Alirocumab after acute coronary syndrome in patients with a history of heart failure

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Abstract

Patients with heart failure (HF) have not been shown to benefit from statins. In a post hoc analysis, we evaluated outcomes in ODYSSEY OUTCOMES in patients with vs. without a history of HF randomized to the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor alirocumab or placebo.

Methods and results

Among 18,924 patients with recent acute coronary syndrome (ACS) receiving intensive or maximum-tolerated statin treatment, the primary outcome of major adverse cardiovascular events (MACE) was compared in patients with or without a history of HF. The pre-specified secondary outcome of hospitalization for HF was also analysed. Overall, 2815 (14.9%) patients had a history of HF. Alirocumab reduced low-density lipoprotein cholesterol and lipoprotein(a) similarly in patients with or without HF. Overall, alirocumab reduced MACE compared with placebo [hazard ratio (HR): 0.85; 95% confidence interval (CI): 0.78–0.93; P = 0.0001], but not in those with a history of HF (HR: 1.17; 95% CI: 0.97–1.40; P = 0.10) (P interaction = 0.0001). Alirocumab did not reduce hospitalization for HF, overall or in patients with or without prior HF.

Conclusion

Alirocumab reduced MACE in patients without a history of HF but not in patients with a history of HF. Alirocumab did not reduce hospitalization for HF in either group. Patients with a history of HF are a high-risk group that does not appear to benefit from PCSK9 inhibition after ACS.

Aims

Patients with heart failure (HF) have not been shown to benefit from statins. In a post hoc analysis, we evaluated outcomes in ODYSSEY OUTCOMES in patients with vs. without a history of HF randomized to the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor alirocumab or placebo.
Key Question

Patients with heart failure (HF) have not been shown to benefit from statins. In a post hoc analysis of the ODYSSEY OUTCOMES trial in patients with recent acute coronary syndrome (ACS), we evaluated major adverse cardiovascular events (MACE) in patients with or without a history of HF assigned to treatment with the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor alirocumab or placebo.

Key Finding

Alirocumab reduced low-density lipoprotein cholesterol similarly in patients with or without HF. However, alirocumab reduced MACE among patients without a history of HF, but not in those with a history of HF.

Take Home Message

The current hypothesis-generating analysis does not provide a basis to recommend PCSK9 inhibitors to patients with recent ACS and a history of HF. A prospective placebo-controlled evaluation of PCSK9 inhibition in this setting is warranted.

Keywords

Acute coronary syndromes • Alirocumab • Heart failure • ODYSSEY OUTCOMES • MACE

Introduction

Statins have been shown to reduce cardiovascular events in most patients in primary or secondary prevention but failed to show benefit in two large clinical trials in patients with a history of heart failure (HF). These findings were surprising considering the high cardiovascular event rate in patients with HF and substantial representation of patients with ischaemic HF in the two trials: 40% of patients in the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza Cardiaca-Heart Failure) trial and 100% in CORONA (CONTrolled ROsvastatin multiNAtional Trial in Heart Failure). Two large, placebo-controlled trials have demonstrated that inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) reduces the risk of cardiovascular events in patients with stable or acute atherosclerotic cardiovascular disease. The ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial included patients with a recent acute coronary syndrome (ACS), while the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial included patients with clinically evident stable atherosclerosis. However, neither trial demonstrated an effect of PCSK9 inhibitors on hospitalizations for HF.

Whether PCSK9 inhibitors reduce major adverse cardiovascular events (MACE) or reduce hospitalizations for HF in patients with a history of HF is unknown. We therefore addressed these questions using data from the ODYSSEY OUTCOMES trial that compared the PCSK9 inhibitor alirocumab with placebo in patients with a recent ACS.
Methods

Study design
The design\(^1\) and primary results\(^4\) of the ODYSSEY OUTCOMES trial (ClinicalTrials.gov: NCT01663402) have been published. Briefly, patients were aged \(\geq 40\) years, had provided written informed consent, and had been hospitalized with an ACS 1–12 months before randomization, and had low-density lipoprotein cholesterol (LDL-C) \(\geq 1.81 \text{ mmol/L (70 mg/dL)}\), or non-high-density lipoprotein cholesterol \(\geq 2.59 \text{ mmol/L (100 mg/dL)}\), or apolipoprotein B \(\geq 380 \text{ mg/dL} \) after \(\geq 2\) weeks of stable treatment with atorvastatin \(40–80\) mg daily, rosuvastatin \(20–40\) mg daily, or the maximum-tolerated dose of one of these statins.

Exclusions included New York Heart Association (NYHA) class III or IV for HF and/or known left ventricular ejection fraction \(<25\). After a pre-randomization run-in phase and completion of all planned coronary revascularizations for the qualifying ACS, patients were randomly assigned to receive blinded treatment with alirocumab 75 mg or matching placebo given by subcutaneous injection every 2 weeks. For patients assigned to alirocumab, blinded protocol-specified dose-adjustment algorithms were used to target achieved LDL-C levels between 0.65 and 1.29 mmol/L (25–50 mg/dL) and to avoid sustained levels \(<0.39 \text{ mmol/L (15 mg/dL)}\).\(^5\) The primary outcome was MACE, defined as the composite of death from coronary heart disease (CHD), non-fatal myocardial infarction (MI), non-fatal or fatal ischemic stroke, or hospitalization for unstable angina. Hospitalization for HF was a pre-specified secondary outcome. Total mortality and a composite of all-cause death, non-fatal MI, and non-fatal ischemic stroke were also pre-specified secondary outcomes.

