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FASTTRACK CLINICAL RESEARCH
Lipids

Effects of alirocumab on types of myocardial infarction: insights from the ODYSSEY OUTCOMES trial

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Aims The third Universal Definition of Myocardial Infarction (MI) Task Force classified MIs into five types: Type 1, spontaneous; Type 2, related to oxygen supply/demand imbalance; Type 3, fatal without ascertainment of cardiac biomarkers; Type 4, related to percutaneous coronary intervention; and Type 5, related to coronary artery bypass surgery. Low-density lipoprotein cholesterol (LDL-C) reduction with statins and proprotein convertase subtilisin–kexin Type 9 (PCSK9) inhibitors reduces risk of MI, but less is known about effects on types of MI. ODYSSEY OUTCOMES compared the PCSK9 inhibitor alirocumab with placebo in 18 924 patients with recent acute coronary syndrome (ACS) and elevated LDL-C (≥1.8 mmol/L) despite intensive statin therapy. In a pre-specified analysis, we assessed the effects of alirocumab on types of MI.

Methods and results Median follow-up was 2.8 years. Myocardial infarction types were prospectively adjudicated and classified. Of 1860 total MIs, 1223 (65.8%) were adjudicated as Type 1, 386 (20.8%) as Type 2, and 244 (13.1%) as Type 4. Few events were Type 3 ($n = 2$) or Type 5 ($n = 5$). Alirocumab reduced first MIs [hazard ratio (HR) 0.85, 95% confidence interval (CI) 0.77–0.95; $P = 0.003$], with reductions in both Type 1 (HR 0.87, 95% CI 0.77–0.99; $P = 0.032$) and Type 2 (0.77, 0.61–0.97; $P = 0.025$), but not Type 4 MI.

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Conclusion After ACS, alirocumab added to intensive statin therapy favourably impacted on Type 1 and 2 MIs. The data indicate for the first time that a lipid-lowering therapy can attenuate the risk of Type 2 MI. Low-density lipoprotein cholesterol reduction below levels achievable with statins is an effective preventive strategy for both MI types.

Keywords Alirocumab • Prevention • MI types • Mortality

Introduction

Lowering of low-density lipoprotein cholesterol (LDL-C) with statins by 1 mmol/L (39 mg/L) is associated with an approximate 20% reduction in the rate of myocardial infarction (MI).[1] The proprotein convertase subtilisin–kexin Type 9 (PCSK9) inhibitors evolocumab and alirocumab reduce LDL-C by >1 mmol/L below statin-treated levels and further reduce the risk of MI among patients treated with statins.[2,3]

In 2007, the Universal Definition of MI Task Force introduced a classification of five types of MI based on presumptive mechanisms, including Type 1 due to spontaneous plaque rupture or fissuring with thrombus, Type 2 due to myocardial supply and/or demand imbalance, Type 3 with cardiac death suggestive of MI without biomarker elevation, Type 4 related to percutaneous coronary intervention (PCI), and Type 5 related to coronary artery bypass grafting (CABG).[4] In the FOURIER trial,[5] which randomized stable patients with a history of MI, stroke, or peripheral vascular disease, evolocumab reduced the number of MIs vs. placebo. Evolocumab reduced the number of Type 1 and Type 4 MIs, but not Type 2 MIs.

In this pre-specified analysis from the ODYSSEY OUTCOMES trial, we studied the occurrence and outcomes of the different types of MIs in patients with recent acute coronary syndrome (ACS) and elevated LDL-C despite intensive statin therapy who were randomized to receive alirocumab or placebo and followed for cardiovascular outcomes.

