| TEAE leading to discontinuation, n (%) | 343 (3.6) | 324 (3.4) | 0.456  |
| Local injection-site reaction, n (%) | 360 (3.8) | 203 (2.1) | <0.0001|
| AST >3 times ULN, n (%)   | 169 (1.8) | 161 (1.7) | 0.658  |
| ALT >3 times ULN, n (%)   | 218 (2.3) | 219 (2.3) | 0.960  |
| Creatine kinase >10 times ULN, n (%) | 49 (0.5) | 47 (0.5) | 0.839  |
| Rhabdomyolysis, n (%)     | 22 (0.2)  | 17 (0.2)  | 0.423  |
| Baseline eGFR <60 mL/min/1.73 m² (n=1077) |         |         |         |
| Any TEAE, n (%)          | 863 (80.1)| 852 (81.5) | 0.413  |
| Any serious TEAE, n (%)  | 353 (32.8)| 366 (35.0) | 0.274  |
| TEAE leading to death, n (%) | 48 (4.5)  | 65 (6.2)  | 0.071  |
| TEAE leading to discontinuation, n (%) | 56 (5.2)  | 53 (5.1)  | 0.894  |
| Local injection-site reaction, n (%) | 28 (2.6)  | 16 (1.5)  | 0.084  |
| AST >3 times ULN, n (%)   | 23 (2.1)  | 19 (1.8)  | 0.560  |
| ALT >3 times ULN, n (%)   | 34 (3.2)  | 22 (2.1)  | 0.131  |
| Creatine kinase >10 times ULN, n (%) | 6 (0.6)  | 8 (0.8)  | 0.553  |
| Rhabdomyolysis, n (%)     | 3 (0.3)   | 2 (0.2)   | 0.679  |
| Baseline eGFR >60 to <90 mL/min/1.73 m² (n=4669) |         |         |         |
| Any TEAE, n (%)          | 3565 (76.4)| 3591 (77.1) | 0.388  |
| Any serious TEAE, n (%)  | 1085 (23.2)| 1179 (25.3) | 0.019  |
| TEAE leading to death, n (%) | 92 (2.0)  | 93 (2.0)  | 0.927  |
| TEAE leading to discontinuation, n (%) | 167 (3.6) | 168 (3.6) | 0.937  |
| Local injection-site reaction, n (%) | 177 (3.8) | 106 (2.3) | <0.0001|
| AST >3 times ULN, n (%)   | 85 (1.8)  | 81 (1.7)  | 0.767  |
| ALT >3 times ULN, n (%)   | 108 (2.3) | 103 (2.2) | 0.742  |
| Creatine kinase >10 times ULN, n (%) | 24 (0.5) | 23 (0.5) | 0.891  |
| Rhabdomyolysis, n (%)     | 11 (0.2)  | 8 (0.2)   | 0.494  |
| Baseline eGFR >90 mL/min/1.73 m² (n=3714) |         |         |         |
| Any TEAE, n (%)          | 2736 (73.7)| 2835 (75.5) | 0.072  |
| Any serious TEAE, n (%)  | 763 (20.5)| 805 (21.4) | 0.346  |
| TEAE leading to death, n (%) | 41 (1.1)  | 64 (1.7)  | 0.028  |
| TEAE leading to discontinuation, n (%) | 120 (3.2) | 103 (2.7) | 0.215  |
| Local injection-site reaction, n (%) | 155 (4.2) | 81 (2.2) | <0.0001|
| AST >3 times ULN, n (%)   | 61 (1.6)  | 61 (1.6)  | 0.950  |
| ALT >3 times ULN, n (%)   | 76 (2.0)  | 94 (2.5)  | 0.186  |
| Creatine kinase >10 times ULN, n (%) | 19 (0.5) | 16 (0.4) | 0.588  |
| Rhabdomyolysis, n (%)     | 8 (0.2)   | 7 (0.2)   | 0.779  |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.
numerator lowest in patients with baseline eGFR $\geq 90 \text{ mL/min/}1.73 \text{ m}^2$ and numerically highest in patients with baseline eGFR $< 60 \text{ mL/min/}1.73 \text{ m}^2$, but with no significant interaction across categories of baseline eGFR. Similarly, the Cholesterol Treatment Trialsists collaboration\textsuperscript{11} has reported a trend towards smaller reduction in the risk of MACE per mmol/L decrease in LDL-C as eGFR declines.

Although there is no complete explanation for this finding, reasons may include differences in the pathophysiology of atherosclerosis in patients with CKD, manifest by enhanced inflammation and complex lipid abnormalities such as excessive LDL-C oxidation and high-density lipoprotein cholesterol dysfunction.\textsuperscript{1,21} Furthermore, non-atherosclerotic comorbidities present in CKD may influence outcomes without modification by lipid-lowering therapies.

Compared to patients with better renal function, patients with lower eGFR were older and had a higher prevalence of cardiovascular risk factors, atherosclerosis, and heart failure, which are associated with greater absolute risk of MACE and death. However, unlike characteristics such as diabetes, polyvascular disease, or prior coronary artery bypass surgery that were associated with both greater risk of MACE and greater MACE reduction with alirocumab in this trial,\textsuperscript{22–24} we did not find evidence for greater absolute reduction of MACE or death with alirocumab among patients with lower eGFR at baseline.

