Effects of alirocumab on cardiovascular and metabolic outcomes after acute coronary syndrome in patients with or without diabetes: a prespecified analysis of the ODYSSEY OUTCOMES randomised controlled trial

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Summary

Background After acute coronary syndrome, diabetes conveys an excess risk of ischaemic cardiovascular events. A reduction in mean LDL cholesterol to 1·4–1·8 mmol/L with ezetimibe or statins reduces cardiovascular events in patients with an acute coronary syndrome and diabetes. However, the efficacy and safety of further reduction in LDL cholesterol with an inhibitor of proprotein convertase subtilisin/kexin type 9 (PCSK9) after acute coronary syndrome is unknown. We aimed to explore this issue in a prespecified analysis of the ODYSSEY OUTCOMES trial of the PCSK9 inhibitor alirocumab, assessing its effects on cardiovascular outcomes by baseline glycaemic status, while also assessing its effects on glycaemic measures including risk of new-onset diabetes.

Methods ODYSSEY OUTCOMES was a randomised, double-blind, placebo-controlled trial, done at 1315 sites in 57 countries, that compared alirocumab with placebo in patients who had been admitted to hospital with an acute coronary syndrome (myocardial infarction or unstable angina) 1–12 months before randomisation and who had raised concentrations of atherogenic lipoproteins despite use of high-intensity statins. Patients were randomly assigned (1:1) to receive alirocumab or placebo every 2 weeks; randomisation was stratified by country and was done centrally with an interactive voice-response or web-response system. Alirocumab was titrated to target LDL cholesterol concentrations of 0·65–1·30 mmol/L. In this prespecified analysis, we investigated the effect of alirocumab on cardiovascular events by glycaemic status at baseline (diabetes, prediabetes, or normoglycaemia)—defined on the basis of patient history, review of medical records, or baseline HbA_{1c} or fasting serum glucose—and risk of new-onset diabetes among those without diabetes at baseline. The primary endpoint was a composite of death from coronary heart disease, non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, or unstable angina requiring hospital admission. ODYSSEY OUTCOMES is registered with ClinicalTrials.gov, number NCT01663402.

Findings At study baseline, 5444 patients (28·8%) had diabetes, 8246 (43·6%) had prediabetes, and 5234 (27·7%) had normoglycaemia. There were no significant differences across glycaemic categories in median LDL cholesterol at baseline (2·20–2·28 mmol/L), after 4 months' treatment with alirocumab (0·80 mmol/L), or after 4 months' treatment with placebo (2·25–2·28 mmol/L). In the placebo group, the incidence of the primary endpoint over a median of 2·8 years was greater in patients with diabetes (16·4%) than in those with prediabetes (9·2%) or normoglycaemia (8·5%); hazard ratio (HR) for diabetes versus normoglycaemia 2·09 (95% CI 1·78–2·46, p<0·0001) and for diabetes versus prediabetes 1·90 (1·65–2·17, p<0·0001). Alirocumab resulted in similar relative reductions in the incidence of the primary endpoint in each glycaemic category, but a greater absolute reduction in the incidence of the primary endpoint in patients with diabetes (2·3%, 95% CI 0·4 to 4·2) than in those with prediabetes (1·2%, 0·0 to 2·4) or normoglycaemia (1·2%, –0·3 to 2·7; absolute risk reduction $p_{interaction}$=0·0019). Among patients without diabetes at baseline, 676 (10·1%) developed diabetes in the placebo group, compared with 648 (9·6%) in the alirocumab group; alirocumab did not increase the risk of new-onset diabetes (HR 1·00, 95% CI 0·89–1·11). HRs were 0·97 (95% CI 0·87–1·09) for patients with prediabetes and 1·30 (95% CI 0·93–1·81) for those with normoglycaemia ($p_{interaction}$=0·11).

Interpretation After a recent acute coronary syndrome, alirocumab treatment targeting an LDL cholesterol concentration of 0·65–1·30 mmol/L produced about twice the absolute reduction in cardiovascular events among patients with diabetes as in those without diabetes. Alirocumab treatment did not increase the risk of new-onset diabetes.

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Research in context

Evidence before this study

We searched PubMed for English-language articles published from database inception to June 1, 2019, using the search terms "cardiovascular events" or "outcomes" and "statin" or "ezetimibe" or "PCSK9" or "alirocumab" or "evolocumab". We selected articles reporting cardiovascular outcomes trials or subanalyses thereof of cholesterol-lowering drugs. In patients with acute coronary syndromes, lowering LDL cholesterol to below 1·81 mmol/L (70 mg/dL) with statins, or further to around 1·42 mmol/L (55 mg/dL) with statins plus ezetimibe, reduces cardiovascular disease events. Little evidence exists for lowering LDL cholesterol to 0·65–1·30 mmol/L (25–50 mg/dL) after an acute coronary syndrome event. The ODYSSEY OUTCOMES trial showed that the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor alirocumab, adjusted to target an LDL cholesterol concentration between 0·65 and 1·30 mmol/L, significantly reduced the risk of cardiovascular events after an acute coronary syndrome event. However, concerns have been raised about intensive lowering of LDL cholesterol because of evidence that statin therapy can increase the risk of diabetes in a dose-dependent manner. An analysis of a large cardiovascular outcomes trial (FOURIER) of the PCSK9 inhibitor evolocumab showed a consistent reduction in the relative risk of cardiovascular events in patients with or without diabetes at baseline and no increase in the risk of new-onset diabetes. However, the median and maximum durations of follow-up were fairly short and an excess risk of new-onset diabetes among patients with normoglycaemia at baseline was not excluded.

Added value of this study

In this prespecified analysis of the ODYSSEY OUTCOMES trial, in which we assessed the efficacy of alirocumab by glycaemic status, over a median follow-up of 2·8 years, the relative risk reduction for cardiovascular events achieved with alirocumab was similar among patients with normoglycaemia, prediabetes, or diabetes at baseline. However, the event rate in patients with diabetes at baseline was two-times higher than that in patients without, such that the absolute risk reduction with alirocumab for patients with diabetes was double that achieved in patients without diabetes. Reassuringly, despite achieving a median LDL cholesterol concentration of 0·80 mmol/L with alirocumab, assigned treatment had no effect on plasma glucose concentrations, HbA_{1c}, or incident diabetes among 13 480 patients without diabetes at baseline, including 5955 patients followed up for 3–5 years.

Implications of all the available evidence

Among patients with atherosclerotic cardiovascular disease, the presence of diabetes identifies a group with significantly higher risk of further cardiovascular events. In the setting of either stable cardiovascular disease or acute coronary syndrome, individuals with diabetes derive greater absolute benefit from the addition of a PCSK9 inhibitor to statin therapy to achieve LDL cholesterol concentrations well below current guideline recommendations. Consideration should be given to recommending LDL cholesterol goals in the 0·65–1·30 mmol/L range for these high-risk individuals in future guidelines. Based on existing trial data, among the overall population without diabetes, PCSK9 inhibitors do not seem to increase the risk of new-onset diabetes.

