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Summary

Background Many patients with acute coronary syndrome have concurrent metabolic risk factors that affect risk of major adverse cardiovascular events (MACE). We aimed to assess the effects of the PCSK9 inhibitor alirocumab compared with placebo on MACE according to baseline metabolic risk factors.

Methods We performed a post-hoc analysis of the ODYSSEY OUTCOMES trial, which was a multicentre, double-blind, randomised controlled trial done in 1315 hospitals and outpatient clinics in 57 countries. Patients aged 40 years or older with recent acute coronary syndrome (ie, in the past 1–12 months) and elevated concentrations of atherogenic lipoproteins, despite high-intensity or maximum-tolerated statin treatment, were eligible for enrolment. Between Nov 2, 2012, and Feb 9, 2017, patients were randomly assigned (1:1) to 75 mg alirocumab by subcutaneous injection every 2 weeks or matching placebo, beginning 1–12 months after acute coronary syndrome and were followed up for a median of 2·8 years (IQR 2·3–3·4). Patients and investigators were masked to group assignment and treatment dose adjustment. The primary outcome was a composite of death from coronary artery disease, non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, or unstable angina requiring hospital admission. Analysis of MACE according to an ordinal number of metabolic risk factors was done post hoc. Metabolic risk factors were defined as blood pressure of at least 130/85 mm Hg or treatment with antihypertensive medication, triglyceride concentration of at least 150 mg/dL, HDL cholesterol concentration less than 40 mg/dL for men and 50 mg/dL women, fasting plasma glucose concentration of at least 100 mg/dL or treatment with glucose-lowering medication, and BMI of at least 30 kg/m^2. Risk of MACE and effect of alirocumab were assessed according to the number of metabolic risk factors. ODYSSEY OUTCOMES is registered with ClinicalTrials.gov, number NCT01663402.

Findings Of 18 924 patients, 3882 (41%) of 9462 in the alirocumab group and 3859 (41%) of 9462 in the placebo group had three or more metabolic risk factors. In the placebo group, MACE incidence increased monotonically with each metabolic risk factor from 7·8% (no risk factors) to 19·6% (five risk factors; HR 1·18, 95% CI 1·13–1·24 per metabolic risk factor). Alirocumab decreased relative risk of MACE consistently across categories defined by the number of metabolic risk factors ($p_{interaction}$=0·77), but absolute risk reduction (aRR) increased with the number of metabolic risk factors (no risk factors aRR 0·7%, –1·81 to 3·29 *vs* five risk factors aRR 3·9%, –1·45 to 9·25; $p_{interaction}$<0·001). Similarly, when patients with diabetes were excluded, the incidence of MACE in the placebo group increased from 7·7% in patients with no metabolic risk factors to 14·6% in those with five metabolic risk factors and aRR with alirocumab increased from 0·91% in patients with no metabolic risk factors to 3·82% in those with five factors. Alirocumab was well tolerated in all subgroups defined by the presence of metabolic risk factors.

Interpretation Accumulation of metabolic risk factors was associated with higher risk of MACE in patients with recent acute coronary syndrome. Alirocumab reduced MACE consistently, but aRR increased with number of metabolic risk factors.

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Introduction

Several metabolic factors have been associated with increased risk of major adverse cardiovascular events (MACE), including diabetes or increased fasting plasma glucose concentrations, abdominal obesity, hypertension, low concentrations of HDL cholesterol, and high triglyceride concentrations. A collection of these metabolic risk factors has been termed metabolic syndrome and is associated with elevated risk of MACE and death.[1–4] Current guidelines emphasise the importance of

Research in context

Evidence before this study

We searched PubMed from Jan 1, 2010, to June 30, 2021, for articles published in English, investigating the effect of proprotein convertase subtilisin or kexin type 9 inhibitors on cardiovascular events using the terms "alirocumab", "evolocumab", "PCSK9 inhibitor", and "cardiovascular event". Inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9) reduce LDL cholesterol concentrations by up to 60% and decrease risk of major adverse cardiovascular events (MACE) in patients with acute coronary syndrome. Many patients with acute coronary syndrome have concurrent metabolic risk factors that affect risk of MACE and efficacy of lipid-lowering therapy. In the cardiovascular outcomes FOURIER trial, the PCSK9 inhibitor evolocumab reduced relative risk of MACE in statin-treated patients with chronic atherosclerotic cardiovascular disease to a similar degree in patients with or without metabolic syndrome, and in patients with or without diabetes. In the placebo-controlled ODYSSEY OUTCOMES trial, patients with acute coronary syndrome on high intensity or maximum-tolerated statin treatment had a reduced relative risk of MACE when randomly assigned to the PCSK9 inhibitor alirocumab regardless of diabetes status. However, the association of metabolic risk factors (hypertension, hypertriglyceridaemia, low HDL cholesterol, hyperglycaemia, obesity) with risk of MACE in patients with acute coronary syndrome on high-intensity or maximum-tolerated statin therapy, and the effect of alirocumab according to the number of metabolic risk factors is unknown.

Added value of this study

In the ODYSSEY OUTCOMES trial, 91·5% of patients with recent acute coronary syndrome (ie, in the past 1–12 months) had at least one metabolic risk factor and 68·8% had two or more. Despite high-intensity or maximum-tolerated statin therapy, each metabolic risk factor (except low HDL cholesterol) remained significantly associated with increased risk of MACE, and accumulation of metabolic risk factors in patients with recent acute coronary syndrome substantially increased risk for further cardiovascular events. Alirocumab reduced relative risk of MACE irrespective of the number of metabolic risk factors, but absolute benefit increased with the number of metabolic risk factors. Absolute risk reduction, and potentially relative risk reduction, appeared more pronounced in patients with at least three metabolic risk factors than in patients with less than three factors, especially in patients without diabetes.

Implications of all the available evidence

Patients with multiple metabolic risk factors, including patients without diabetes, might derive a large absolute benefit of alirocumab treatment after acute coronary syndrome. Counting the number of risk factors could be a simple way for clinicians to identify patients considered for PCSK9 inhibitor therapy after acute coronary syndrome.