Alirocumab did not affect the eGFR values, suggesting that the drug does not directly affect renal function, and corroborating findings by Toth et al.\textsuperscript{14} in an analysis of 4629 hypercholesterolaemic patients treated with alirocumab or placebo up to 104-weeks. Likewise, the FOURIER study, which included 27 564 patients with a median follow-up of 2.2 years, demonstrated no difference in renal function between the evolocumab and placebo groups.\textsuperscript{15} Moreover, eGFR did not appear to influence the safety and tolerability of alirocumab. In each category of baseline eGFR, the only adverse event with greater incidence in the alirocumab group was local injection-site reactions.

**Limitations**

Estimated glomerular filtration rate $<30 \text{ mL/min/}1.73 \text{ m}^2$ was an exclusion criterion, as is common in cardiovascular outcomes trials. Thus, the potential benefits and risks of alirocumab treatment in patients with severe CKD, or in those receiving dialysis treatment, were not determined. The proportion of patients with eGFR $<60 \text{ mL/min/}1.73 \text{ m}^2$ was relatively modest (11.2%; $n = 2122$), limiting power to detect an effect of alirocumab on MACE in this population. In contrast, there were many patients with eGFR between 60 and $<90 \text{ mL/min/}1.73 \text{ m}^2$ (Stage 2 CKD). Previous analyses\textsuperscript{25} as well as the present data indicate that these patients have an elevated risk of MACE and death compared to those with preserved renal function, and thus comprise an important group to assess the efficacy of PCSK9 inhibition. Finally, the effect of alirocumab on eGFR must be interpreted with caution given a relatively short follow-up, limiting the ability to detect a potential influence on CKD progression.

**Conclusions**

In patients with recent ACS, alirocumab treatment was associated with a reduction in MACE and fewer deaths, independent of baseline eGFR, across a broad range above 30 mL/min/1.73 m$^2$. This reduction did not achieve statistical significance in the subgroup of patients with eGFR $<60 \text{ mL/min/}1.73 \text{ m}^2$. Other than local injection-site reactions, no differences in the rates of adverse events were apparent between treatment groups across the range of eGFR values studied.

**Supplementary material**

**Supplementary material** is available at European Heart Journal online.

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**Conflict of interest**

J.T. reports personal fees from Sanofi, Amgen, and Diasorin Iberia. P.G.S. reports grants and nonfinancial support (cochair of the ODYSSEY OUTCOMES trial; as such, he received no personal fees, but his institution has received funding for the time he has devoted to trial coordination, and he has received support for travel related to trial meetings) from Sanofi; research grants and personal fees from Bayer (Steering Committee MARINER, grant for epidemiological study), Merck (speaker fees, grant for epidemiological studies); Sanofi (cochair of the ODYSSEY OUTCOMES trial; cochair of the SCOREd trial; consulting, speaking), Servier (Chair of the CLARIFY registry; grant for epidemiological research), and Amarin (executive steering committee for the REDUCE-IT trial [Disease Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial]; consulting); and personal fees from Amgen, Bristol-Myers Squibb, Boehringer Ingelheim, Pfizer, Novartis, Regeneron Pharmaceuticals, Lilly, and AstraZeneca. P.G.S. also has a European application number/patient number, issued on 26 October 2016 (no. 157122417), for a method for reducing cardiovascular risk.

D.L.B. reports advisory board fees from Cardax, Cereno Scientific, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, Regado Biosciences; Board of Directors membership for Boston VA Research Institute, Society of Cardiovascular Patient Care, Tobesoft; position of Chair for the American Heart Association Quality Oversight Committee; membership of Data Monitoring Committees for the Bain Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo), Population Health Research Institute; honoraria from the American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Vice-Chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferrin Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Medelligence/ReachMD (CME steering committees), Population Health Research...
Major Adverse Cardiovascular Events and Conversion to Type 2 Diabetes Mellitus in Obese and Overweight Subjects With Cardiovascular Disease or Multiple Cardiovascular Risk Factors) from Eisai Inc., for the dal-GenE study (Effect of Dalteparin vs. Placebo on CV Risk in a Genetically Defined Population With a Recent ACS) from DalCor Pharma UK Inc., for the AEGIS-II study from CSL Behring, for the SCOREd trial (Effect of Sotaglitazone on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk) and the SOLOIST-WHF trial (Effect of Sotaglitazone on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure) from Sanofi-Aventis Australia Pty Ltd, and for the CLEAR Outcomes Study (Evaluation of Major Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated With Bempedoic Acid [ETC-1002] or Placebo) from Esperion Therapeutics Inc. Dr White was on the Advisory Boards for Acetelion, Sirtex and Genentech, Inc. (an affiliate of F. Hoffmann-La Roche Ltd, ‘Roche’; Lytics Post-PCI Advisory Board at European Society of Cardiology), and received lecture fees from AstraZeneca. Dr AMZ, reports receiving fees for serving on a steering committee for the ODYSSEY OUTCOMES trial from Sanofi, and advisory board and speaker fees from Sanofi, Amgen, Boehringer Ingelheim, Bayer, Novartis, Pfizer, AstraZeneca, and Vifor. G.G.S. reports research grants to the University of Colorado from Resverlogix, Sanofi, The Medicines Company, and Roche; and is co-inventor of pending US patent 62/806,313 (‘Methods for Reducing Cardiovascular Risk’) assigned in full to the University of Colorado.

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