In the current analysis, the effects of alirocumab on MACE, components of MACE including types of MI, hospitalization for HF, and death were compared between patients with a history of HF and those without a history of HF. Change in high-sensitivity C-reactive protein (hs-CRP) was also analysed in the two groups.

History of HF was defined from case report forms and reasons for hospitalization\(^6\) as shown in Supplementary material online, Text S2. Data on timing of diagnosis, ejection fraction, or classification as HF with reduced ejection fraction or preserved ejection fraction were not collected. MACE, hospitalization for HF, and causes of death were adjudicated by a blinded clinical events committee. In a post hoc classification, patients were considered to have a probable ischemic basis for HF if there was documentation of coronary artery stenosis \(\geq 70\%\) by coronary angiography, a history of MI, or percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) antedating the qualifying ACS. Patients without such medical history were considered to have a non-ischemic or undetermined basis for HF.

Statistical analyses
Baseline characteristics, including patient demographics, medical history before index ACS, type of index ACS, renal function, and concomitant medications are presented by history of HF at randomization. Categorical variables are presented as counts and percentages and were compared with \(\chi^2\) tests. Continuous variables are presented as medians and quartiles (Q1, Q3) and were compared with Wilcoxon tests. Event rates were estimated per 100 patient-years of follow-up. A Cox proportional hazards model was used to compare the treatment effect (alirocumab vs. placebo) in the subgroups of patients with and without a previous history of HF. The heterogeneity of treatment effect between patients with and without a previous history of HF was analysed with a test for treatment-by-history of HF interaction. We also used a Fine–Gray model for MACE to account for competing risks.\(^7\) Recurrent hospitalizations for HF were analysed with the Cox proportional hazards model with robust sandwich variance estimates. All models were stratified by region. The cumulative incidence of MACE and HF hospitalization by treatment and history of HF was estimated by the Kaplan–Meier method. The distribution of causes of death by history of HF and by history of HF and treatment were compared using \(\chi^2\) tests. All analyses were performed separately from the sponsor by an independent academic statistician using SAS System version 9.4 (TSTM6).

Results
Overall, 18 924 patients were randomized at 1315 sites in 57 countries, at a median (Q1, Q3) of 2.6 (1.7, 4.3) months after the qualifying ACS. There were 2815 patients (14.9%) with a history of HF and 16 109 patients (85.1%) without a history of HF. Median (Q1, Q3) follow-up in patients with or without a history of HF was the same, 2.8 (2.3, 3.4) years. Table 1 shows the baseline demographics of the two groups.

Compared with patients without a history of HF, those with a history of HF were older (median 61 vs. 58 years) and more likely to be women (30.0% vs. 24.3%), white (86.7% vs. 78.1%), and enrolled in Eastern Europe (61.0% vs. 23.1%). Patients with a history of HF were more likely to have characteristics associated with cardiovascular risk including diabetes, hypertension, atrial fibrillation, prior MI or stroke, and impaired renal function (Table 1). They were more likely to have had coronary revascularization before the qualifying ACS, but less likely to have had coronary revascularization for the qualifying ACS. Compared with those without a history of HF, patients with a history of HF had higher median baseline concentrations of LDL-C [2.3 (1.9, 2.8) vs. 2.2 (1.9, 2.7) mmol/L; \(P < 0.0001\)] and hs-CRP [2.0 (0.9, 4.5) vs. 1.6 (0.8, 3.7) mg/L; \(P < 0.0001\)] and lower levels of lipoprotein(a) [18.5 (5.9, 56.6) vs. 21.6 (6.8, 59.9) mg/dL, respectively; \(P = 0.0008\)].

The proportions of patients randomized to alirocumab or placebo were approximately equal in both HF subgroups. The utilization of evidence-based medical therapy for HF in the patients with a history of HF included beta-blockers in 87.8%, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in 82.9%, and aldosterone antagonists in 25.1% (Table 1).

Persistence and intensity of study treatment
Patient-reported adherence with study medication (i.e. self-administered from diaries) (data not shown) and premature discontinuation of treatment (Supplementary material online, Table S1) did not differ according to HF category. There were also no differences in the distribution of alirocumab doses, treatment duration, or number of injections received by HF category (Supplementary material online, Tables S2 and S3).