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See **Online** for appendix

managing metabolic syndrome and recommend lifestyle modifications and pharmacological therapy, including lipid-lowering drugs, especially for secondary prevention.[5–7] High-intensity statin therapy has been shown to decrease risk of MACE in patients with metabolic syndrome and chronic coronary artery disease[8] or acute coronary syndrome.[9] Nevertheless, residual risk in individuals with metabolic syndrome remains high.

Inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9) reduce concentrations of LDL cholesterol by up to 60% and decrease risk of MACE in patients with chronic atherosclerotic cardiovascular disease[10] or acute coronary syndrome.[9] In the placebo-controlled FOURIER trial, evolocumab reduced relative risk of MACE in statin-treated patients with chronic atherosclerotic cardiovascular disease at similar rates in patients with or without metabolic syndrome and in patients with or without diabetes.[11] In the placebo-controlled ODYSSEY OUTCOMES trial, patients with recent acute coronary syndrome on high intensity or maximum-tolerated statin treatment had a reduced relative risk of MACE when randomly assigned to alirocumab, regardless of diabetes status.[12]

In this post-hoc analysis of the ODYSSEY OUTCOMES trial, we aimed to describe the association of metabolic risk factors with risk of MACE in a population of patients with acute coronary syndrome on high-intensity or maximum-tolerated statin therapy and assess the effect of alirocumab according to the number of metabolic risk factors present.

Methods

Study design and participants

In this study we did a post-hoc analysis of the results of the ODYSSEY OUTCOMES trial. ODYSSEY OUTCOMES was a randomised, double-blind trial[9] that compared the efficacy and safety of alirocumab versus placebo in patients with recent acute coronary syndrome (ie, in the past 1–12 months) on high-intensity or maximum-tolerated statin treatment. The study was done at 1315 hospitals and outpatient clinics in 57 countries, and enrolment occurred between Nov 2, 2012, and Feb 9, 2017. 18 924 patients aged 40 years or older with elevated concentrations of atherogenic lipoproteins (LDL cholesterol ≥70 mg/dL, non–HDL cholesterol ≥100 mg/dL, or apolipoprotein B ≥80 mg/dL), despite high-intensity or maximum-tolerated statin treatment, were eligible for enrolment and randomly assigned to placebo or alirocumab. The study protocol, design, and primary results have been published elsewhere.[9,13] The trial was approved by the institutional review board or ethics committee at each site. All participants provided written informed consent.

Patients were randomly assigned (1:1) to 75 mg alirocumab by subcutaneous injection every 2 weeks or

matching placebo, beginning 1–12 months after acute coronary syndrome and were followed up for a median of 2·8 years (IQR 2·3–3·4). Patients were randomly assigned centrally and stratified by country using an interactive voice-response or web-response system.[9,13]

The aim of the treat-to-target design was to achieve an LDL cholesterol concentration of 25–50 mg/dL in patients receiving alirocumab. Alirocumab was blindly titrated from 75 mg to 150 mg if the LDL cholesterol concentration was 50 mg/dL or more. If LDL cholesterol concentration was less than 15 mg/dL on two consecutive measurements on 75 mg alirocumab, placebo was blindly substituted for the rest of the trial. In patients on 150 mg alirocumab, the dose could be titrated down to 75 mg if LDL cholesterol concentration was less than 15 mg/dL on two consecutive measurements. The trial had a double-blind design, with patients and investigators masked to treatment assignment, dose adjustments, and lipid concentrations.

Outcomes

The primary outcome for this analysis was composite of death from coronary artery disease, non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, or unstable angina requiring hospital admission. The analysis of subgroups defined by metabolic syndrome status at baseline (ie, presence of three or more metabolic risk factors) was prespecified in a statistical analysis plan, published elsewhere;[9] the analysis of MACE according to ordinal number of metabolic risk factors was done on a