Introduction

Major guidelines for the prevention of cardiovascular disease agree that people with diabetes and established cardiovascular disease are in the highest risk category for future atherosclerotic cardiovascular disease, warranting intensive lipid lowering. However, guidelines vary with respect to the initiation threshold for intensified therapeutic approaches and potential treatment targets, emphasising the need for more evidence of absolute and relative treatment effects from intensive lipid lowering. Furthermore, in acute coronary syndromes, patients with diabetes have some of the highest reported rates of recurrent cardiovascular events,[1,2] with the 2017 American College of Endocrinology guidelines referring to these patients as an extreme-risk group in whom physicians should aim for LDL cholesterol concentrations below 1·42 mmol/L (55 mg/dL).[3] Whether such patients benefit from achieving even lower LDL cholesterol concentrations (ie, below current treatment goals) is unknown.[4,5]

Observations that statins increase the risk of new-onset diabetes[6,7] raise theoretical concerns that proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors might also increase this risk, as has been suggested by findings from mendelian randomisation studies.[8] A pooled analysis[9] of the phase 3 trials of the PCSK9 inhibitor alirocumab showed no adverse effect of treatment on HbA_{1c} or excess risk of new-onset diabetes; although reassuring, the number of years of exposure from this analysis is fairly small. Although there was no increased risk of new-onset diabetes with the PCSK9 inhibitor evolocumab compared with placebo over a median 2·2 years (maximum 3·75 years) of follow-up in 16 533 patients without diabetes at baseline, an increased risk of new-onset diabetes was seen among a subgroup of 6189 patients with normoglycaemia at baseline (hazard ratio [HR] 1·60, 95% CI 1·13–2·28).[10] A small but significant increase in fasting glucose without excess risk of new-onset diabetes was reported with bococizumab compared with placebo over a median exposure of about 1 year.[11] Further data in large populations over a longer observation period are needed to determine the glycometabolic safety of PCSK9 inhibition.

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See **Online** for appendix

ODYSSEY OUTCOMES was a cardiovascular outcomes trial that compared treatment with alirocumab or placebo, beginning 1–12 months after an acute coronary syndrome event. Here, we report the efficacy of alirocumab on cardiovascular events by baseline glycaemic status and the effects of treatment on measures of glycaemia and new-onset diabetes.

Methods

Study design and participants

ODYSSEY OUTCOMES was a randomised, double-blind, placebo-controlled trial, done at 1315 sites in 57 countries, that compared alirocumab with placebo in patients who had been admitted to hospital with an acute coronary syndrome (myocardial infarction or unstable angina) 1–12 months before randomisation. The trial design has been described previously.[12] Randomisation outside of China was done between Nov 2, 2012, and Nov 11, 2015. In China, 614 patients were randomly assigned between May 5, 2016, and Feb 9, 2017. Patients had an LDL cholesterol concentration of at least 1·81 mmol/L (70 mg/dL), a non-HDL cholesterol concentration of at least 2·59 mmol/L (100 mg/dL), or an apolipoprotein B concentration of at least 0·8 g/L, measured after a minimum 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 (including no statin in case of documented intolerance).

Ethics committee approval was obtained at all participating institutions. All participants provided informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) to treatment with alirocumab 75 mg subcutaneously every 2 weeks or matching placebo, stratified by country. Randomisation was done centrally with an interactive voice-response or web-response system (appendix).

The treat-to-target design aimed to achieve an LDL cholesterol concentration of 0·65–1·30 mmol/L (25–50 mg/dL) among patients treated with alirocumab. Alirocumab 75 mg could be uptitrated to 150 mg if the LDL cholesterol concentration was 1·30 mmol/L or higher. If the LDL cholesterol concentration was less than 0·39 mmol/L (15 mg/dL) on two consecutive measurements on the 75 mg dose of alirocumab, placebo was substituted for the remainder of the trial. In patients who were given the 150 mg dose, the dose was downtitrated to 75 mg if the LDL cholesterol was less than 0·39 mmol/L on two consecutive measurements. The trial had a double-blind design, with patients and investigators masked to treatment assignment, including titration and substitution, and to lipid concentrations.

Procedures

Patients were classified into three prespecified baseline glycaemic categories: diabetes, prediabetes, and normoglycaemia. Diabetes was defined by one or more of the following criteria: type 1 or type 2 diabetes reported in the medical history or as an adverse event before first injection of study medication; HbA_{1c} greater than 6·5% (48 mmol/mol) at randomisation (or at the preceding screening visit if randomisation data were unavailable); fasting serum glucose concentration of 7·0 mmol/L (126 mg/dL) or higher at both screening and randomisation visits; or use of diabetes medication before randomisation, with a diabetes diagnosis confirmed by an external diabetes expert committee that was masked to group assignment. Prediabetes was defined by one or more of the following criteria: impaired glucose control reported in the medical history or as an adverse event before first injection of study medication; HbA_{1c} from 5·7% (39 mmol/mol) to less than 6·5% (48 mmol/mol) at randomisation (or at the screening visit if randomisation data were unavailable); or fasting serum glucose concentration of at least 5·6 mmol/L at both screening and randomisation visits, but with no more than one value of 7·0 mmol/L or higher. Patients who did not meet the criteria for either diabetes or prediabetes were classified as normoglycaemic.

Outcomes

In this prespecified analysis, we examined the cardiovascular efficacy and safety of alirocumab by baseline diabetes status. As in the overall study, the primary endpoint for this analysis was the composite of death from coronary heart disease, non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, or unstable angina requiring hospital admission, analysed in the intention-to-treat population (defined as all randomly assigned patients analysed according to allocated treatment group). All components of the primary composite endpoint were adjudicated with group assignment masked. In order to contextualise the effect of alirocumab on the primary endpoint (prespecified analysis) by diabetes status, we compared the association between presence of diabetes or absence of diabetes at study entry on the risk of the composite primary endpoint and its components (post-hoc analysis) in the placebo group. The effect of alirocumab on individual components of the composite primary endpoint was not analysed due to insufficient power.

The overall safety of alirocumab in ODYSSEY OUTCOMES has been reported previously.[13] Prespecified secondary outcomes reported here are measures of glycometabolic safety, including the effects of alirocumab on HbA_{1c} and fasting serum glucose concentration, analysed in the intention-to-treat population. New-onset diabetes was analysed in the safety population, consisting of randomly assigned patients who received at least one dose of study treatment, analysed according to the treatment actually received. The incidence of new-onset diabetes among participants with prediabetes or normoglycaemia was prespecified; we also report post-hoc HRs for new-onset diabetes in these two

subgroups. Principal analyses were done with Cox regression. Because alirocumab reduced the risk of dying from all causes, we also did competing-risk analyses to take survival benefit among alirocumab-treated patients into account with respect to new-onset diabetes. Individuals with normoglycaemia or prediabetes at baseline were considered to have new-onset diabetes during the trial if one or more of the following criteria were met: at least one HbA_{1c} value of 6·5% or higher; two fasting serum glucose values of at least 7·0 mmol/L; an investigator-reported diabetes-related adverse event; or receipt of diabetes medication for a diagnosis of diabetes that was confirmed by an external expert committee who were masked to treatment assignment and post-randomisation lipid concentrations and who reviewed the medical history and other documentation (appendix).

We also report results of prespecified analyses of the effect of alirocumab on a range of lipid parameters (LDL cholesterol, non-HDL cholesterol, HDL cholesterol, and triglycerides) by baseline glycaemic category.