Effects on lipids and high-sensitivity C-reactive protein
At month 4, alirocumab produced similar relative median (Q1, Q3) decreases in LDL-C in patients with vs. without a history of HF: \(-1.4 (-1.9, -0.9)\) vs. \(-1.4 (-1.8, -0.9)\) mmol/L (\(P = 0.62\)). Figure 1 shows the effect of alirocumab and placebo on median LDL-C levels over 36 months.
Table 1  Baseline characteristics by history of heart failure

| Variables                        | History of HF (n = 2815) | No history of HF (n = 16 109) | P-value |
|----------------------------------|--------------------------|------------------------------|---------|
| Age (years), median (Q1, Q3)     | 61 (54, 67)              | 58 (51, 65)                  | <0.0001 |
| Women, n (%)                     | 845 (30.0)               | 3917 (24.3)                  | <0.0001 |
| Race, n (%)                      |                          |                              | <0.0001 |
| White                            | 2441 (86.7)              | 12 583 (78.1)                |         |
| Asian                            | 179 (6.4)                | 2319 (14.4)                  |         |
| Black                            | 79 (2.8)                 | 394 (2.4)                    |         |
| Other                            | 116 (4.1)                | 813 (5.0)                    |         |
| Geographic region, n (%)         |                          |                              | <0.0001 |
| Eastern Europe                   | 1717 (61.0)              | 3720 (23.1)                  |         |
| Western Europe                   | 240 (8.5)                | 3935 (24.4)                  |         |
| North America                    | 281 (10.0)               | 2590 (16.1)                  |         |
| South America                    | 310 (11.0)               | 2278 (14.1)                  |         |
| Asia                             | 167 (5.9)                | 2126 (13.2)                  |         |
| Rest of world                    | 100 (3.6)                | 1460 (9.1)                   |         |
| Body mass index (kg/m²), median (Q1, Q3) | 28.6 (25.9, 31.8) | 27.8 (25.1, 30.9) | <0.0001 |
| Systolic blood pressure (mmHg), median (Q1, Q3) | 126 (119, 136) | 127 (117, 138) | 0.27    |
| NYHA class, n (%)                |                          |                              |         |
| I                                | 923 (32.9)               | –                            |         |
| II                               | 1879 (67.0)              | –                            |         |
| III                              | 3 (0.1)                  | –                            |         |
| Diabetes, n (%)                  | 974 (34.6)               | 4470 (27.7)                  | <0.0001 |
| Current smoking, n (%)           | 566 (20.1)               | 3994 (24.8)                  | <0.0001 |
| Hypertension, n (%)              | 2327 (82.7)              | 9922 (61.6)                  | <0.0001 |
| History of MI, n (%)             | 973 (34.6)               | 2666 (16.5)                  | <0.0001 |
| History of stroke, n (%)         | 167 (5.9)                | 444 (2.8)                    | <0.0001 |
| History of atrial fibrillation, n (%) | 131 (4.7)               | 280 (1.7)                    | <0.0001 |
| History of PAD, n (%)            | 185 (6.6)                | 574 (3.6)                    | <0.0001 |
| History of VTE, n (%)            | 37 (1.3)                 | 162 (1.0)                    | 0.14    |
| History of COPD, n (%)           | 188 (6.7)                | 558 (3.5)                    | <0.0001 |
| History of cerebrovascular disease, n (%) | 232 (8.2)               | 712 (4.4)                    | <0.0001 |
| History of malignant disease, n (%) | 76 (2.7)                 | 456 (2.8)                    | 0.70    |
| History of revascularization, n (%) | 746 (26.5)               | 2989 (18.6)                  | <0.0001 |
| PCI                              | 614 (21.8)               | 2627 (16.3)                  | <0.0001 |
| CABG                             | 271 (9.6)                | 776 (4.8)                    | <0.0001 |
| Coronary artery stenosis on angiography ≥70%, n (%) | 482 (17.2)               | 3363 (20.9)                  | <0.0001 |
| Prior coronary events, procedures, or CAD, n (%) | 1406 (49.9)             | 6186 (38.4)                  | <0.001  |
| GFR <60 mL/min/1.73 m², n (%)    | 629 (22.3)               | 1910 (11.9)                  | <0.0001 |

Index event

| Variables                              | History of HF (n = 2815) | No history of HF (n = 16 109) | P-value |
|----------------------------------------|--------------------------|------------------------------|---------|
| Time from ACS to randomization (months), median (Q1, Q3) | 2.5 (1.7, 3.9)           | 2.6 (1.7, 4.4)               | 0.0006  |
| ACS type, n (%)                        |                          |                              | <0.0001 |
| NSTEMI                                 | 1373 (48.8)              | 7802 (48.5)                  |         |
| STEMI                                  | 896 (31.9)               | 5640 (35.1)                  |         |
| Unstable angina                        | 543 (19.3)               | 2639 (16.4)                  |         |
| Revascularization for index event, n (%) | 1682 (59.8)             | 11 995 (74.5)                | <0.0001 |
| Medications, n (%)                     |                          |                              |         |
| Aspirin                                | 2625 (93.3)              | 15 461 (96.0)                | <0.0001 |
| High-intensity statin                  | 2528 (89.8)              | 14 283 (88.7)                | 0.08    |
| Oral ADP receptor antagonist           | 2753 (97.8)              | 15 951 (99.0)                | <0.0001 |
| ACE inhibitor or ARB                   | 2335 (82.9)              | 12 381 (76.9)                | <0.0001 |
| Beta-blocker                           | 2471 (87.8)              | 13 524 (84.0)                | <0.0001 |

Continued
At month 4, in patients with vs. without a history of HF, alirocumab also produced similar relative median (Q1, Q3) decreases in lipoprotein(a): –0.12 (–0.98, 0.63) vs. –0.07 (–0.83, 0.51) mg/L (P = 0.052) and hs-CRP: –0.12 (–0.98, 0.63) vs. –0.07 (–0.83, 0.51) mg/L (P = 0.35).