Methods

The study design[6] and primary results[3] have been published. Qualifying patients were ≥40 years, provided written informed consent, had been hospitalized with ACS (acute MI or unstable angina) 1–12 months before randomization, and had an LDL-C level ≥1.81 mmol/L (70 mg/dL), non-high-density lipoprotein cholesterol (non-HDL-C) ≥2.59 mmol/L (100 mg/dL), or apolipoprotein B ≥2.07 mmol/L (80 mg/dL), measured after ≥2 weeks of stable treatment with atorvastatin 40–80 mg daily, rosuvastatin 20–40 mg daily, or the maximum-tolerated dose of either statin (including no statin in case of documented intolerance). Randomization (1:1) to treatment with alirocumab 75 mg or matching placebo, stratified by country, was performed, with 18 924 patients meeting the entry criteria. Study medication was given by subcutaneous injection every 2 weeks. The dose of alirocumab was adjusted under blinded conditions to target an LDL-C level of 0.6–1.3 mmol/L (details on the dosing strategy are provided in Supplementary material online, *Text S1*).

The primary composite endpoint was death due to coronary heart disease, non-fatal MI, fatal and non-fatal ischaemic stroke, or unstable angina requiring hospitalization. The incidence of MI was defined as the time to first occurrence of MI. In a pre-specified analysis, the types of MI were defined according to the Third Universal Definition[7] and were adjudicated by a central clinical events committee blinded to the treatment assignment and lipid levels. Biomarker measurements were not mandated after PCI or CABG. The definitions of Type 1 and Type 2 MIs are detailed in Supplementary material online, *Tables S1* and *S2*. Predictors of Type 1 and Type 2 MI and total mortality after MI were assessed. Silent MIs were not included.

Statistical analysis

Continuous variables are expressed as median (quartile 1–quartile 3) and categorical variables as count (percentage). Comparisons of baseline characteristics grouped by type of first MI during follow-up (none, Type 1, or Type 2) were by the Wilcoxon rank-sum tests for continuous variables and the χ^2 and Fisher's exact tests (where possible) for categorical variables. For all analyses, *P*-values <0.05, two-tailed, were considered statistically significant, with no adjustment for multiple testing.

The treatment effect on time to first MI of any type and time to first Type 1, 2, or 4 MI was initially assessed in Cox proportional hazard models, with stratification by geographic region; competing risk analyses with all-cause death as the competing event were performed as sensitivity analyses.[8] Multivariable Cox regression models of baseline demographics and clinical characteristics (candidate variables are listed in Supplementary material online, *Tables S3* and *S4*) to predict Type 1 or Type 2 MI were then determined by stepwise selection, with *P*-value <0.05 for model entry or exit. Models to estimate the associations between all-cause and cause-specific (cardiovascular or non-cardiovascular) death and incident Type 1 or Type 2 MI as a time-varying covariate were determined, with adjustment for treatment assignment and baseline covariates previously determined to be prognostic for survival.[9] The effects of treatment assignment on death before or after a Type 1 or Type 2 MI were determined in separate Cox regression models for each MI type by interactions between incident MI as a time-varying covariate and treatment, with stratification by geographical region. For a given patient, an MI that occurred on the same day as death was excluded from the analysis. Sensitivity analyses of time to MI included events on the same day as death.

All analyses were conducted according to intention-to-treat, including all patients and events from randomization to common study end date (11 November 2017). Unless otherwise indicated, analyses were pre-specified before unblinding of the study database. Analyses were performed in SAS 9.4 and S + 8.2.

Results

A total of 18 924 patients were randomized at 1315 sites in 57 countries, with 9462 patients assigned to alirocumab and 9462 patients to placebo. Median follow-up was 2.8 (2.3–3.4) years. A total of 1860 post-randomization MIs occurred in 1383 (7.3%) patients. Of these, 991 patients had a total of 1223 Type 1 MIs, 287 patients had 386 Type 2 MIs, 225 patients had 244 Type 4 MIs, and a remaining 7 patients had Type 3 or Type 5 MIs. The baseline characteristics of the

Table 1 Selected baseline characteristics of patients with Type 1 and 2 myocardial infarctions