Statistical analysis

Time to first occurrence and cumulative incidence of the primary endpoint were determined within each baseline glycaemic category. Formal power calculations were not done for this prespecified analysis, but statistical assumptions for the overall trial have been reported previously,[12] including a primary endpoint incidence rate of 11·4% at 4 years in the placebo group, a median baseline LDL cholesterol of 2·33 mmol/L (90 mg/dL), a reduction in LDL cholesterol of 50% with alirocumab, and an overall 15% reduction in the HR, providing 90% power at a significance level of 0·05 with 1613 primary endpoint events in the overall trial population. For each glycaemic category, treatment HRs and 95% CIs were estimated by Cox proportional-hazards models, stratified by geographical region. We calculated p values via stratified log-rank tests, using an intention-to-treat analysis. Heterogeneity of alirocumab treatment effects by glycaemic category was assessed by Cox regression models with interaction terms for relative risk reduction and Gail-Simon tests for absolute risk reduction.

Among patients without diabetes at randomisation, HbA_{1c} and fasting serum glucose concentrations were analysed in repeated-measures mixed-effects models with random effects for slope and intercept and fixed effects for treatment, baseline value, and time. If treatment with a diabetes medication was started, subsequent values of HbA_{1c} and glucose were excluded from the analyses.

The ODYSSEY OUTCOMES trial is registered with ClinicalTrials.gov, number NCT01663402.

Role of the funding source

PGS, GGS, and MS developed the ODYSSEY OUTCOMES trial protocol and statistical analysis plan in conjunction with the other members of the executive steering committee, which includes representatives of the funders (appendix). The funders selected the study sites and monitored and supervised data collection. Analyses in the present report were performed independently of the funders by the academic statistician (MS); the funders contributed to data interpretation and provided input on the report. PGS, GGS, and MS had full access to all the data in the study. The executive steering committee decided to publish the paper and takes responsibility for the completeness and accuracy of the data and the fidelity of the trial to the protocol.

	Normoglycaemia (n=5234)	Prediabetes (n=8246)	Diabetes (n=5444)
Age, years	56 (50–63)	59 (52–65)	59 (53–66)
Sex			
Women	1078 (20·6%)	1948 (23·6%)	1736 (31·9%)
Men	4156 (79·4%)	6298 (76·4%)	3708 (68·1%)
BMI, kg/m²	27 (25–30)	28 (25–31)	29 (26–33)
Blood pressure, mm Hg			
Systolic	125 (115–135)	126 (117–137)	130 (120–140)
Diastolic	78 (70–83)	79 (70–83)	79 (70–84)
Index acute coronary syndrome event			
Non-ST-segment elevation myocardial infarction	2478 (47·4%)	3921 (47·6%)	2776 (51·1%)
ST-segment elevation myocardial infarction	1922 (36·8%)	2971 (36·1%)	1643 (30·3%)
Unstable angina	826 (15·8%)	1344 (16·3%)	1012 (18·6%)
Laboratory values at randomisation			
LDL cholesterol, mmol/L	2·23 (1·92–2·69)	2·28 (1·92–2·69)	2·20 (1·84–2·69)
Non-HDL cholesterol, mmol/L	2·90 (2·51–3·47)	2·97 (2·59–3·52)	3·03 (2·61–3·62)
HDL cholesterol, mmol/L	1·14 (0·98–1·35)	1·11 (0·96–1·32)	1·06 (0·91–1·24)
Triglycerides, mmol/L	1·32 (0·98–1·85)	1·44 (1·05–2·00)	1·66 (1·20–2·32)
HbA_{1c}, %	5·4 (5·3–5·5)	5·9 (5·7–6·0)	7·0 (6·5–8·2)
Fasting serum glucose, mmol/L	5·2 (4·9–5·5)	5·6 (5·2–6·0)	7·4 (6·2–9·4)
High-intensity statin treatment*	4624 (88·3%)	7403 (89·8%)	4784 (87·9%)
Ezetimibe	171 (3·3%)	234 (2·8%)	149 (2·7%)
Fibrates	49 (0·9%)	95 (1·2%)	174 (3·2%)
Duration of follow-up, years	2·9 (2·3–3·5)	2·8 (2·3–3·4)	2·7 (2·3–3·4)
Eligible for ≥3 years of follow-up†	2405 (45·9%)	3550 (43·1%)	2287 (42·0%)

Data are n (%) or median (IQR). LDL cholesterol was calculated via the Friedewald formula. To convert the values for cholesterol to mg/dL, divide by 0·0259. To convert the values for triglycerides to mg/dL, divide by 0·0113. To convert the values for glucose to mg/dL, divide by 0·0555. *Atorvastatin 80 mg or rosuvastatin 40 mg. †Subset of participants that either were or could have been followed up for 3 years or longer because they were randomly assigned on or before Nov 11, 2014 (≥3 years before the common study end date).

Table: **Baseline characteristics**

Results

Between Nov 2, 2012 and Feb 9, 2017, we randomly assigned 18 924 patients at 1315 sites in 57 countries (appendix). At randomisation, 5444 (28·8%) patients had

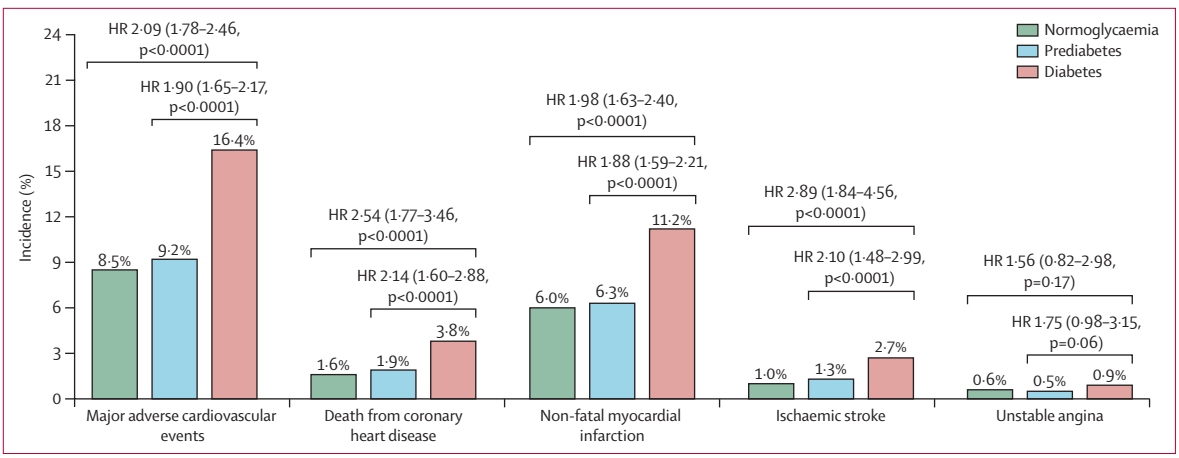

Figure 1: **Incidence of cardiovascular events in the placebo group, by baseline glycaemic status**
Median follow-up was 2·8 years (IQR 2·3–3·4). There were no significant differences between participants with normoglycaemia and those with prediabetes for any of the outcomes (data not shown).