**Effects on major adverse cardiovascular events**

The rates of MACE was higher in patients with vs. without a history of HF (6.34 vs. 3.43 events per 100 patient-years). As shown in Figures 2 and 3, there were reductions in MACE with alirocumab vs. placebo in the overall trial cohort [3.53 vs. 4.16 events per 100 patient-years; hazard ratio (HR), 0.85; 95% confidence interval (CI): 0.78–0.93; P = 0.0001] and in the subgroup of patients with no history of HF (3.00 vs. 3.87 events per 100 patient-years; HR: 0.78; 95% CI: 0.70–0.86; P < 0.0001). Conversely, in patients with a history of HF, there was no reduction in MACE with alirocumab vs. placebo (6.87 vs. 5.84; HR: 1.17; 95% CI: 0.97–1.40; P = 0.10) (Graphical abstract).

The interaction between randomized treatment and history of HF on MACE was significant (Pinteraction = 0.0001).

Based on the Fine–Gray model, in the subgroup of patients with a history of HF vs. those with no history of HF, the effects on MACE were the same as the analysis using the Cox model (HR: 1.17; 95% CI: 0.97–1.40 and 0.78; 95% CI: 0.70–0.86, respectively; Pinteraction<0.0001).

**Effects on components of major adverse cardiovascular events**

Figure 2 shows the randomized treatment effects on components of MACE in patients with and without HF. In the overall trial cohort, alirocumab reduced non-fatal MIs (2.43 vs. 2.83 per 100 patient-years; HR: 0.86; 95% CI: 0.77–0.96; P = 0.006). This was the result of a reduction in non-fatal MIs with alirocumab in patients without a history of HF (2.13 vs. 2.75 per 100 patient-years; HR: 0.78; 95% CI:

### Table 1 - Continued

| Variables | History of HF (n = 2815) | No history of HF (n = 16 109) | P-value |
|-----------|--------------------------|-------------------------------|---------|
| Loop diuretics, n (%) | | | |
| Furosemide | 478 (17.0) | 925 (5.7) | <0.0001 |
| Bumetamide | 13 (0.5) | 21 (0.1) | 0.0001 |
| Torsemide, n (%) | 225 (8.0) | 213 (1.3) | <0.0001 |
| Thiazides, n (%) | 121 (4.3) | 722 (4.5) | 0.6632 |
| Aldosterone antagonists | 707 (25.1) | 1146 (7.1) | <0.0001 |
| Specific oral anticoagulant | 223 (7.9) | 558 (3.5) | <0.0001 |

ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; ADP, adenosine diphosphate; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; hs-CRP, high-sensitivity C reactive protein; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; Q, quartile; STEMI, ST-elevation myocardial infarction; VTE, venous thromboembolism. 

*Mi/PCI/CABG/coronary artery stenosis >=70%.
0.69–0.88; P < 0.0001), with an excess of non-fatal MIs with alirocumab compared with placebo in those with a history of HF (4.32 vs. 3.28 per 100 patient-years; HR: 1.30; 95% CI: 1.02–1.64; P = 0.032) (Pinteraction = 0.0002).

The distribution of types of MI differed in patients with vs. without a history of HF (Supplementary material online, Table S4). Type 2 MIs comprised a greater proportion of MI endpoints in patients with vs. without a history of HF (28.1% vs. 15.2%). Periprocedural MIs (Types 4 and 5) comprised a smaller proportion of MI endpoints in patients with vs. without HF (6.5% vs. 16.4%). Type 1 MIs comprised a similar proportion of MI endpoints in patients with vs. without a history of HF (65.5% vs. 68.3%).

There was no significant interaction of treatment and HF history on the other components of MACE (CHD death, ischaemic stroke, or hospitalization for unstable angina).

### Effects on hospitalization for heart failure
There were more HF hospitalizations in patients with vs. without a history of HF (2.20 vs. 0.42 per 100 patient-years, P = 0.0001) (Figure 4). Alirocumab did not reduce HF hospitalizations compared with placebo, either overall (0.66 vs. 0.68 per 100 patient-years; HR: 0.98; 95% CI: 0.79–1.20; P = 0.84) or in patients with HF (2.43 vs. 1.98 per 100 patient-years; HR: 1.22; 95% CI: 0.90–1.66; P = 0.20; Figure 2).

There was also no effect of treatment on hospitalization in patients without a history of HF (0.38 vs. 0.45 per 100 patient-years; HR: 0.84; 95% CI: 0.63–1.12; P = 0.24) (Pinteraction = 0.08).

Effects of alirocumab on total HF hospitalizations (first and recurrent) in patients with vs. without a history of HF were similar to effects of alirocumab on first hospitalization for HF, as shown in Supplementary material online, Table S5.

### Effects on death
The rate of all-cause death was higher among patients with vs. without a history of HF (3.07 vs. 1.05 per 100 patient-years; P < 0.0001). Cause-specific mortality rates were generally higher among patients with a history of HF (see Supplementary material online, Table S6).