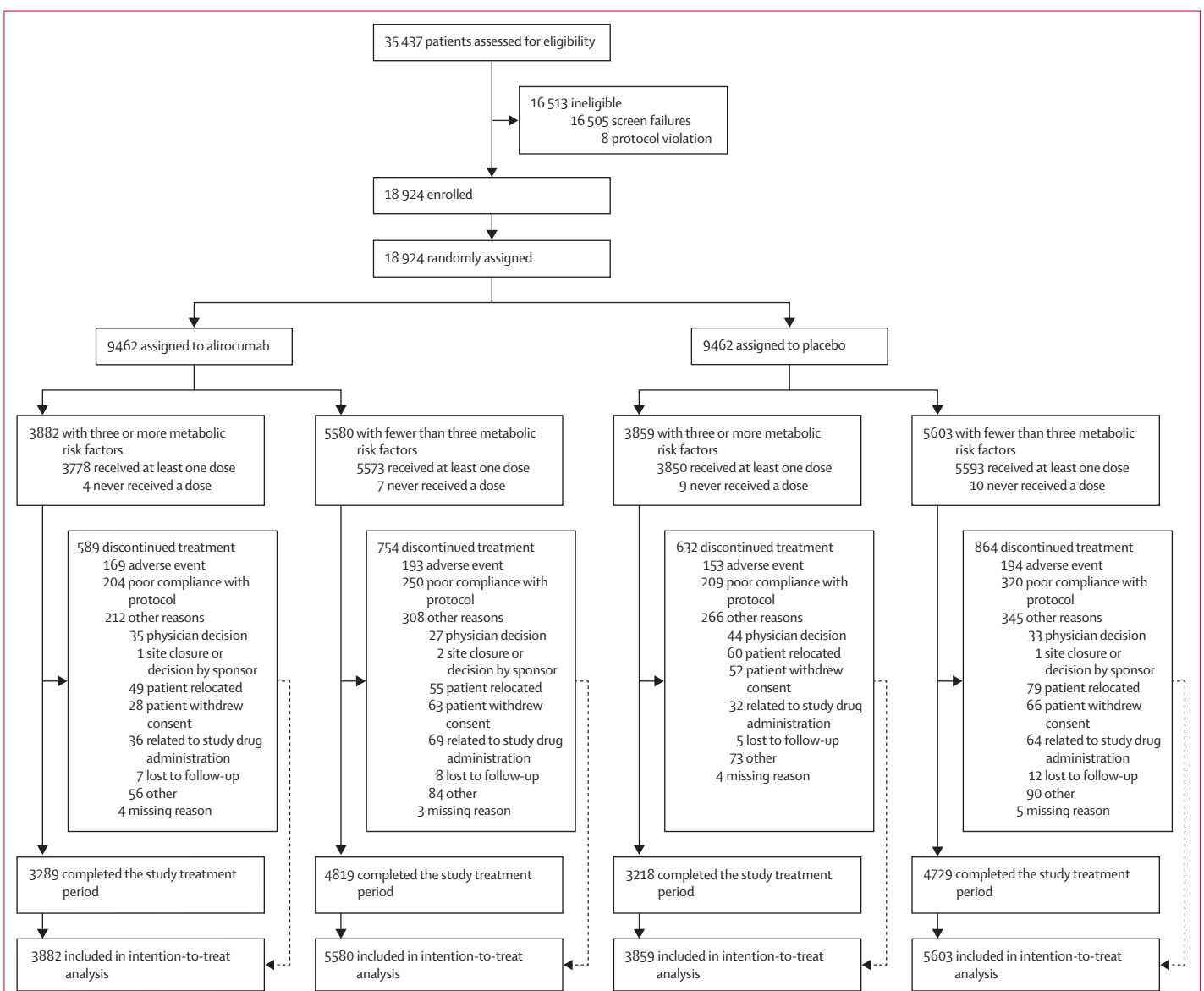

Figure 1: **Profile of the post-hoc analysis**

post-hoc basis. Metabolic risk factors were defined using the following criteria: hypertension (blood pressure of at least 130/85 mm Hg or use of antihypertensive medication; β blocker and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker were considered as antihypertensive therapy only if a hypertension diagnosis was indicated by the investigator); hypertriglyceridaemia (triglycerides ≥150 mg/dL); low HDL cholesterol concentration (<40 mg/dL in men and <50 mg/dL in women); dysglycaemia (fasting plasma glucose concentration ≥100 mg/dL or use of glucose-lowering medication); and obesity (BMI ≥30 kg/m²). An alternative measure of abdominal obesity, waist circumference, was not recorded in the trial.[1,14] Additionally, diabetes was defined as a fasting plasma glucose concentration of at least 125 mg/dL or use of glucose-lowering medication. Patients with missing laboratory or categorical data at baseline were considered as not meeting criteria. The effect of alirocumab was compared across subgroups by ordinal number of metabolic risk factors and between subgroups with at least three and fewer than three metabolic risk factors; patients with at least three metabolic risk factors correspond with the definition of metabolic syndrome when the criterion of waist circumference is substituted by BMI. As diabetes is a strong independent risk factor for cardiovascular events, we aimed to examine burden of risk and benefit of alirocumab by metabolic risk factors in all patients and after exclusion of patients with diabetes.

Statistical analysis

Design assumptions of the ODYSSEY OUTCOMES trial included incidence of the composite primary outcome of 11·4% at 4 years in the placebo group and a median baseline LDL cholesterol concentration of 90 mg/dL, with an anticipated 50% lower LDL cholesterol concentration in the alirocumab group than in the placebo group,[13] projected to result in an expected 15% lower risk of the primary outcome with alirocumab than with placebo.

The ODYSSEY OUTCOMES trial was not designed to enrol a specific number of patients within each subgroup defined by status of metabolic syndrome at baseline, hence no power calculation has been made on any of the subgroups. Calculations were based on the primary efficacy variable and have been previously described elsewhere.[13,15] In brief, we estimated that in the ODYSSEY OUTCOMES trial 1613 events would be needed to have 90% power (with one-sided log-rank test at the overall 0·025 α level) to show an effect versus placebo assuming 15% risk reduction associated with alirocumab treatment (ie, hazard ratio [HR] 0·85) and considering two interim analyses: a first interim analysis for futility and a second for efficacy.[15]

Controls of type I and type II error were ensured using gamma (–5) spending function for type II error (futility) and gamma (–22) for type I error (efficacy). Analyses presented in this Article are post hoc, hence there was no adjustment for multiplicity.

Kaplan-Meier curves are presented by randomised treatment and subgroups with at least three and fewer than three metabolic risk factors. HR and 95% CI were generated using proportional hazard models, including treatment, region, sex, age, subgroup, and treatment-by-subgroup interaction as covariates. Possible heterogeneity of randomised treatment effects on MACE for selected subgroups was tested by incorporating interaction terms into proportional hazards models for relative risk reductions and by quantitative interactions based on observed incidences for absolute risk reductions. $p_{interaction}$ less than 0·1 was considered a sign of potential treatment interaction. The intention-to-treat population was used for the efficacy analysis.

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

Role of the funding source

The funders selected the study sites and monitored and supervised data collection, did the statistical analysis, contributed to data interpretation, and provided input on the report. The executive steering committee decided to publish the manuscript and takes responsibility for the completeness and accuracy of the data and the fidelity of the trial to the protocol.

Results

Of 18 924 patients, 3882 (41%) of 9462 in the alirocumab group and 3859 (41%) of 9462 in the placebo group had three or more metabolic risk factors (figure 1, appendix p 10). Overall, 17 311 (92%) patients had at least one metabolic risk factor and 13 014 (69%) had two or more metabolic risk factors. The prevalence of metabolic

	All (n=18 924)	Alirocumab group (n=9462)	Placebo group (n=9462)
Metabolic risk factors			
Dysglycaemia*	10 512 (56%)	5262 (56%)	5250 (56%)
Hypertriglyceridemia†	7085 (37%)	3498 (37%)	3587 (38%)
Hypertension‡	9408 (50%)	4797 (51%)	4611 (49%)
Low HDL cholesterol§	8997 (48%)	4480 (47%)	4517 (48%)
BMI ≥30 kg/m²	6262 (33%)	3122 (33%)	3140 (33%)
Number of metabolic risk factors¶			
None	1613 (9%)	813 (9%)	800 (9%)
One	4297 (23%)	2161 (23%)	2136 (23%)
Two	5273 (28%)	2606 (28%)	2667 (28%)
Three	4330 (23%)	2162 (23%)	2168 (23%)
Four	2624 (14%)	1300 (14%)	1324 (14%)
Five	787 (4%)	420 (4%)	367 (4%)

Data are n (%). *Fasting plasma glucose of 100 mg/dL or more, or use of glucose-lowering medication. †Fasting triglycerides of 150 mg/dL or more. ‡Blood pressure of 130/85 mm Hg or more, or use of antihypertensive medication. §HDL cholesterol less than 40 mg/dL in men and less than 50 mg/dL in women. ¶Percentages might not add up to 100% because of rounding.