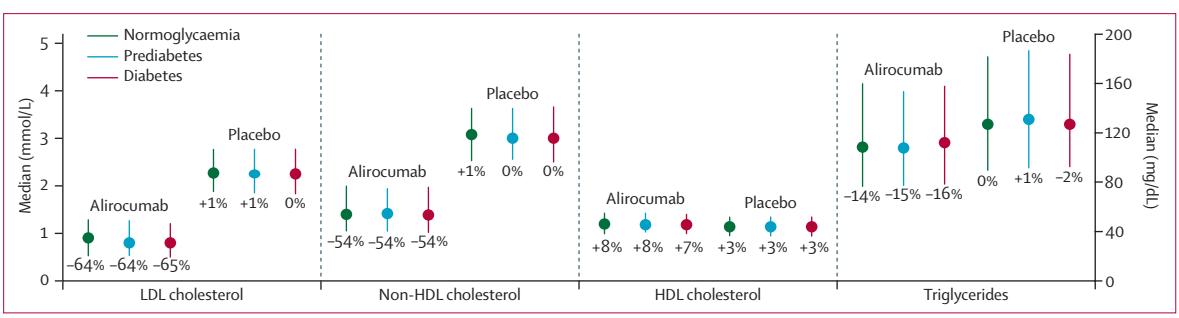

Figure 2: **Lipid concentrations at 4 months after randomisation, by baseline glycaemic status (intention-to-treat analysis)**
Error bars are IQRs. Median within-patient percentage changes from baseline are shown below each data point.

diabetes (n=37 with type 1 diabetes), 8246 (43·6%) patients had prediabetes, and 5234 (27·7%) patients had normoglycaemia. Within each glycaemic category, baseline characteristics were similar in the alirocumab and placebo groups (table, appendix). Most patients had coronary revascularisation for their index acute coronary syndrome event and received evidence-based treatment with dual antiplatelet therapy, β-blockers, and inhibitors of the renin-angiotensin system (appendix).

Baseline values of BMI, non-HDL cholesterol, and triglycerides were highest among patients with diabetes and lowest among those in the normoglycaemia group, with the opposite relation seen for HDL cholesterol concentrations. LDL cholesterol concentration did not differ across the three groups. Use of high-intensity statin by protocol was high overall (88·8% at baseline), but use of ezetimibe was low (2·9%), as was fibrate use (mostly fenofibrate; 1·7%). Of the 5444 patients with diabetes at baseline, 47 (0·9% [or 0·2% of the overall study population of 18 924]) were receiving a glucagon-like peptide-1 (GLP-1) receptor agonist at baseline and 26 (0·5% [0·1% of the overall study population]) were receiving a sodium-glucose co-transporter-2 (SGLT2) inhibitor at baseline (appendix); no patients in the prediabetes or normoglycaemia groups were receiving these medications. During the study, the number of participants using GLP-1 receptor agonists increased to 173 (0·9% of the total study population) and the number using SGLT2 inhibitors increased to 290 (1·5% of the total study population) (appendix).

Median follow-up duration was 2·8 years, with 8242 patients eligible for 3–5 years of follow-up (ie, randomly assigned at least 3 years before the common study end date of Nov 11, 2017). In the placebo group, the rate of the primary endpoint was 6·5 per 100 person-years for patients with diabetes at baseline, 3·4 per 100 person-years for those with prediabetes, and 3·1 per 100 person-years for those with normoglycaemia. The HR for the primary endpoint among patients with diabetes at baseline versus those with normoglycaemia was 2·09 (95% CI 1·78–2·46, p<0·0001); for those with diabetes versus those with prediabetes, the HR was 1·90 (1·65–2·17, p<0·0001; figure 1). There was no significant difference between those with normoglycaemia and those with prediabetes (data not shown). The presence of diabetes at baseline was associated with a significantly increased risk of the

composite primary endpoint and all of its components apart from unstable angina (assessed in the placebo group) compared with those with normoglycaemia and those with prediabetes at baseline (figure 1).

Changes from baseline to month 4 in LDL cholesterol were similar in each glycaemic category (figure 2). In patients treated with alirocumab, median LDL cholesterol concentrations at month 4 were 0·80 mmol/L (IQR 0·52–1·22) in those with diabetes, 0·80 mmol/L (0·54–1·27) in those with prediabetes, and 0·80 mmol/L (0·54–1·30) in those with normoglycaemia. In patients given placebo, these values were 2·25 mmol/L (1·84–2·77) for those with diabetes, 2·25 mmol/L (1·86–2·77) for those with prediabetes, and 2·28 mmol/L (1·89–2·77) for those with normoglycaemia. Over the course of the trial, patients treated with alirocumab had lower LDL cholesterol concentrations, irrespective of baseline glycaemic category (figure 3). The effects of alirocumab on non-HDL cholesterol, triglycerides, and HDL cholesterol were also similar across the baseline glycaemic categories (figure 2).

In the alirocumab group, the relative reduction in risk of the primary endpoint was similar among patients with diabetes (HR 0·84, 95% CI 0·74–0·97), prediabetes (0·86, 0·74–1·00), and normoglycaemia (0·85, 0·70–1·03). However, the substantially higher absolute risk among patients with diabetes resulted in a greater absolute risk reduction with alirocumab treatment (2·3%, 95% CI 0·4 to 4·2) compared with patients with prediabetes (1·2%, 0·0 to 2·4) or normoglycaemia (1·2%, –0·3 to 2·7; $p_{interaction}$=0·0019 among the three glycaemic categories), resulting in a number needed to treat of 43 for people with diabetes and 82 for those without (figure 4, appendix).

Of the patients without diabetes at baseline, 5955 (44·2%) were eligible for 3–5 years of follow-up (table). In patients without diabetes at baseline, mean HbA_{1c} after randomisation was slightly lower in the alirocumab group than in the placebo group (5·78% *vs* 5·80%, p=0·0008), with no difference in mean fasting glucose concentrations (5·67 *vs* 5·68 mmol/L, p=0·84; figure 5). These findings were similar among patients with either prediabetes (HbA_{1c}: 5·92% with alirocumab *vs* 5·95% with placebo; fasting serum glucose 5·85 *vs* 5·85 mmol/L) or normoglycaemia (HbA_{1c}: 5·55% *vs* 5·56%; fasting serum glucose: 5·40 *vs* 5·40 mmol/L) at baseline (figure 5). The risk of developing new-onset diabetes in patients without diabetes at baseline did not differ between alirocumab and placebo: 648 patients (9·6%) in the alirocumab group developed diabetes after randomisation, compared with 676 patients (10·1%) in the placebo group (HR 1·00, 95% CI 0·89–1·11). As expected, developing diabetes during the trial was more common in patients with prediabetes at baseline (13·8% [570/4128] in the alirocumab group and 15·3% [614/4017] in the placebo group) than in those who were normoglycaemic at baseline (3·0% [78/2635] and 2·4% [62/2589]). There were 13 459 patients in the safety population who had normoglycaemia or prediabetes at baseline; 1324 of these patients had new-onset diabetes and there were 348 competing deaths (152 in the alirocumab group and 196 in the placebo group). In a competing-risks model, the treatment HR for new-onset diabetes for the patients with baseline normoglycaemia or prediabetes was 0·95 (95% CI 0·85–1·05). In a model