In the overall trial population, alirocumab reduced all-cause death vs. placebo (1.24 vs. 1.46 per 100 patient-years; HR: 0.85; 95% CI: 0.73–0.98; P = 0.026) and in patients with no history of HF (0.94 vs. 1.17 per 100 patient-years; HR: 0.80; 95% CI: 0.67–0.95; P = 0.0135) (Figure 2). However, there was no effect of alirocumab on death among patients with a history of HF (3.06 vs. 3.08 per 100 patient-years; HR: 0.99; 95% CI: 0.77–1.28; P = 0.95). Treatment HRs for cardiovascular death and non-cardiovascular death were numerically more favourable in patients without a history of HF than in those with a history of HF and were significantly different for non-cardiovascular death in patients without HF, but there was no significant interaction of treatment and HF history (Supplementary material online, Table S6).

### Effects on cardiovascular death or hospitalization for heart failure
Effects of treatment on this post hoc composite endpoint are shown for the overall trial population in Figure 2. There was no significant reduction with alirocumab, but a significant heterogeneity of effects was observed with a non-significant decrease in patients with no history of HF (0.95 vs. 1.13 per 100 patient-years; HR: 0.84; 95% CI: 0.70–1.01; P = 0.06) and a non-significant increase in patients with a history of HF (alirocumab vs. placebo: 4.48 vs. 3.94 per 100 patient-years; HR: 1.14; 95% CI: 0.91–1.42; P = 0.25) (Pinteraction = 0.038).

### Effects on death, non-fatal myocardial infarction, or non-fatal ischaemic stroke
In the overall trial cohort, there was a significant reduction in the composite endpoint of death, non-fatal MI or non-fatal ischaemic stroke with alirocumab (3.80 vs. 4.44 per 100 patient-years; HR: 0.86; 95% CI: 0.79–0.93; P = 0.0003). In patients with a history of HF, there was a non-significant increase in this endpoint (7.25 vs. 6.35 per 100 patient-years; HR: 1.13; 95% CI: 0.95–1.35; P = 0.1656). In patients with no history of HF, there was a significant decrease in this endpoint (3.25 vs. 4.10 per 100 patient-years; HR: 0.79; 95% CI: 0.72–0.88; P < 0.0001). The interaction of history of HF and treatment on this composite endpoint was significant (Pinteraction = 0.0001).

### Effects in patients with previous coronary events, procedures, or angiographic evidence of coronary artery disease
We evaluated the effect of alirocumab in patients with a probable ischaemic basis for HF, based on a prior history of MI, PCI or CABG, or coronary artery stenosis ≥70% documented on angiography. Overall, 49.9% of patients with a history of HF fulfilled at least one of these criteria, compared with 38.4% of those without a history of HF (Table 1). Supplementary material online, Table S7 shows the effects of alirocumab on MACE, its components, hospitalization for HF, and other secondary endpoints in these patients. Alirocumab reduced MACE vs. placebo in the patients with prior coronary events, procedures, or angiographic documentation of disease without a history of HF (3.91 vs. 5.22 per 100 patient-years; HR: 0.75; 95% CI: 0.65–0.86; P < 0.0001). However, alirocumab had no significant effect in patients with prior coronary events, procedures, or angiographic documentation of disease and a history of HF (9.03 vs. 7.83 per 100 patient-years; HR: 1.13; 95% CI: 0.90–1.41; P = 0.28) (Pinteraction = 0.002). There were parallel, significant interactions for HF hospitalizations and non-fatal MI.

### Adverse events
Overall rates of adverse events were similar in patients with or without a history of HF, but serious adverse events were more frequent among patients with a history of HF. The incidence of total and serious adverse events was similar with alirocumab vs. placebo within each HF category. These data, as well as data on specific types of adverse events and laboratory abnormalities, are shown in Supplementary material online, Table S8.

### Discussion
In the ODISSEY OUTCOMES trial, 14.9% of patients had a history of HF. Alirocumab reduced atherogenic lipoproteins to a similar extent in patients with or without a history of HF. However, despite a
significant effect of alirocumab at reducing MACE in the overall trial cohort and in those without a history of HF, there was no reduction in MACE in patients with a history of HF, with a significant increase in non-fatal MIs. Alirocumab had no effect on hospitalizations for HF, overall or in patients with or without prior HF. Similarly, alirocumab reduced all-cause death in the overall population and patients without a history of HF, but not in patients with a history of HF. Alirocumab was not associated with an excess of adverse events in patients with or without a history of HF.

The absence of benefit of alirocumab on MACE, hospitalizations for HF, or death in patients with recent ACS and a history of HF is unexpected given the large reduction in LDL-C. There are several explanations for these findings. First, patients with a history of HF may have had competing risks from mechanisms such as cardiac pump failure or arrhythmias that were not modified by PCSK9 inhibition. Second, there were differences in the baseline characteristics of patients with vs. without a history of HF, suggesting that the former may have had disease processes that were more advanced or less

Figure 2 Forest plot of major adverse cardiovascular events, components of major adverse cardiovascular events, hospitalization for heart failure, all-cause death, and the composite of cardiovascular death and hospitalization for heart failure according to history of heart failure. CHD, coronary heart disease; CI, confidence interval; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; PY, patient-years.
modifiable with lipid-lowering therapy. Third, an association of lower lipoprotein concentrations with impaired survival in patients with chronic HF has been reported, but may reflect reverse causality and confounding by unadjusted or unknown factors.