	(A) No event (*N* = 17 719)	(B) First event = Type 1 (*N* = 963)	(C) First event = Type 2 (*N* = 242)	*P*-value for (A) vs. (B) vs. (C)[a]	*P*-value for (B) vs. (C)[b]
Age (years)	58 (52–65)	59 (52–66)	65 (59–72)	<0.0001	<0.0001
Women	4416 (24.9)	267 (27.7)	79 (32.6)	0.004	NS
Race				<0.0001	NS
White	14 039 (79.2)	788 (81.8)	197 (81.4)		
Asian	2390 (13.5)	86 (8.9)	22 (9.1)		
Black	411 (2.3)	44 (4.6)	18 (7.4)		
Other	879 (5.0)	45 (4.7)	5 (2.1)		
Region of enrolment				<0.0001	0.029
Western Europe	3894 (22.0)	232 (24.1)	49 (20.2)		
Eastern Europe	5185 (29.3)	199 (20.7)	53 (21.9)		
North America	2555 (14.4)	234 (24.3)	82 (33.9)		
South America	2469 (13.9)	103 (10.7)	16 (6.6)		
Asia	2194 (12.4)	80 (8.3)	19 (7.9)		
Rest of world	1422 (8.0)	115 (11.9)	23 (9.5)		
Medical history before index ACS					
Hypertension	11 277 (63.6)	758 (78.1)	214 (88.4)	<0.0001	0.0005
Diabetes	4924 (27.8)	404 (42.0)	116 (47.9)	<0.0001	NS
Current smoker	4261 (24.0)	252 (26.2)	47 (19.4)	NS	0.0305
MI	3174 (17.9)	373 (38.7)	92 (38.0)	<0.0001	NS
PCI	2805 (15.8)	347 (36.0)	89 (36.8)	<0.0001	NS
CABG	844 (4.8)	162 (16.8)	41 (16.9)	<0.0001	NS
Stroke	541 (3.1)	55 (5.7)	15 (6.2)	<0.0001	NS
Malignant disease	475 (2.7)	36 (3.7)	21 (8.7)	<0.0001	0.0033
COPD	637 (3.6)	68 (7.1)	41 (16.9)	<0.0001	<0.0001
Peripheral artery disease	628 (3.5)	89 (9.2)	42 (17.4)	<0.0001	0.0007
Heart failure	2542 (14.3)	195 (20.2)	78 (32.2)	<0.0001	0.0001
Index ACS				<0.0001	NS
NSTEMI	8443 (47.7)	587 (61.0)	145 (59.9)		
STEMI	6209 (35.1)	259 (26.9)	68 (28.1)		
Unstable angina	3037 (17.2)	116 (12.1)	29 (12.0)		
PCI or CABG for index ACS	12 886 (72.7)	630 (65.4)	161 (66.5)	<0.0001	NS
GFR (mL/min/1.73 m^2)	79 (68–90)	76 (63–88)	67 (54–84)	<0.0001	<0.0001
GFR <60 mL/min/1.73 m^2	2256 (12.7)	199 (20.7)	84 (34.7)	<0.0001	<0.0001
Time from index ACS to randomization (months)	2.6 (1.7–4.4)	2.5 (1.7–3.9)	2.5 (1.7–4.2)	0.037	NS
Body mass index (kg/m^2)	28 (25–31)	29 (26–32)	29 (26–33)	<0.0001	NS
LDL-C (mg/dL)	86 (73–103)	91 (76–113)	91 (75–109)	<0.0001	NS
LDL-C ≥100 mg/dL	5177 (29.2)	365 (37.9)	87 (36.0)	<0.0001	NS
Triglycerides (mg/dL)	128 (94–181)	138 (100–201)	130 (90–178)	<0.0001	0.012
Lipoprotein(a) (mg/dL)	20.8 (6.6–59.0)	25.4 (7.3–70.0)	34.9 (9.3–76.8)	<0.0001	NS
Randomized to placebo	8808 (49.7)	512 (53.2)	142 (58.7)	0.003	NS