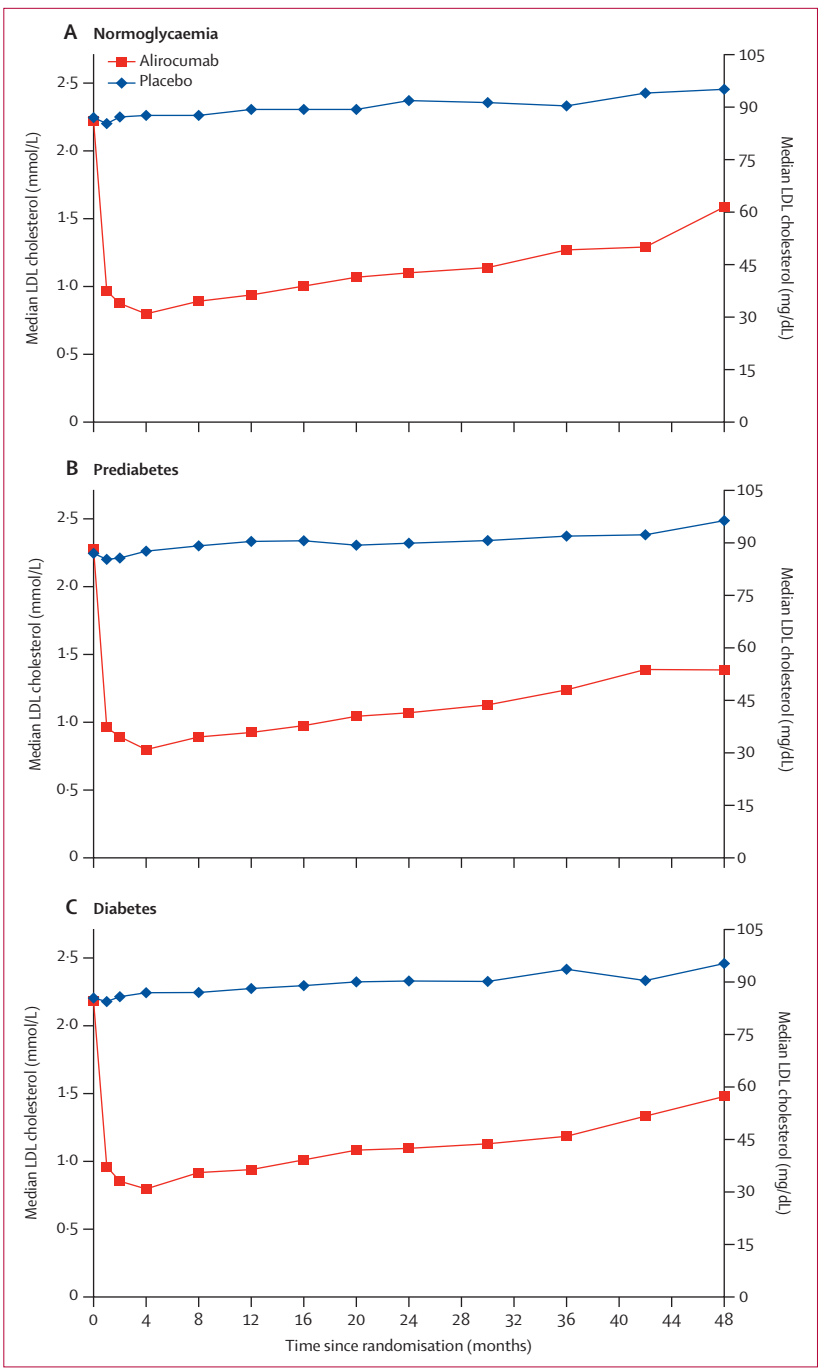

Figure 3: **LDL cholesterol concentrations over time (intention-to-treat analysis)**

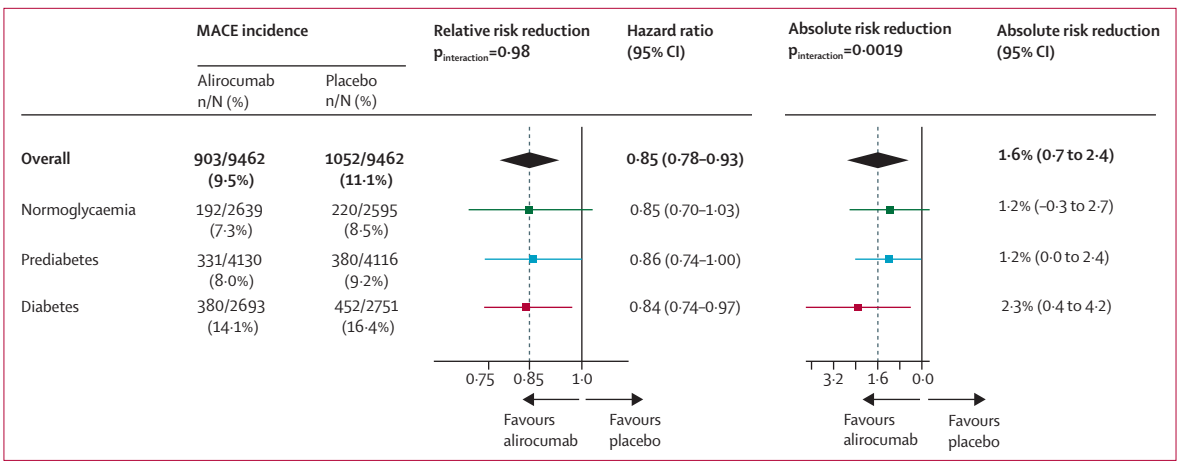

Figure 4: **Relative and absolute risk reduction with alirocumab, by baseline glycaemic status**
Median follow-up was 2·8 years (IQR 2·3–3·4). MACE=major adverse cardiovascular events.