The absence of a favourable effect of alirocumab on MACE in patients with a history of HF is consistent with previous large, randomized trials with statins in patients with HF. The GISSI-HF trial randomized 4631 patients with chronic HF of NYHA class II–IV irrespective of cause or ejection fraction. ACS <1 month ago was an exclusion criterion, and follow-up was 3.9 years. There was no effect of rosuvastatin 10 mg/day vs. placebo on the primary endpoints of death or death/admission to hospital for cardiovascular reasons. There was also no effect in the 40% of patients where the aetiology of a history of HF was ischaemic in nature.

In CORONA, 5011 patients with NYHA class II–IV ischaemic HF were randomly assigned to receive rosuvastatin 10 mg/day or placebo. Rosuvastatin did not reduce the primary outcome of death from cardiovascular causes, non-fatal MI, or non-fatal stroke.

In the CORONA and GISSI-HF studies, the intensity of randomized statin therapy was moderate (10 mg rosuvastatin), which lowered LDL-C by 45.0% at 3 months and 32.0% at 1 year from an untreated baseline. In the current study, patients were randomized to alirocumab or placebo on a background of intensive statin therapy, and alirocumab produced a further reduction of LDL-C by a mean of 63.4%. As in CORONA and GISSI-HF, the effects of the lipid-lowering intervention in patients with a history of HF were neutral.

In an analysis from the CORONA trial and Heart Protection Study, patients had a decrease in the benefit of rosuvastatin and simvastatin, respectively, with higher N-terminal pro-B-type natriuretic peptide levels, suggesting that there may be a transition point of less severe HF where patients with HF may benefit from statins.

In BIOSTAT-CHF (BIOlogy Study to TAilored Treatment in Chronic Heart Failure), which included 2174 patients with worsening HF, multivariable analysis revealed a positive linear association between PCSK9 levels and the risk of mortality, and also with the composite of mortality and unplanned HF hospitalization. This led to the hypothesis that higher PCSK9 levels may contribute to worsening HF. A corollary would be that PCSK9 inhibitors would be beneficial in patients with a history of HF and reduce MACE and hospitalizations for HF. However, the current findings do not support this hypothesis.

**Effects on non-fatal myocardial infarction**

Pooled individual-patient data re-analysis of CORONA and GISSI-HF reported a significant reduction in MI (HR: 0.81; 95% CI: 0.66–0.99; P < 0.05). In the current study, findings for MACE were mirrored by findings for non-fatal MI. Alirocumab decreased the risk of MI in patients without a history of HF and increased non-fatal MI in patients with a history of HF. The distribution of MI type differed according to HF category, with a greater proportion of Type 2 MIs and a smaller proportion of Types 4 and 5 MIs in those with a history of HF. However, these are small numbers of events when considered according to combinations of MI type, HF category, and treatment group, and inference regarding triple interaction of these factors cannot be reliably drawn. Although the treatment HR for non-fatal MI was unfavourable in patients with a history of HF, there is no plausible mechanism for provocation of MI by PCSK9 inhibition in this subgroup, and this may be a chance finding.

**No effect of alirocumab on hospitalizations for heart failure**

Alirocumab did not significantly reduce hospitalizations for HF, overall or in the subgroups of patients with or without a history of HF.
The results for total hospitalizations for HF were consistent with the rates for first hospitalizations for HF favouring placebo in patients with HF and favouring alirocumab in patients without HF.

As alirocumab treatment was associated with a numerical excess of non-fatal MI in patients with a history of HF, a lack of effect on downstream hospitalization for HF may not be surprising in this subgroup. However, alirocumab reduced non-fatal MIs by 14% overall and 22% in patients without a history HF. The incidences of both Type 1 and 2 MIs were reduced overall and in patients without a history of HF. Therefore, it is unexpected that there was no effect of treatment on hospitalization for HF overall or in patients without prior HF. Longer follow-up may be required to see a reduction in hospitalization for HF in the wake of a reduction in non-fatal MIs.

A recent study showed that 28% of patients presenting with HF from the community have HF with preserved ejection fraction. In the current analysis, it is also likely that a proportion of those with a history of HF had HF with preserved ejection fraction. Interestingly, a recent study in mice showed that PCSK9 deficiency contributes to the development of HF with preserved ejection fraction.

**Effects on death**

Alirocumab reduced all-cause death, overall and in patients without HF, but not in patients with a history of HF. The latter finding is not surprising given the lack of benefit of treatment on MACE or hospitalization for HF in this subgroup. Sudden cardiac death (presumed arrhythmic) was the most common cause of death, followed by deaths due to fatal MI and to HF with cardiogenic shock. Alirocumab did not affect the risk of these or any other subcategory of death, either overall or in patients with or without prior HF. However, small numbers of events in individual subcategories of death may have limited the power to detect potential treatment effects.