Data are represented as median (quartile 1–quartile 3) or *n* (%). Additional information on baseline characteristics is presented in Supplementary material online, *Table S5*.
[a]Rank-based tests, comparing A vs. B vs. C.
[b]Rank-based test, comparing B vs. C.
ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NS, not significant; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

patients without an MI, and with Type 1 or Type 2 MI, are detailed in *Table 1* and Supplementary material online, *Table S5*. Compared to patients without an MI, those with an MI were older and the proportion of women was greater. Compared to patients with a first post-randomization event of Type 1 MI, patients with a first post-randomization event of Type 2 MI were older, more likely to be from North America, to have a lower glomerular filtration rate, and were more likely to have a history of hypertension, heart failure, chronic

Table 2 Types of myocardial infarctions and effects of alirocumab

	Alirocumab		Placebo		Treatment HR (95% CI)[a]	*P*-value[a]
	Patients with MI,[a] *n* (%)	Total MIs	Patients with MI,[a] *n* (%)	Total MIs		
Any MI	639 (6.8)	866	744 (7.9)	994	0.85 (0.77–0.95)	0.003
Universal classification						
Type 1[b]	463 (4.9)	560	528 (5.6)	663	0.87 (0.77–0.99)	0.032
Type 2[c]	125 (1.3)	180	162 (1.7)	206	0.77 (0.61–0.97)	0.025
Type 3[d]	2 (<0.1)	2	0	0	–	–
Type 4A[e]	22 (0.2)	23	28 (0.3)	29	0.94 (0.72–1.22)[f]	0.62
Type 4B[g]	50 (0.5)	55	46 (0.5)	49		
Type 4C[h]	37 (0.4)	44	42 (0.4)	44		
Type 5[i]	2 (<0.1)	2	3 (<0.1)	3	–	–
ECG classification						
NSTEMI	437 (4.6)	576	529 (5.6)	692	0.82 (0.72–0.93)	0.002
STEMI	92 (0.5)	96	109 (1.2)	116	0.84 (0.64–1.11)	0.22
ECG not interpretable or not available	161 (1.7)	194	162 (1.7)	186	1.01 (0.81–1.25)	0.96
Q-wave classification						
Q-wave	52 (0.5)	52	71 (0.9)	73	0.73 (0.51–1.04)	0.08
Non-Q-wave	483 (5.1)	634	560 (5.9)	725	0.86 (0.76–0.97)	0.013
ECG not interpretable or available	146 (1.5)	180	165 (1.7)	196	0.88 (0.71–1.10)	0.27

[a]Analysis of time to first Type 1, Type 2, or Type 4A, 4B, 4C MI by Cox proportional hazards models, stratified by geographical region.
[b]Spontaneous.
[c]Supply/demand imbalance.
[d]Cardiac death suggestive of MI without increased biomarkers.
[e]Peri-percutaneous coronary intervention.
[f]Correspond to any Type 4 MI.
[g]Stent thrombosis.
[h]Restenosis.
[i]Peri-coronary artery bypass grafting.
CI, confidence interval; ECG, electrocardiogram; HR, hazard ratio; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

obstructive pulmonary disease, peripheral artery disease, or malignant disease, and were less likely to be smokers. Baseline LDL-C, lipoprotein(a), and high-sensitivity C-reactive protein levels were higher in patients with than without MI. Baseline LDL-C, lipoprotein(a), and high-sensitivity C-reactive protein did not differ between those with Type 1 or Type 2 MI. Triglyceride levels were higher at baseline in patients who had MIs compared with those not having MIs, and patients with Type 2 MIs had lower triglyceride levels than patients with Type 1 MIs ($P = 0.012$).