Table 1: **Patients with each metabolic risk factor in total population and treatment groups**

risk factors was similar in both groups. At baseline, dysglycaemia was present in 10512 (56%) of patients, hypertriglyceridaemia in 7085 (37%), hypertension in 9408 (50%), low HDL cholesterol in 8997 (48%), and BMI of at least 30 kg/m^2 in 6262 (33%; table 1; appendix p 2). 11183 patients (59%) had fewer than three factors, and 7741 (41%) had at least three factors (table 1).

Table 2 shows that patients with at least three metabolic risk factors were more likely to be female, reside in North America or Eastern Europe (less likely to reside in Western Europe or Asia), and to have a medical history including heart failure, previous myocardial infarction, or coronary revascularisation procedures compared with those who had fewer than three metabolic risk factors. Although statin treatment was used in almost all patients in both metabolic risk factor groups and use of evidence-based therapies was high overall, a higher percentage among those with at least three metabolic risk factors used β blockers and renin-angiotensin system inhibitors. A more extensive breakdown of baseline characteristics in subgroups with zero to five metabolic risk factors is shown in the appendix (pp 3–5).

Lipid concentrations in patients on alirocumab or placebo in metabolic risk factor groups are shown in the appendix (p 11). The concentration of LDL cholesterol was similar in patients with three or more versus those with fewer than three metabolic risk factors. As expected, patients with three or more metabolic risk factors had higher concentrations of triglyceride, non-HDL cholesterol, and apolipoprotein B, and a lower concentration of HDL cholesterol. Alirocumab had a similar lowering effect on concentrations of total cholesterol, LDL cholesterol, triglycerides, non-HDL cholesterol, and apolipoprotein B, and an increasing effect on HDL cholesterol concentration compared with placebo in both metabolic risk factor groups (appendix p 11).

	Three or more metabolic risk factors		Fewer than three metabolic risk factors	
	Alirocumab (n=3882)	Placebo (n=3859)	Alirocumab (n=5580)	Placebo (n=5603)
Age, years	58·2 (9·1)	58·3 (9·2)	58·7 (9·4)	58·9 (9·5)
Sex				
Female	1156 (30%)	1176 (31%)	1234 (22%)	1196 (21%)
Male	2726 (70%)	2683 (69%)	4346 (78%)	4407 (79%)
Race				
White	3155 (81%)	3137 (81%)	4345 (78%)	4387 (78%)
Black	112 (3%)	113 (3%)	123 (2%)	125 (2%)
Asian	403 (10%)	416 (11%)	848 (15%)	831 (15%)
Other	212 (6%)	193 (5%)	264 (5%)	260 (5%)
Region of enrolment				
North America	697 (18%)	703 (18%)	738 (13%)	733 (13%)
South America	590 (15%)	559 (15%)	703 (13%)	736 (13%)
Western Europe	701 (18%)	734 (19%)	1383 (25%)	1357 (24%)
Eastern Europe	1201 (31%)	1170 (30%)	1518 (27%)	1548 (28%)
Asia	365 (9%)	371 (10%)	785 (14%)	772 (14%)
Rest of world	328 (8%)	322 (8%)	453 (8%)	457 (8%)
Index ACS subtype				
STEMI	1294 (33%)	1203 (31%)	2007 (36%)	2032 (36%)
NSTEMI	1925 (50%)	1969 (51%)	2649 (48%)	2632 (47%)
Unstable angina	656 (17%)	682 (18%)	912 (16%)	932 (17%)
PCI or CABG for ACS index	2765 (71%)	2727 (71%)	4033 (72%)	4151 (74%)
Median time from index ACS event to randomisation, months	3·8 (2·9)	3·7 (2·7)	3·6 (2·8)	3·6 (2·7)
BMI, kg/m^2	31·1 (5·1)	31·1 (5·0)	26·7 (3·8)	26·7 (3·8)
Systolic blood pressure, mm Hg	132·3 (15·4)	131·9 (15·8)	124·3 (15·4)	123·9 (15·6)
Diastolic blood pressure, mm Hg	79·7 (9·7)	79·7 (9·9)	75·9 (9·4)	75·5 (9·4)
Heart rate, bpm	68·6 (10·3)	68·5 (10·4)	65·6 (10·1)	65·8 (10·0)
eGFR, mL/min per 1·73 m^2	78·8 (20·3)	78·8 (20·4)	80·0 (18·7)	80·5 (18·2)
Fasting glucose (mg/dL)	127·8 (49·1)	128·2 (50·2)	102·7 (29·0)	102·7 (28·7)
HbA_{1c}	6·6% (1·4)	6·6% (1·5)	5·9% (1·0)	5·9% (0·9)
Haemoglobin, g/L	141·9 (14·5)	141·9 (14·4)	142·0 (13·5)	141·9 (13·4)
Total cholesterol, mg/dL	168·9 (39·0)	169·9 (39·7)	164·8 (35·0)	164·3 (35·5)
LDL cholesterol, mg/dL	91·3 (33·2)	91·9 (33·1)	93·2 (29·6)	92·5 (29·1)

(Table 2 continues on next page)