**Effects on cardiovascular death or hospitalization for heart failure, and death, non-fatal myocardial infarction, and non-fatal ischaemic stroke**

In HF trials, the composite of cardiovascular death or hospitalizations for HF is often the primary efficacy measure. We examined this composite as a post hoc outcome in ODYSSEY OUTCOMES according to history of HF. The outcome was not modified by alirocumab in the overall trial population or in patients with or without prior HF. Similarly, the PCSK9 inhibitor evolocumab did not modify this outcome in the FOURIER trial, despite a 27% reduction in non-fatal MIs. However, in ODYSSEY OUTCOMES, we observed a significant interaction of treatment and HF history on the composite of cardiovascular death or hospitalization for HF, resulting from a non-significant reduction in patients without HF and a non-significant increase in patients with HF.

For the pre-specified composite of death, non-fatal MI, or non-fatal ischaemic stroke, the results were similar to the MACE endpoints.

**Effects in patients with previous coronary events, procedures, or angiographic evidence of coronary artery disease**

We defined a subgroup of patients with HF who had a probable ischaemic aetiology for HF based on a history of coronary events, procedures, or angiographic evidence of CAD. We hypothesized that intensive lipid lowering with alirocumab would be more likely to reduce MACE in patients with a probable ischaemic basis for HF than in patients with a non-ischaemic or undetermined basis for HF. However, similar to the entire trial population, among these patients, the treatment HRs for MACE, death, HF hospitalization, and other
were high: TNT (Treating to New Targets), mean 3.15 mmol/L; A to Z trial, median 2.87 mmol/L; PROVE IT-TIMI 22, median 2.74 mmol/L; IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering), mean 3.15 mmol/L. These were lowered to moderate levels on intensive statin treatment: TNT: 2.07, A to Z: 1.63, PROVE IT-TIMI 22: 1.60, and IDEAL: 2.07 mmol/L. In contrast, median baseline LDL-C in ODYSSEY OUTCOMES was 2.34 mmol/L among those with a history of HF in the alirocumab arm and was lowered to a mean of 0.88 mmol/L at 4 months. It is possible that a benefit of lipid lowering on hospitalization for HF is achieved when LDL-C is reduced from high to moderate levels, but no further benefit is achieved when LDL-C is lowered from very low levels when a PCSK9 inhibitor is added to background statin treatment.

**Guidelines**

The 2019 European Society of Cardiology/European Atherosclerosis Society guidelines for the management of dyslipidaemias state that ‘initiation of lipid-lowering therapy is not recommended in patients with HF in the absence of other indications for their use’ and ‘routine administration of statins in patients with HF without other indications for their use (e.g. CAD) is not recommended’. Regarding PCSK9 inhibition in patients with chronic HF, the guidelines state ‘there is no evidence regarding the effect of PCSK9 inhibition in patients with chronic HF. In the recent PCSK9 clinical outcomes trials, FOURIER and ODYSSEY OUTCOMES, PCSK9 inhibition in patients with atherosclerotic cardiovascular disease or after an ACS did not reduce the risk of HF hospitalization’.

The current post hoc analysis does not provide a basis to recommend PCSK9 inhibitors to patients with recent ACS and a history of HF but should be viewed as hypothesis generating. A prospective placebo-controlled evaluation of the efficacy of PCSK9 inhibition in this setting is warranted.

**Limitations and strengths**

There are a number of limitations to this study. Patients with known ejection fraction <25% or NYHA class III–IV were exclusion factors of the trial. Information on admission for HF before randomization was not collected. Information on ejection fraction was not collected and there was no documentation of the basis for the history of HF. Therefore, a history of HF with reduced ejection fraction could not be distinguished from a history of HF with preserved ejection fraction.

Most patients randomized with a recent ACS in ODYSSEY OUTCOMES would be expected to have CAD, although ~5% could have had MI with non-obstructive coronary arteries due to epicardial coronary artery spasm or microvascular disease. It is possible that some of the patients with a history of HF may have had a qualifying ACS event with troponin elevations being due to HF and not due to a Type 1 MI with acute plaque rupture or a supply demand imbalance Type 2 MI. We did not collect information to classify the qualifying ACS events into Type 1 or 2 MI and angiographic data were not systematically collected.

Levels of B-type natriuretic peptide were not available for this analysis and PCSK9 levels are not reported. Median (Q1, Q3) follow-up was 2.8 (2.3, 3.4) years and longer follow-up would have provided more events and more time to observe effects of alirocumab on cardiovascular risk in patients with a history of HF. Milder episodes of HF not requiring hospitalization were not reported.

Strengths of the current study include the large number of patients with a history of HF with a large number of events in those patients, and the blinded adjudication of MACE and HF hospitalizations.

**Conclusion**

In ODYSSEY OUTCOMES, a substantial proportion of patients had a history of HF. These patients had a rate of MACE almost twice as high as patients without a history of HF. Although alirocumab lowered LDL-C and lipoprotein(a) by similar amounts in patients with or without a history of HF, it reduced MACE only in patients without prior HF and not in patients with a history of HF. Moreover, alirocumab had no effect on hospitalizations for HF either overall or in patients with or without HF.

Patients with ACS and a history of HF on optimized statin therapy do not appear to benefit from treatment with the PCSK9 inhibitor alirocumab.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

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

Declaration of Helsinki
This study complies with the Declaration of Helsinki and the locally appointed ethics committee has approved the research protocol and informed consent has been obtained from the subjects (or their legally authorized representatives).