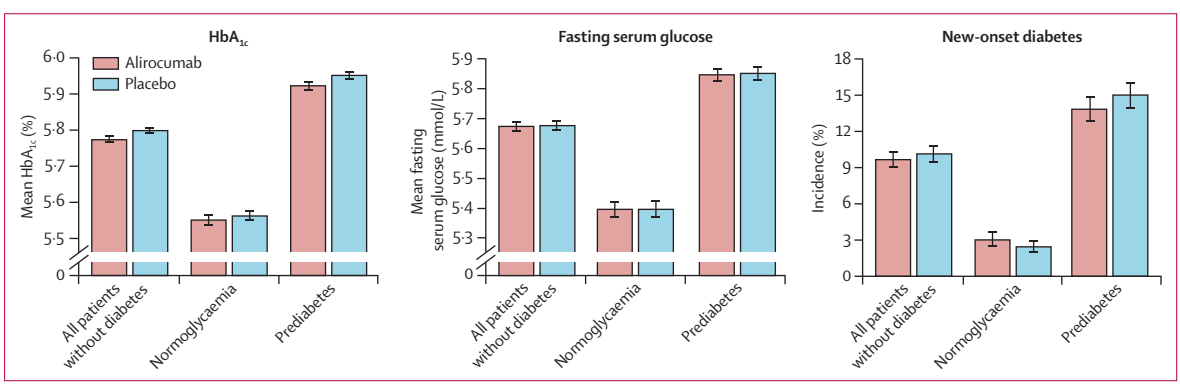

Figure 5: **Post-randomisation HbA_{1c}, fasting serum glucose, and new-onset diabetes, by baseline glycaemic status**
Error bars are 95% CIs. Only post-randomisation values before diabetes medication was started were included in the analysis. The difference in least squares means among all patients without diabetes was 0·02% for HbA_{1c} and 0·003 mmol/L for fasting glucose. HbA_{1c}, all patients without diabetes: alirocumab 5·78% (95% CI 5·77–5·79) *vs* placebo 5·80% (5·79–5·81; p=0·0008); HbA_{1c}, prediabetes subgroup: alirocumab 5·92% (5·91–5·94) *vs* placebo 5·95% (5·94–5·96; p=0·0008); HbA_{1c}, normoglycaemia subgroup: alirocumab 5·55% (5·54–5·57) *vs* placebo 5·56% (5·55–5·58; p=0·23). Fasting serum glucose, all patients without diabetes: alirocumab 5·67 mmol/L (95% CI 5·66–5·69) *vs* placebo 5·68 mmol/L (5·66–5·69; p=0·84); fasting serum glucose, prediabetes subgroup: alirocumab 5·85 mmol/L (5·83–5·87) *vs* placebo 5·85 mmol/L (5·83–5·87; p=0·81); fasting serum glucose, normoglycaemia subgroup: alirocumab 5·40 mmol/L (5·37–5·43) *vs* placebo 5·40 mmol/L (5·37–5·43; p=0·86). New-onset diabetes, all patients without diabetes: alirocumab 9·6% (95% CI 8·9–10·3) *vs* placebo 10·1% (9·4–10·8; p=0·98); new-onset diabetes, prediabetes subgroup: alirocumab 13·8% (12·8–14·9) *vs* placebo 15·3% (13·9–16·1; p=0·60); new-onset diabetes, normoglycaemia subgroup: alirocumab 3·0% (2·4–3·7) *vs* placebo 2·4% (1·9–3·0; p=0·15). *Includes patients categorised as having prediabetes or normoglycaemia.

including the interaction with normoglycaemia and prediabetes status, the subgroup HRs were 1·23 (95% CI 0·88–1·71) for those with baseline normoglycaemia and 0·92 (0·82–1·03) for those with baseline prediabetes ($p_{interaction}$=0·11).

Discussion

Abnormal glycometabolic status is common in patients after an acute coronary syndrome, with about a third having diabetes and a similar proportion having prediabetes.[14] After an acute coronary syndrome, patients with diabetes are at particularly high risk of recurrent ischaemic cardiovascular events, and also derive the greatest absolute benefit from a given degree of lipid lowering with high-intensity statins[15] or statins plus ezetimibe.[2,16]

The distribution of patients with glycometabolic abnormalities in our trial was similar to that in an earlier study of people with a previous acute coronary syndrome,[14] with about 70% of the cohort having diabetes or prediabetes. The presence of diabetes at baseline did not affect LDL cholesterol concentrations at baseline or during assigned treatment with alirocumab or placebo. In the placebo group of the present study, the annual event rate of the primary outcome among patients with diabetes at baseline was 6·5 per 100 person-years, compared with 3·4 per 100 person-years among those with prediabetes and 3·1 per 100 person-years in those with normoglycaemia. Although age and BMI were higher in patients with baseline diabetes than in those with normoglycaemia, lipid profiles were only modestly worse in those with diabetes at baseline (table). In a study with

an average follow-up duration of 2·8 years, it is unlikely that these differences alone would result in a doubling of the absolute risk of cardiovascular events. Thus, our observed event rate in the placebo group reinforces the hypothesis that the presence of diabetes per se carries a significant excess cardiovascular risk in patients with a recent acute coronary syndrome. The relative reduction in risk of ischaemic cardiovascular events with alirocumab compared with placebo was similar between those with and without diabetes. However, patients with diabetes, compared to those without diabetes, had a substantially higher absolute risk of recurrent cardiovascular events after acute coronary syndrome and about twice the absolute reduction in that risk with alirocumab (2·3% *vs* 1·2%). These benefits were achieved on a background of extensive use of evidence-based therapies, including high-intensity statins, revascularisation for the index acute coronary syndrome event, dual antiplatelet therapy, and blockade of the β-adrenergic and renin–angiotensin systems, and with good control of blood glucose (mean baseline HbA_{1c} of 7·0% in patients with diabetes at baseline).

Our findings build upon previous evidence supporting the use of intensive lipid-lowering therapy and ezetimibe in patients with diabetes and acute coronary syndrome, and are aligned with the recent updating of some clinical guidelines[3,17,18] in which LDL cholesterol treatment goals have been successively lowered from less than 2·59 mmol/L to less than 1·81 mmol/L,[17,18] and even to less than 1·42 mmol/L,[3] in these very high-risk patients. The American College of Cardiology and American Heart Association guidelines—although acknowledging that PCSK9 inhibitors are an option to lower LDL cholesterol to below 1·81 mmol/L in very high-risk patients—noted that PCSK9 inhibitors are likely to be less cost-effective than ezetimibe. These guidelines suggest that there is a need to easily identify very high-risk groups who derive greater absolute benefits from these more expensive therapies. The findings of our study suggest that, among patients with a recent acute coronary syndrome, the presence of diabetes highlights a large subgroup (about a third) with substantially enhanced risk and who derive greater benefits from targeting even lower LDL cholesterol concentrations of 0·65–1·30 mmol/L. The corresponding number needed to treat for a median of 2·8 years to avoid one primary endpoint event was 43 for patients with diabetes at baseline versus 82 for patients without diabetes at baseline. Accordingly, patients with diabetes and acute coronary syndrome are a group in whom the cost-effectiveness of alirocumab treatment is more favourable.

An additional goal of our study was to examine the glycaemic safety of alirocumab treatment among patients without diabetes at baseline. Concerns about the effects of lipid-lowering therapies on glucose homeostasis have come from observations that statins increase the risk of new-onset diabetes by 9% versus placebo, and by an additional 12% when comparing high-intensity statins with moderate-intensity statins.[7] Furthermore, mendelian randomisation studies[8,19–21] of genetic polymorphisms that mimic the effects of statins, ezetimibe, or PCSK9 inhibitors suggest that lifelong reductions in LDL cholesterol, irrespective of the mechanism, are associated with an increased risk of diabetes. These findings have raised theoretical concerns about the risk of new-onset diabetes with the use of PCSK9 inhibitors.

In the present analysis, no excess risk of new-onset diabetes with alirocumab was seen in patients with prediabetes or normoglycaemia at baseline. Findings from an analysis of the FOURIER cardiovascular outcomes trial[10] with the PCSK9 inhibitor evolocumab suggested a possible increased risk of new-onset diabetes among patients with normoglycaemia at baseline, but not among those with prediabetes at baseline, albeit with a small number of events and wide CIs. This finding was not seen in the present analysis, with no adverse effect of alirocumab on HbA_{1c}, fasting glucose, or new-onset diabetes in patients with either normoglycemia or prediabetes at baseline.