	Three or more metabolic risk factors		Fewer than three metabolic risk factors	
	Alirocumab (n=3882)	Placebo (n=3859)	Alirocumab (n=5580)	Placebo (n=5603)
(Continued from previous page)				
HDL cholesterol, mg/dL	39·6 (9·3)	39·5 (9·2)	47·7 (11·5)	47·4 (11·6)
Triglycerides, mg/dL	191·0 (94·1)	193·7 (102·6)	118·2 (55·0)	120·4 (58·8)
Non-HDL cholesterol, mg/dL	130·7 (38·1)	129·6 (37·3)	117·1 (32·6)	117·4 (32·6)
Apolipoprotein B, g/L	0·884 (0·229)	0·878 (0·227)	0·798 (0·198)	0·797 (0·195)
High-sensitivity C-reactive protein, mg/L	4·30 (6·90)	4·28 (6·88)	3·25 (7·74)	3·13 (7·06)
Previous myocardial infarction	866 (22%)	867 (23%)	924 (17%)	976 (17%)
Previous PCI	804 (21%)	774 (20%)	822 (15%)	841 (15%)
Previous CABG	269 (7%)	255 (7%)	252 (5%)	271 (5%)
Previous stroke	165 (4%)	149 (4%)	141 (3%)	156 (3%)
Family history of premature coronary heart disease	1449 (37%)	1453 (38%)	1959 (35%)	1912 (34%)
Cerebrovascular disease	245 (6%)	225 (6%)	235 (4%)	245 (4%)
Peripheral artery disease	170 (4%)	179 (5%)	203 (4%)	207 (4%)
Hypertension	2984 (77%)	2871 (74%)	3221 (58%)	3173 (57%)
Heart failure	666 (17%)	651 (17%)	699 (13%)	798 (14%)
Diabetes	1597 (41%)	1555 (40%)	708 (13%)	785 (14%)
Cigarette smoking				
Current	915 (24%)	900 (23%)	1367 (25%)	1378 (25%)
Former	1559 (40%)	1625 (42%)	2316 (42%)	2311 (41%)
Never	1408 (36%)	1333 (35%)	1897 (34%)	1914 (34%)
Cardiovascular medication				
β blocker	3378 (87%)	3381 (88%)	4620 (83%)	4611 (82%)
Aspirin	3706 (96%)	3694 (96%)	5344 (96%)	5342 (95%)
P2Y12 inhibitor	3361 (87%)	3349 (87%)	4935 (88%)	4896 (87%)
ACE inhibitor or ARB	3177 (82%)	3158 (82%)	4179 (75%)	4202 (75%)
Statin	3773 (97%)	3755 (97%)	5457 (98%)	5480 (98%)

Data are number (%) or mean (SD). ACE=angiotensin-converting enzyme. ACS=acute coronary syndrome. ARB=angiotensin receptor blocker. CABG=coronary artery bypass grafting. CHD=coronary heart disease. eGFR=estimated glomerular filtration rate. PCI=percutaneous coronary intervention. STEMI=ST-elevated myocardial infarction. NSTEMI=non-ST-elevated myocardial infarction.

Table 2: **Baseline characteristics in total population and treatment groups according to presence of at least three or fewer than three metabolic risk factors**

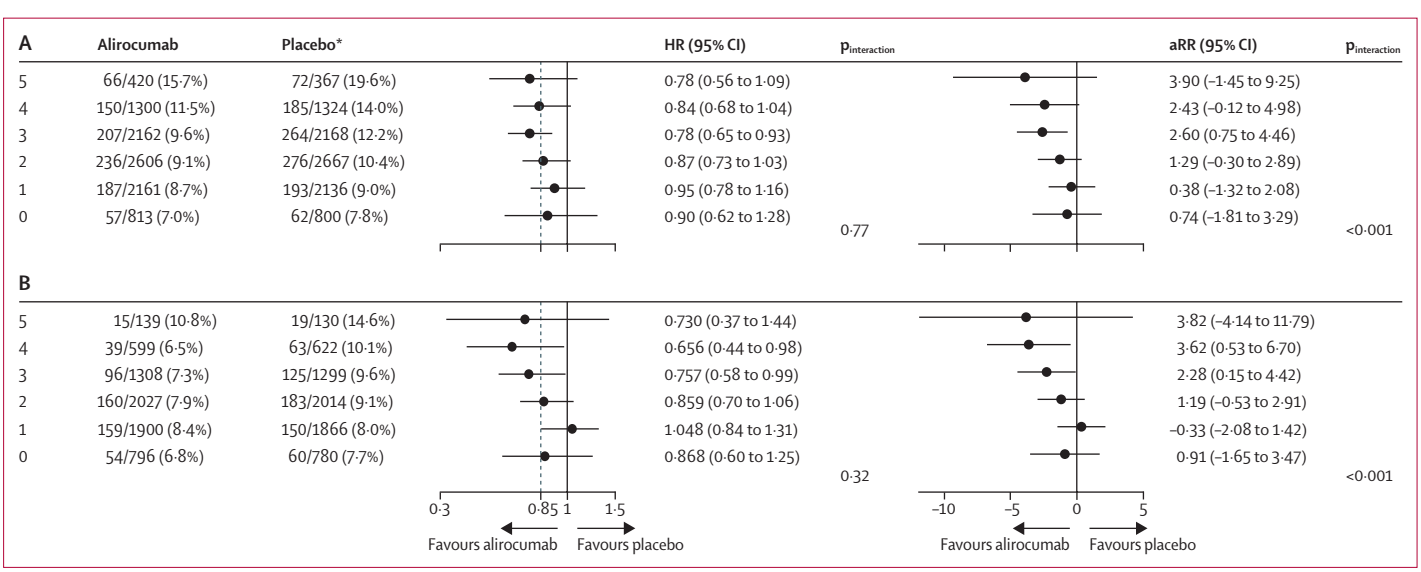

Figure 2: **Effect of alirocumab on MACE in subgroups by number of metabolic risk factors in (A) the overall study population and (B) after exclusion of patients with diabetes**
aRR=absolute risk reduction. MACE=major adverse cardiovascular event. *HR in placebo group 1·18 (95% CI 1·13 to 1·24) per incremental risk factor.