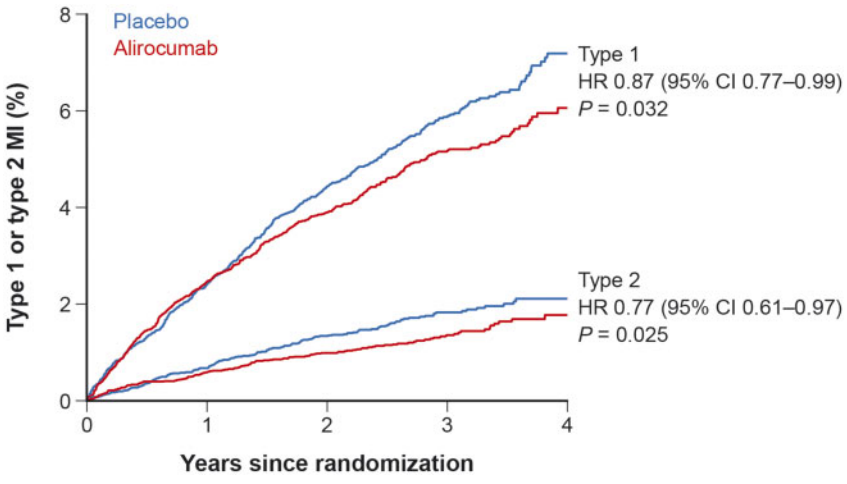
Mean LDL-C levels were reduced by 54% with alirocumab vs. placebo, from 2.39 mmol/L (92 mg/dL) to 1.24 mmol/L (48 mg/dL), at 12 months. Alirocumab reduced the occurrence of post-randomization MI vs. placebo [6.8% vs. 7.9%; hazard ratio (HR) 0.85, 95% confidence interval (CI) 0.77–0.95; $P = 0.003$]. Both Type 1 MIs ($P = 0.032$) and Type 2 MIs ($P = 0.025$) were reduced with alirocumab (*Table 2*). There was no apparent effect on Type 3, 4, or 5 MIs.

Take home figure shows the Kaplan–Meier curve of the occurrence of Type 1 and Type 2 MIs after randomization by treatment group. A benefit of alirocumab treatment on Type 1 MI was apparent after year 1 and increased after year 2, whereas the treatment effect on Type 2 MI appeared more constant over time (*Figure 1*). These observations are supported by *post hoc* model results: allowing the treatment HR to change for each of the time intervals indicated in *Figure 1* fit the data better than a constant HR for Type 1 MI ($P = 0.05$) but not for Type 2 MI ($P = 0.34$).

Most MIs (82.7%) were non-ST-segment elevation MI (non-STEMI) and were significantly reduced with alirocumab (HR 0.82, 95% CI 0.72–0.93; $P = 0.002$). There were consistent effects on STEMIs. Q-wave MIs were identified in a minority (10.5%) of patients with interpretable electrocardiograms (ECGs), with consistent effects of alirocumab for Q-wave and non-Q-wave MIs (*Table 2*).

A sensitivity analysis including patients who died on the day of MI ($n = 7$ alirocumab; $n = 11$ placebo) showed similar effects of alirocumab on reducing both Type 1 and Type 2 MIs (Supplementary material online, *Table S6*).

Supplementary material online, *Table S7* shows the effect of alirocumab on biomarker levels, predominantly cardiac troponin (92%) and high-sensitivity troponins (29%), at various cut-points. Alirocumab treatment was associated with no apparent reduction in smaller MIs (with peak biomarker levels <3 times the upper limit of normal) but with large reductions in larger MIs as defined by peak biomarker value.



Take home figure Kaplan–Meier curves for the first occurrence of Type 1 and Type 2 myocardial infarctions and the effects of alirocumab over time. MI, myocardial infarction.

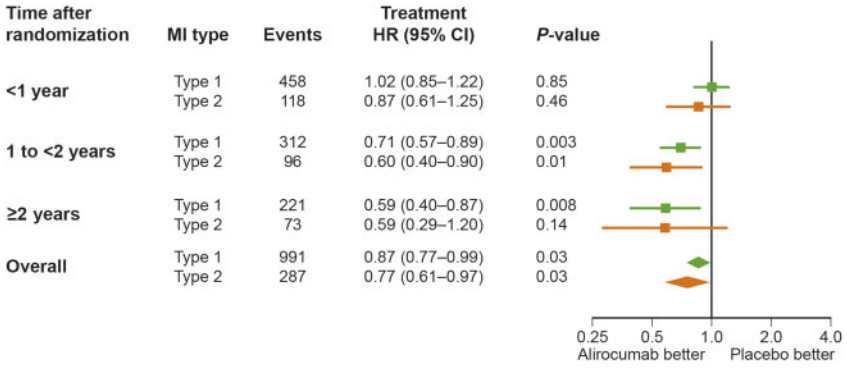


Figure 1 Treatment effect of alirocumab categorized according to the time between randomization and the first occurrence of myocardial infarction. CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