There are some notable differences between the methods used to assess glycaemic safety in the FOURIER trial[10] and in the current analysis. Our trial had longer follow-up than FOURIER to assess safety and efficacy and a masked diabetes endpoint adjudication committee to determine cases of new-onset diabetes. In the present analysis, fasting glucose and HbA_{1c} values collected after initiation of diabetes medication were censored because initiation of diabetes medications would lower any subsequent measurements of glucose concentration and HbA_{1c}, and thus confound the assessment of any direct effect of randomised treatment assignment on these measures. Because such censoring was not used in the FOURIER analysis, a potential effect of study treatment on glucose or HbA_{1c} could have been masked.[10] The present findings provide greater reassurance about the glycaemic safety of PCSK9 inhibitors as a class. However, new-onset diabetes with statins was only confirmed many years after regulatory approval through meta-analyses of multiple trials. Thus, although the present results are reassuring, the long-term effects (ie, beyond 5 years) of PCSK9 inhibitors on glycaemic status are still unknown.

Mendelian randomisation analyses[8,20,21] have shown that genetically determined loss of function of PCSK9 is associated with an increased risk of incident diabetes, but clinical trials of PCSK9 inhibitors have shown no such effect.[9] These findings, although divergent, might not necessarily be inconsistent. First, the timeframe of mendelian randomisation analyses is substantially longer than that of clinical trials, providing more opportunity to observe the effects of genetic variants in PCSK9 on incident diabetes. Second, in clinical trials that enrol patients with established atherosclerosis, about 70% already have a glycometabolic abnormality at

randomisation (prediabetes or diabetes). The effects of pharmacological PCSK9 inhibition on incident diabetes in such a population could be different than the longitudinal effects of genetic variants in PCSK9 in a healthy population with a low prevalence of glycaemic abnormality at baseline.

Mostly, the analyses of the FOURIER[10] and ODYSSEY OUTCOMES trials have consistent findings with respect to diabetes. FOURIER used a fixed dose of evolocumab and the LDL cholesterol concentrations described are for patients who remained on treatment, had follow-up laboratory measurements, and had no change in background statin treatment. By contrast, the LDL cholesterol concentrations presented in our study are from the intention-to-treat analysis and ODYSSEY OUTCOMES used a treat-to-target design. Despite these differences, the results among participants with diabetes at baseline were similar. The relative risk reduction for the primary endpoint of five-point major adverse cardiovascular events in FOURIER among those with diabetes at baseline was 17%, similar to the 16% relative reduction in the risk of four-point major adverse cardiovascular events in ODYSSEY OUTCOMES. At 3 years, the proportion of individuals with diabetes in the placebo group who had experienced a primary endpoint event was 17·1% in FOURIER, and was reduced in absolute terms by 2·7% with evolocumab. In ODYSSEY OUTCOMES, at the median follow-up of 2·8 years, the comparable figures for individuals with diabetes were a 16·4% risk of a primary endpoint event among patients in the placebo group, which was reduced in absolute terms by 2·3% with alirocumab treatment.

Although patients with prediabetes have been reported to have worse cardiovascular outcomes than those with normoglycaemia,[22,23] the observed rates were similar in the present analysis. This finding might reflect the fact that we used both contemporary HbA_{1c} definitions and fasting glucose criteria to define glycaemic status, so that patients who might historically have been classified as having prediabetes would now be classified as having diabetes by the present definition. An alternative explanation for the similar event rates between those with prediabetes and normoglycaemia could be index event bias (ie, in a population defined by acute coronary syndrome, those with normoglycaemia are enriched with other competing risk factors, identifiable or not). In this regard, high use of aggressive lipid-lowering and other guideline-based secondary prevention therapies (appendix) might mean that the median follow-up of 2·8 years was not long enough to observe the previously well-established differences in risk between those with prediabetes and those with normoglycaemia in population-based cohort studies with longer follow-up durations. Our findings of a consistent relative benefit of alirocumab among patients with normoglycaemia, prediabetes, or diabetes in the post-acute coronary syndrome setting is consistent with, and extends, previous observations in stable cardiovascular disease, in which people with and without diabetes derive similar relative benefits from PCSK9 inhibition.[10]

A limitation of our study is that it was started before GLP-1 receptor agonists[24] and SGLT2 inhibitors[25] were shown to reduce major cardiovascular events and mortality in patients with stable cardiovascular disease and type 2 diabetes. At baseline, 0·2% (n=47) of the total study population were receiving a GLP-1 receptor agonist, which increased to 0·9% (n=173) during the study (appendix). For SGLT2 inhibitors, the corresponding numbers were 0·1% (n=26) at baseline, increasing to 1·5% (n=290) during the study. It is uncertain whether greater use of these classes of drugs would affect the magnitude of the observed benefit of alirocumab treatment in patients with acute coronary syndrome and diabetes, although the evidence to date suggests that the benefits of newer diabetes treatments and lipid lowering are complementary.[26] Moreover, GLP-1 receptor agonists and SGLT2 inhibitors have shown benefit in patients with chronic stable cardiovascular disease, but efficacy has not been shown in the post-acute coronary syndrome setting.[27]

In summary, in the post-acute coronary syndrome context, compared with patients without diabetes, those with diabetes had twice the excess risk of cardiovascular events when LDL cholesterol was greater than 1·8 mmol/L despite intensive statin treatment. The patients with diabetes also derived twice as much benefit when alirocumab was used to target an LDL cholesterol concentration between 0·65 mmol/L and 1·30 mmol/L. With a median follow-up of 2·8 years and with 5955 (44·2%) patients without diabetes eligible for 3–5 years of follow-up, alirocumab did not adversely affect measures of glycaemia or increase the risk of new-onset diabetes. These findings provide further evidence that future guidelines should recommend much lower LDL cholesterol targets for patients with vascular disease when diabetes is present.

Contributors

GGS and PGS are the chief investigators. MS, DLB, VAB, RD, SGG, RAH, JWJ, RP, RDL, MTR, HDW, AMZ, GGS, and PGS designed the trial. PGS, GGS, and MS developed the ODYSSEY OUTCOMES trial protocol and statistical analysis plan in conjunction with the other members of the executive steering committee (appendix). MS did the statistical analyses. MS and VL vouch for the data and analysis. KKR wrote the first draft of the report, with input from all authors, all of whom reviewed the final draft before its submission for publication.