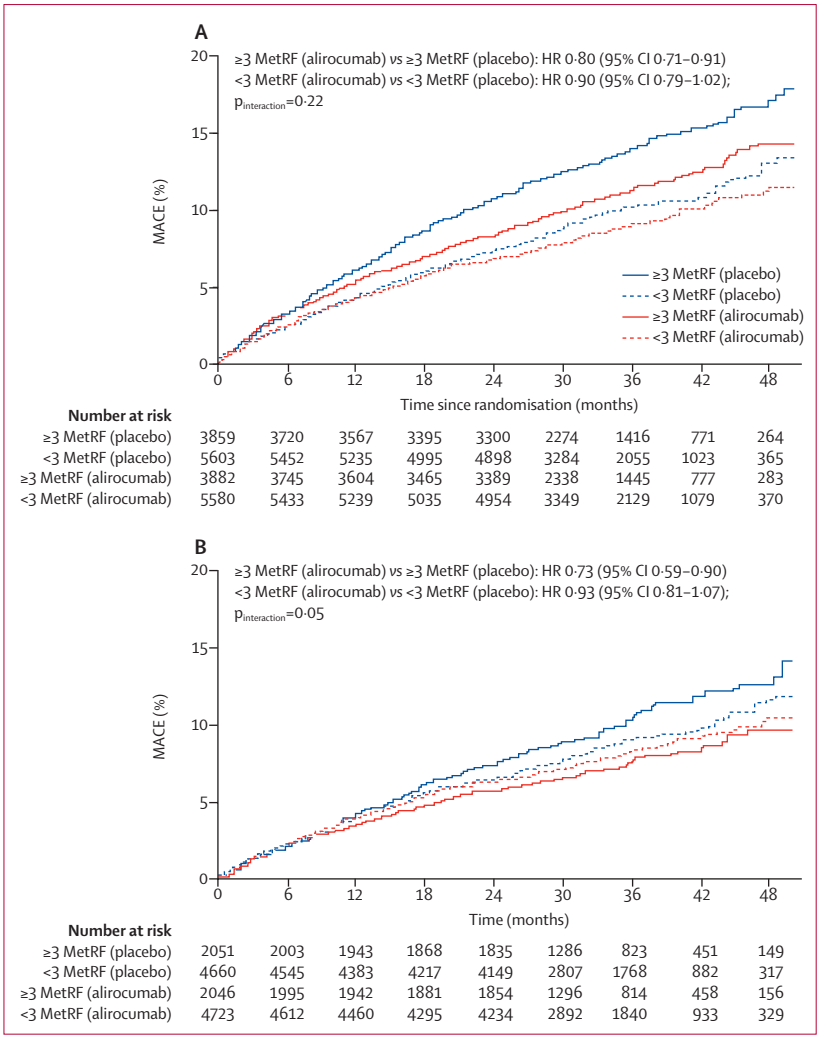

Figure 3: **Kaplan-Meier curves for MACE and effect of alirocumab in subgroups with at least three or fewer than three metabolic risk factors in (A) the overall study population and (B) after exclusion of patients with diabetes**

HR=hazard ratio. MACE=major adverse cardiovascular event. MetRF=metabolic risk factor.

In the placebo group, incidence of MACE increased monotonically with each metabolic risk factor from 7·8% (no risk factors) to 19·6% (five risk factors; overall HR 1·18, 95% CI 1·13–1·24 per metabolic risk factor; figure 2A). The relative risk of MACE in the placebo group associated with the presence of each of the five metabolic risk factors is in the appendix (p 6). Dysglycaemia had the strongest association with risk of MACE (HR 1·43, 95% CI 1·26–1·62), followed by hypertension (HR 1·31, 95% CI 1·16–1·49). In the placebo group, patients with at least three metabolic risk factors (corresponding with presence of metabolic syndrome) had a greater risk of MACE than those with fewer than three risk factors (521 [14%] of 3859 *vs* 531 [10%] of 5603; HR 1·43, 95% CI 1·27–1·62; figure 3A, 4A).

Alirocumab decreased the relative risk of MACE consistently across categories defined by the number of metabolic risk factors ($p_{interaction}$=0·77), but absolute risk reduction (aRR) increased per incremental metabolic risk factor from 0·74% (95% CI –1·81 to 3·29) with 0 risk factors to 3·90% (–1·45 to 9·25) with five risk factors ($p_{interaction}$<0·001; figure 2A; appendix pp 12–16). Similarly, relative reductions in MACE by alirocumab were consistent in patients with at least three versus fewer than three metabolic risk factors (HR 0·80, 95% CI 0·71–0·91 *vs* HR 0·90, 0·79–1·02; $p_{interaction}$=0·22; figures 3A, 4A). However, aRR with alirocumab was greater in patients with at least three metabolic factors than in those with fewer than three factors (aRR 2·60%, 95% CI 1·15–4·06 *vs* aRR 0·87%, –0·19 to 1·94; $p_{interaction}$=0·08; figure 4A). The corresponding number needed to treat for a median of 2·8 years to avoid one primary endpoint event was 38 for patients with at least three metabolic risk factors compared with 115 for patients with fewer than three factors. The effect of alirocumab on MACE remained similar after inclusion of baseline concentration of LDL cholesterol into the model and in on-treatment analysis (appendix pp 17, 18).

An analysis excluding patients with diabetes yielded qualitatively similar results as in the full study population. Incidence of MACE in the placebo groups increased from 7·7% (no metabolic risk factors) to 14·6% (five factors; figure 2B). Alirocumab consistently decreased relative risk of MACE across subgroups defined by ordinal number of metabolic risk factors ($p_{interaction}$=0·32); however, aRR increased with increasing number of metabolic risk factors from none to five (aRR 0·91, 95% CI –1·65 to 3·47 *vs* aRR 3·82, –4·14 to 11·79; $p_{interaction}$<0·001; figure 2B; appendix pp 12–15). In the comparison of subgroups without diabetes who had at least three metabolic risk factors versus fewer than three factors (corresponding with the presence or absence of metabolic syndrome), there was an interaction of the effect of alirocumab on MACE: benefit appeared more pronounced in patients with at least three metabolic risk factors (HR 0·73, 95% CI 0·59–0·90) than in patients with fewer than three metabolic risk factors (HR 0·93, 95% CI 0·81–1·07; $p_{interaction}$=0·05; figures 3B, 4B). Again, the effect of alirocumab on MACE was minimally affected by the inclusion of baseline concentration of LDL cholesterol into the model and in the treatment analysis (appendix pp 17, 18). aRR with alirocumab was higher in patients with at least three metabolic risk factors than in those with fewer than three factors (aRR 2·76%, 95% CI 1·04–4·49 *vs* aRR 0·54%, 95% CI –0·57 to 1·64; $p_{interaction}$=0·04; figure 4B). The corresponding number needed to treat for a median of 2·8 years to avoid one primary endpoint event was 36 for patients with at least three factors versus 185 for patients with fewer than three factors.