Predictors of Type 1 and Type 2 myocardial infarction

Tables 3 and *4* and Supplementary material online, *Figure S1* show the independent predictors for Type 1 and Type 2 MIs, respectively. Most of the factors predicting occurrence of Type 1 or Type 2 MI were similar. Of note, baseline LDL-C was an independent predictor of occurrence of Type 1 but not Type 2 MI. Similarly, previous CABG, revascularization at the time of the index ACS event, current smoking, and previous stroke were significant predictors of occurrence of subsequent Type 1 MI but not Type 2 MI. Conversely, age (by discrete categories), history of chronic obstructive pulmonary disease, and lower baseline HDL-C levels were significant predictors of Type 2 but not Type 1 MI. Race, history of diabetes, hypertension, and peripheral artery disease were risk factors for both types of MI. Randomization to alirocumab was associated with lower risk of both types of MI.

Mortality in patients with Type 1 or Type 2 myocardial infarction

During 1.6 (0.8–2.4) and 1.3 (0.5–2.3) years of follow-up following Type 1 and Type 2 MI, respectively, mortality following the occurrence of Type 2 MI ($n = 73$, 25.4%) was more than double that of patients with Type 1 MI ($n = 118$, 11.9%). In *post hoc* analyses, rates of death were 10.2% with alirocumab vs. 13.4% with placebo (HR 0.69, 95% CI 0.48–1.00) following Type 1 MI and 24.8% vs. 25.9% (HR 0.98, 95% CI 0.62–1.56) following Type 2 MI.

Discussion

After an index ACS, there is a substantial incidence of recurrent MI. In the placebo group of the ODYSSEY OUTCOMES trial, this incidence was 7.9% over a median follow-up of 2.8 years, despite

Table 3 Independent predictors of Type 1 myocardial infarction following initial acute coronary syndrome

Baseline characteristics	HR (95% CI)	*P*-value
Medical history		
Peripheral artery disease	1.61 (1.29–2.00)	<0.0001
Percutaneous coronary intervention	1.51 (1.27–1.79)	<0.0001
CABG	1.74 (1.45–2.09)	<0.0001
Diabetes	1.57 (1.38–1.79)	<0.0001
Current smoker	1.23 (1.06–1.42)	0.006
Hypertension	1.54 (1.31–1.81)	<0.0001
MI	1.46 (1.23–1.74)	<0.0001
Heart failure	1.33 (1.12–1.57)	0.001
Stroke	1.34 (1.02–1.75)	0.034
Region		<0.0001
Western Europe	Reference	
Eastern Europe	0.50 (0.41–0.61)	
North America	0.93 (0.77–1.13)	
South America	0.65 (0.51–0.84)	
Asia	2.03 (0.97–4.26)	
Rest of world	1.16 (0.92–1.46)	
LDL-C per 1 mmol/L increment	1.19 (1.11–1.27)	<0.0001
GFR <60 mL/min/1.73 m^2	1.37 (1.17–1.60)	0.0001
Revascularization for index event	0.80 (0.70–0.91)	0.0009
Race		0.009
White	Reference	
Asian	0.38 (0.19–0.77)	
Black	1.37 (1.01–1.87)	
Other	0.97 (0.70–1.33)	
Alirocumab treatment	0.87 (0.77–0.99)	0.029

CABG, coronary artery bypass grafting; CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction.