Declaration of interests

KKR reports personal fees from AbbVie, AstraZeneca, Medco, Resverlogix, Akcea, Boehringer Ingelheim, Novo Nordisk, Takeda, Kowa, Algorithm, Cipla, Cerenis, Dr Reddy's, Lilly, Bayer, and Zuellig Pharma; and research grants and personal fees from Amgen, Sanofi, Regeneron Pharmaceuticals, MSD, and Pfizer. HMC reports research support and honoraria from, and membership of advisory panels or speakers' bureaus for, Sanofi-Aventis, Regeneron Pharmaceuticals, Novartis, Novo Nordisk, and Eli Lilly; reports non-binding research support from Pfizer, AstraZeneca, and Novo Nordisk; and is a shareholder of Roche and Bayer. MS reports serving as a consultant or on advisory boards (or both) for CiVi, Resverlogix, Baxter, Esperion, and Regeneron Pharmaceuticals. MB-D is an employee of Sanofi. DLB reports serving on advisory boards for Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, PhaseBio, and Regado Biosciences; serving on the board of directors for

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RAH reports research grants from Apple, CSL, Sanofi, AstraZeneca, Portola, Janssen, Bristol-Myers Squibb, Novartis, and The Medicines Company; serving as a consultant or on advisory boards (or both) for Amgen, Bayer, Gilead, MyoKardia, and WebMD; and serving on the boards of directors (unpaid) for the American Heart Association and Stanford HealthCare. JWJ reports research grants from the Netherlands Heart Foundation, the Interuniversity Cardiology Institute of the Netherlands, and the European Commission Seventh Framework Programme; and research support from Amgen, Astellas, AstraZeneca, Daiichi-Sankyo, Lilly, Merck-Schering-Plough, Pfizer, Roche, and Sanofi. VL is an employee of and shareholder in Sanofi. RDL reports research grants from Amgen and Sanofi-Aventis; personal fees from Bayer, Portola, and Boehringer Ingelheim; and research grants and personal fees from Bristol-Myers Squibb, GlaxoSmithKline, and Pfizer. AM is employed by Sanofi. 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MTR reports research grant funding from Sanofi-Aventis, Janssen, AstraZeneca, Patient-Centered Outcomes Research Institute, Ferring Pharmaceuticals, MyoKardia, American College of Cardiology, American Heart Association, Familial Hypercholesterolemia Foundation; and consulting fees or honoraria from AstraZeneca, Amgen, Eli Lilly, Roche–Genentech, Janssen, Regeneron Pharmaceuticals, Ardea Biosciences, Novo Nordisk, Flatiron, Merck, Pfizer, Sanofi-Aventis, Signal Path, and Elsevier. JT reports personal fees from Sanofi, Amgen, and Diasorin Iberia. HDW reports receiving grant support (paid to institution) and fees for serving on a steering committee from Sanofi-Aventis and Regeneron Pharmaceuticals (for the ODYSSEY OUTCOMES trial), Eli Lilly (for the ACCELERATE trial), Omthera Pharmaceuticals (for the STRENGTH trial), Pfizer (for the SPIRE trial), American Regent (for the HEART-FID trial), Eisai (for the CAMELLIA-TIMI trial), DalCor (for the dal-GenE trial), CSL Behring (for the AEGIS-II trial), Sanofi-Aventis (for the SCORED and SOLOIST trials), and Esperion Therapeutics (for the CLEAR Outcomes trial). AMZ reports receiving fees for serving on a steering committee for the ODYSSEY OUTCOMES trial from Sanofi, and advisory board membership, speaker fees, or both from Sanofi, Amgen, Boehringer Ingelheim, Bayer, Novartis, Pfizer, AstraZeneca, and Vifor. GGS reports research grants (to the University of Colorado) from Resverlogix, Sanofi, and Roche; and is co-inventor of pending US patent 14/657192 ("Methods of Reducing Cardiovascular Risk") assigned in full to the University of Colorado. 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Data sharing

Individual participant data are not available.

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References

1 Bonaca MP, Gutierrez JA, Cannon C, et al. Polyvascular disease, type 2 diabetes, and long-term vascular risk: a secondary analysis of the IMPROVE-IT trial. *Lancet Diabetes Endocrinol* 2018; **6:** 934–43.

2 Giugliano RP, Cannon CP, Blazing MA, et al. Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus: results from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial). *Circulation* 2018; **137:** 1571–82.

3 Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. *Endocr Pract* 2017; **23:** 1–87.

4 Catapano AL, Graham I, De Backer G, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. *Eur Heart J* 2016; **37:** 2999–3058.

5 Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2019; **73:** 3168–209.

6 Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA* 2011; **305:** 2556–64.

7 Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 2010; **375:** 735–42.

8 Ference BA, Robinson JG, Brook RD, et al. Variation in *PCSK9* and *HMGCR* and risk of cardiovascular disease and diabetes. *N Engl J Med* 2016; **375:** 2144–53.

9 Colhoun HM, Ginsberg HN, Robinson JG, et al. No effect of PCSK9 inhibitor alirocumab on the incidence of diabetes in a pooled analysis from 10 ODYSSEY phase 3 studies. *Eur Heart J* 2016; **37:** 2981–89.

10 Sabatine MS, Leiter LA, Wiviott SD, et al. Cardiovascular safety and efficacy of the PCSK9 inhibitor evolocumab in patients with and without diabetes and the effect of evolocumab on glycaemia and risk of new-onset diabetes: a prespecified analysis of the FOURIER randomised controlled trial. *Lancet Diabetes Endocrinol* 2017; **5:** 941–50.

11 Ridker PM, Revkin J, Amarenco P, et al. Cardiovascular efficacy and safety of bococizumab in high-risk patients. *N Engl J Med* 2017; **376:** 1527–39.

12 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:** 682–89.

13 Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018; **379:** 2097–107.

14 Norhammar A, Tenerz A, Nilsson G, et al. Glucose metabolism in patients with acute myocardial infarction and no previous diagnosis of diabetes mellitus: a prospective study. *Lancet* 2002; **359:** 2140–44.

15 Ahmed S, Cannon CP, Murphy SA, Braunwald E. Acute coronary syndromes and diabetes: is intensive lipid lowering beneficial? Results of the PROVE IT-TIMI 22 trial. *Eur Heart J* 2006; **27:** 2323–29.

16 Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015; **372:** 2387–97.

17 National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002; **106:** 3143–421.

18 Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *J Am Coll Cardiol* 2004; **44:** 720–32.

19 Swerdlow DI, Preiss D, Kuchenbaecker KB, et al. HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials. *Lancet* 2015; **385:** 351–61.

20 Schmidt AF, Swerdlow DI, Holmes MV, et al. *PCSK9* genetic variants and risk of type 2 diabetes: a mendelian randomisation study. *Lancet Diabetes Endocrinol* 2017; **5:** 97–105.

21 Lotta LA, Sharp SJ, Burgess S, et al. Association between low-density lipoprotein cholesterol-lowering genetic variants and risk of type 2 diabetes: a meta-analysis. *JAMA* 2016; **316:** 1383–91.

22 Stranders I, Diamant M, van Gelder RE, et al. Admission blood glucose level as risk indicator of death after myocardial infarction in patients with and without diabetes mellitus. *Arch Intern Med* 2004; **164:** 982–88.

23 Bhadriraju S, Ray KK, DeFranco AC, et al. Association between blood glucose and long-term mortality in patients with acute coronary syndromes in the OPUS-TIMI 16 trial. *Am J Cardiol* 2006; **97:** 1573–77.

24 Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016; **375:** 1834–44.

25 Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015; **373:** 2117–28.

26 Verma S, Leiter LA, Mazer CD, et al. Liraglutide reduces cardiovascular events and mortality in type 2 diabetes mellitus independently of baseline low-density lipoprotein cholesterol levels and statin use. *Circulation* 2018; **138:** 1605–07.

27 Pfeffer MA, Claggett B, Probstfield JL. Lixisenatide in type 2 diabetes and acute coronary syndrome. *N Engl J Med* 2016; **374:** 1095–96.