Overall alirocumab was well tolerated with incidence of serious adverse events and treatment-emergent adverse events similar to placebo, except for injection site reactions which were more frequent with alirocumab. Treatment

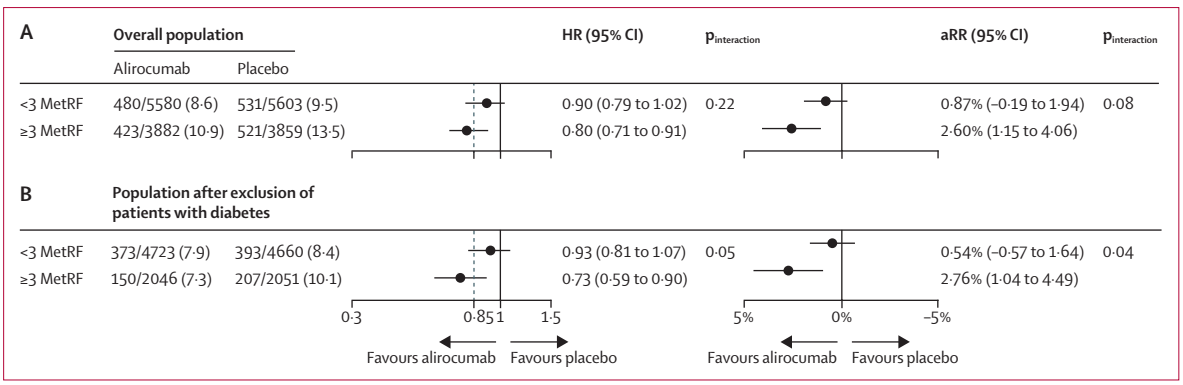

Figure 4: **Effect of alirocumab on MACE in subgroups according to presence of at least three and fewer than three metabolic risk factors in (A) the overall study population and (B) after exclusion of patients with diabetes**

aRR=absolute risk reduction. HR=hazard ratio. MACE=major adverse cardiovascular event. MetRF=metabolic risk factor.

emergent adverse events were more common in the group with at least three metabolic risk factors compared to those with fewer than three metabolic risk factors. Incidence of type 2 diabetes in patients without diabetes at baseline was higher in the group with at least three factors than those with fewer than three metabolic risk factors, and in patients with prediabetes at baseline than in those with normoglycaemia (appendix 7). However, the incidence of the new diabetes onset in each subgroup was similar in the alirocumab and placebo groups (appendix p 8).

Discussion

There are three key findings from this post-hoc analysis. First, in the ODDESSY OUTCOMES trial, 91·5% of patients with recent acute coronary syndrome had at least one metabolic risk factor and 68·8% had two or more. Second, despite high-intensity or maximum-tolerated statin therapy, metabolic risk factors (except low concentration of HDL cholesterol) remained associated with increased risk of MACE, and accumulation of metabolic risk factors in patients with past acute coronary syndrome substantially increased risk for further cardiovascular events. Third, alirocumab reduced risk of MACE irrespective of the number of metabolic risk factors, but the absolute benefit increased with the number of risk factors. aRR, and potentially the relative risk reduction, appeared more pronounced in patients with at least three metabolic risk factors (corresponding with the presence of metabolic syndrome) than in those with fewer than three factors, especially in patients without diabetes.

The accumulation of metabolic risk factors and associated metabolic syndrome are known risk factors for MACE.[1–4] High-intensity statin therapy reduces risk in this population.[8,16] Our analysis indicates that accumulation of metabolic risk factors remains associated with increased risk of MACE after acute coronary syndrome, even when patients received evidence-based therapy, including high-intensity or maximum-tolerated statin treatment, use of β blockers, renin-angiotensin system blockers, dual antiplatelet therapy, and coronary revascularisation procedures. Moreover, in the placebo group, each metabolic risk factor except low HDL cholesterol (ie, dysglycaemia, hypertriglyceridaemia, hypertension, and BMI ≥30 kg/m²) was significantly associated with increased risk of MACE. The absence of association of risk after acute coronary syndrome with HDL cholesterol concentration was also observed in an analysis of the dal-OUTCOMES trial, comparing dalcetrapib with placebo in patients with acute coronary syndrome.[17]

Reduction of MACE associated with alirocumab in patients with and without at least three metabolic risk factors in our study was in accordance with other analyses from the ODYSSEY OUTCOMES trial, demonstrating consistent reduction in MACE across various subgroups, with more pronounced aRR in patients at higher risk.[9,12,18–23] Of particular importance was the observation in the ODYSSEY OUTCOMES trial of similar risk of MACE in patients with baseline normoglycaemia and prediabetes compared with markedly increased risk in patients with diabetes.[12] Because dysglycaemia comprises patients with prediabetes or diabetes, we assessed the effect of metabolic risk factors other than diabetes on risk and risk reduction with alirocumab. In patients without diabetes, the risk of MACE remained strongly associated with a larger ordinal number of metabolic risk factors and with at least three factors versus fewer than three factors. Relative reduction in risk of MACE with alirocumab was more pronounced in the subgroup with at least three metabolic risk factors. Importantly, the subgroup of patients without diabetes with at least three factors had more than five-times greater aRR with alirocumab than did the subgroup without diabetes and fewer than three risk factors (2·76% *vs* 0·54%). This suggests that in patients without diabetes, the accumulation of more metabolic risk factors helps to identify individuals in whom a greater absolute benefit of alirocumab might be expected. The risk of recurrent cardiovascular events in patients with at least three

metabolic risk factors remains high despite intensive lipid-lowering therapy with a statin and PCSK9 inhibitor and highly prevalent use of other evidence-based treatments, which indicates a need for additional therapies to improve the prognosis of these patients.

Our results are consistent with a report from the FOURIER trial[11] showing that patients with chronic atherosclerotic cardiovascular disease and metabolic syndrome remain at higher risk of future cardiovascular events despite statin therapy, and that treatment with the PCSK9 inhibitor evolocumab is associated with a reduction in cardiovascular events regardless of the presence or absence of diabetes.