References
1. Mach F, Baigent C, Catapano AL et al.; The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020; 41:111–188.
2. Tavazzi L, Maggioni AP, Marchioni R et al.; GISSI-HF Investigators. Effect of rosvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008;372:1231–1239.
3. Kjekshus J, Apetrei E, Barrios V et al.; CORONA Group. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007;357:2248–2261.
4. Schwartz GG, Steg PG, Szarek M et al.; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379:2097–2107.
5. Steg PG, Szarek M, Bhatt DL et al.; For the ODYSSEY OUTCOMES Committees and Investigators. Effect of alirocumab on mortality after acute coronary syndrome. Circulation. 2019;140:103–112.
6. Sabatine MS, Giugliano RP, Keech AC et al.; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713–1722.
7. Schwartz GG, Bessac L, Berdan LG et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY outcomes trial. Am Heart J 2014;168:682–689.
8. Robinson JG, Farnier M, Krempf M et al.; ODYSSEY LONG TERM Investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 2015;372:1489–1499.
9. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation 2016;133:601–609.
10. Rauchhaus M, Clark AL, Doehner W et al. The relationship between cholesterol and survival in patients with chronic heart failure. J Am Coll Cardiol 2003;42:1933–1940.
11. Horwich TB, Hamilton MA, MacLellan WR, Fonarow GC. Low serum total cholesterol is associated with marked increase in mortality in advanced heart failure. J Card Fail 2002;8:216–224.
12. Rauchhaus M, Koloszek V, Volk H et al. Inflammatory cytokines and the possible immunological role for lipoproteins in chronic heart failure. Int J Cardiol 2000;76:125–133.
13. Cleland JG, Squire I, Ng L. Interpretation of amino-terminal pro-brain natriuretic peptide levels in the HPS and the CORONA study. J Am Coll Cardiol 2008;52:1104–1105.
14. Cleland JGF, McMurray JVF, Kjekshus J et al.; CORONA Study Group. Plasma concentration of amino-terminal pro-brain natriuretic peptide in chronic heart failure: prediction of cardiovascular events and interaction with the effects of rosuvastatin: a report from CORONA. J Am Coll Cardiol 2009;54:1850–1859.
15. Bayes-Genis A, Nunez J, Zamad F et al. The PCSK9-LDL receptor axis and outcomes in heart failure. BIOSTAT-CHF subanalysis. J Am Coll Cardiol 2017;70:2128–2136.
16. Francis GS. Cholesterol and heart failure: is there an important connection? J Am Coll Cardiol 2017;70:2137–2138.
17. Feinsteinn MJ, Jhund P, Kang J et al. Do statins reduce the risk of myocardial infarction in patients with heart failure? A pooled individual-level reanalysis of CORONA and GISSI-HF. Eur J Heart Fail 2015;17:434–441.
18. White HD, Steg PG, Szarek M et al.; ODYSSEY OUTCOMES Investigators. Effects of alirocumab on types of myocardial infarction: insights from the ODYSSEY OUTCOMES trial. Eur Heart J 2019;40:2801–2809.
19. White HD, Steg PG, Schwartz GG. Myocardial infarction and evolocumab JAMA Cardiol 2021;6:1220.
20. Lam CSP, Gamble GD, Ling LH et al. Mortality associated with heart failure with preserved vs. reduced ejection fraction in a prospective international multi-ethnic cohort study. Eur Heart J 2018;39:1770–1780.
21. Da Dalt L, Castiglioni L, Baragetti A et al. PCSK9 deficiency rewrites heart metabolism and drives heart failure with preserved ejection fraction. Eur Heart J 2021;42:2078–2090.
22. Rogers JK, Jhund PS, Perez AC et al. Effect of rosuvastatin on repeat heart failure hospitalizations: the CORONA trial (Controlled Rosuvastatin Multinational Trial in Heart Failure). JACC Heart Fail 2014;2:289–297.
23. Scirica BM, Morrow DA, Cannon CP et al.; PROVE IT-TIMI 22 Investigators. Intensive statin therapy and the risk of hospitalization for heart failure after an acute coronary syndrome in the PROVE IT-TIMI 22 study. J Am Coll Cardiol 2006;47:2326–2331.
24. Cannon CP, Braunwald E, McCabe CH et al.; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495–1504.
25. de Lemos JA, Blazing MA, Wiviott SD et al.; A to Z Investigators. Early intensive vs. a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA 2004;292:1307–1316.
26. Pedersen TR, Faergeman O, Kastelein JJ et al.; ATOM Investigators. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA 2005;294:2437–2445.
27. LaRosa JC, Grundy SM, Waters DD et al.; Treating to New Targets Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005;352:1425–1435.
28. Tsimis-Holland JE, Insel H, Reynolds HR et al.; American Heart Association Interventional Cardiovascular Care Committee of the Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing Council on Epidemiology and Prevention; and Council on Quality of Care and Outcomes Research. Contemporary diagnosis and management of patients with myocardial infarction in the absence of obstructive coronary artery disease: scientific statement from the American Heart Association. Circulation 2019;139:e891–e908.