In the ODYSSEY OUTCOMES trial, waist circumference (the criterion for abdominal obesity required for the diagnosis of metabolic syndrome) was not recorded; therefore, patients with strictly defined metabolic syndrome[1] could not be identified. To mitigate this limitation, the presence of obesity was evaluated according to BMI (≥30 kg/m²), another recognised factor associated with increased risk.[14,24–26] and incorporated in some definitions of metabolic syndrome.[27] In clinical practice, weight is measured more commonly than waist circumference.[28] Thus, the present analytical framework might have practical relevance in the decision to treat with a PCSK9 inhibitor. The absence of ethnic-specific thresholds for BMI is a potential source of bias. Baseline lipid concentrations including triglyceride concentrations in the ODYSSEY OUTCOMES trial were measured in patients who already received high-intensity or maximally tolerated dose of statin. Because statins generally reduce triglycerides, the true prevalence of hypertriglyceridaemia according to the definition of metabolic syndrome[1] was probably higher than observed in the present analysis. Median follow-up in the ODYSSEY OUTCOMES trial was 2·8 years. Longer observation might have revealed greater differences in risk between metabolic risk factor groups and greater risk reduction with alirocumab, as has been shown in a subset of the overall study cohort eligible for at least 3 years of observation.[29,30] The safety observations from the present analysis should also be put in the context of a brief follow-up. Although we focused on metabolic risk factors, recognising that other clinical characteristics affect risk of MACE following acute coronary syndrome and that other high-risk subgroups can be defined by those criteria is important.[20–22,31] Statistical inference should be considered in the context of the fact that the trial was not powered for the current subgroup analyses and that there was no allowance for multiplicity of assessments.

Metabolic risk factors remain important factors for subsequent MACE despite high-intensity or maximum-tolerated statin therapy in patients with recent acute coronary syndrome. Alirocumab treatment resulted in a consistent relative reduction in the risk of MACE in patients with or without accumulation of multiple metabolic risk factors, although absolute risk reduction was more pronounced with a greater number of risk factors. Both the relative and absolute effects of alirocumab were more pronounced in patients with at least three factors. Patients with multiple metabolic risk factors, including those without diabetes, might derive a large absolute benefit of alirocumab treatment after acute coronary syndrome. Counting the number of metabolic risk factors could help clinicians to identify patients to be considered for PCSK9 inhibitor therapy after acute coronary syndrome.

Contributors

PO, GS, and GGS conceived and designed the study. PGS and GGS obtained funding and supervised the work. PO, PGS, DLB, VAB, TC, RD, SGG, JWJ, YK, HDW, YH, and GGS acquired, analysed, or interpreted the data. PO drafted the manuscript. YP did the statistical analysis. All authors critically revised the manuscript for important intellectual content. PO, PGS, GGS, and MSz developed the trial protocol and statistical analysis plan in conjunction with the other members of the executive steering committee, which includes representatives of the funders (appendix p 19). PO, PGS, and GGS take responsibility for the integrity of data and accuracy of the data analysis. All authors had full access to all the data in the study and final responsibility for the decision to submit for publication. PO, PGS, GGS and YP have accessed and verified the data.

Declaration of interests

PO reports research grants or speaker and consulting honoraria (or both) from Amgen, AstraZeneca, Edwards, Getinge, Novartis, Promedica, Promedcs, Sanofi, and Servier. PGS reports grants, personal fees, and non-financial support from Sanofi; grants and personal fees from Amarin, Servier and Bayer; personal fees from Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Idorsia, Pfizer, and Novartis; and has patent use of alirocumab to reduce risk after ACS (royalties to Sanofi) pending. YP and MSc are employees of Sanofi. DLB reports grants from Sanofi, Regeneron Pharmaceuticals, Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Sanofi Aventis, The Medicines Company, Forest Laboratories/AstraZeneca, Ischemix, Amgen, Lilly, Chiesi, Ironwood, Abbott, Idorsia, Synaptic, Fractyl, Afimmune, Ferring Pharmaceuticals, Lexicon, Contego Medical, Owkin, HLS Therapeutics, 89Bio, and Garmin; is a Board Director at Boston Scientific and Boston VA Research Institute; receives unfunded research collaboration from Merck, FlowCo, and Takeda; is a site co-investigator for Svelte, CSI, Boston Scientific, Philips, St Jude Medical (Abbott), and Biotronik; is on the Advisory Board for Medscape Cardiology and Regado Biosciences; receives a grant from Roche and Pfizer; is a Deputy Editor for Clinical Cardiology; is a Chair at VA; receives grants from and is on the Scientific Advisory Board at Cardax, PLx Pharma, PhaseBio, Novo Nordisk, Cereno Scientific, CellProthera, MyoKardia/BMS, Janssen, Novartis, and NirvaMed; receives personal fees from Duke Clinical Research Institute, Mayo Clinic, Population Health Research Institute, Belvoir Publications, Slack Publications, WebMD, Elsevier, HMP Global, Harvard Clinical Research Institute (Baim Institute for Clinical Research), Journal of the American College of Cardiology, Cleveland Clinic, Mount Sinai School of Medicine, TobeSoft, Bayer, Medtelligence/ReachMD, CSL Behring, MJH Life Sciences, Level Ex, K2P, and the Canadian Medical and Surgical Knowledge Translation Research Group; reports personal fees and non-financial support from, and is a Senior Associate Editor, Chair, and Trustee at American College of Cardiology; reports personal fees and non-financial support from the Society of Cardiovascular Patient Care; non-financial support from American Heart Association; and grants, personal fees, and editorial support services from Boehringer Ingelheim. VAB reports grant support from Sanofi, Regeneron Pharmaceuticals, Astra Zeneca, DalCor, Esperion, and Novartis; consulting fees from Pfizer; honoraria from Medscape; and fees for participating on a Data Safety Monitoring Board or Advisory Board from the National Institutes of Health. RD reports research grants from Sanofi, DalCor Pharmaceuticals, Population Health Research Institute, Duke Clinical Research Institute, the TIMI group, Amgen, Cirius, Montreal Health Innovations Coordinating Center, and Lepetit, and personal fees, as a member of the Executive Steering Committee, from Amgen and Cirius.

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Data sharing

Individual participant data are not available. The study protocol and statistical analysis plan have been previously published.[9]

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