Table 4 Independent predictors of Type 2 myocardial infarction following initial acute coronary syndrome

Baseline characteristics	HR (95% CI)	*P*-value
Medical history		
Peripheral artery disease	2.49 (1.83–3.39)	<0.0001
Percutaneous coronary intervention	1.48 (1.09–2.01)	0.012
COPD	2.26 (1.63–3.15)	<0.0001
Heart failure	2.36 (1.80–3.09)	<0.0001
Diabetes	1.76 (1.38–2.25)	<0.0001
Hypertension	2.66 (1.79–3.97)	<0.0001
MI	1.49 (1.11–2.01)	0.009
Region		<0.0001
Western Europe	Reference	
Eastern Europe	0.45 (0.30–0.65)	
North America	1.16 (0.83–1.64)	
South America	0.44 (0.25–0.76)	
Asia	1.23 (0.36–4.21)	
Rest of world	1.22 (0.77–1.94)	
HDL-C per 1 mg/dL increment	1.01 (1.00–1.02)	0.017
GFR <60 mL/min/1.73 m^2	2.05 (1.57–2.67)	<0.0001
Age category		<0.0001
<65 years	Reference	
65 to <75 years	1.46 (1.11–1.91)	
≥75 years	2.26 (1.58–3.23)	
Race		0.021
White	Reference	
Asian	0.76 (0.24–2.36)	
Black	1.92 (1.22–3.02)	
Other	0.62 (0.27–1.45)	
Alirocumab treatment	0.77 (0.61–0.97)	0.029

CI, confidence interval; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; MI, myocardial infarction.

high-intensity statin treatment and high use of other evidence-based therapies. The rate of Type 1 MI was more than double that of all other types combined. Alirocumab treatment reduced the overall incidence of MI, an observation that appears driven by a reduction in both Type 1 and Type 2 MIs. The treatment benefit on Type 1 MI increased with time elapsed since randomization, suggesting that treatment benefit may increase with longer treatment duration. The finding that a lipid-lowering treatment could reduce the incidence of Type 2 MI is novel. The benefit of alirocumab on reducing both types of MI was more pronounced when biomarker elevation, as a measure of infarct size, exceeded three times the upper limit of normal.

It is unlikely that the reduced occurrence of Type 2 MI with alirocumab treatment resulted from an effect on myocardial oxygen demand. However, alirocumab treatment may have improved myocardial oxygen supply. In the GLAGOV trial,[10] evolocumab treatment added to statin treatment in patients with coronary artery disease (CAD) produced substantial further lowering of LDL-C and reduced the volume of coronary artery plaque within 18 months, compared with placebo. In the current study, alirocumab reduced LDL-C levels by 54% from baseline to 12 months. Alirocumab may therefore have had similar effects in ODYSSEY OUTCOMES in preventing plaque progression or promoting plaque regression, resulting in greater capacity for myocardial oxygen delivery and consequently a lower risk of Type 2 MI. It is not known whether PCSK9 inhibitors have favourable effects on coronary endothelial or microvascular function.

The incidence of Type 2 MI as a proportion of total MIs has varied from around 1.6% to 29.6% in randomized trials and population studies.[11] Here, the incidence was in the higher portion of that range. In this trial, potent lipid-lowering with alirocumab reduced the occurrence of Type 2 MI. To our knowledge, this is the first such observation and contrasts with the lack of effect on Type 2 MI seen in the FOURIER trial.[5] The reason for this contrast is unknown, but could be related to differences in patient populations, number of events, duration of follow-up, definitions, and adjudication processes. Specifically, the ODYSSEY OUTCOMES trial included high-risk patients with recent ACS rather than stable patients with a history of MI, stroke, or peripheral vascular disease, and they were followed for longer (2.8 vs 2.2 years in the FOURIER trial[5]). Differences between

the studies in the effects of treatment with a PSCK9 inhibitor on specific types of MI might also be related to differences in prevailing biomarker assays, and cut-off values.

Some reports ascertaining the incidence of Type 2 MI have used specific defined oxygen supply/demand mismatch criteria,[11,12] whereas others have used more liberal criteria.[13] The ischaemic thresholds for myocardial oxygen supply/demand imbalance vary markedly in respect to the magnitude of the stressor and the amount of underlying CAD.[14] Most studies have shown a higher frequency of Type 2 MI in patients with comorbid conditions. Similarly, we found that patients with Type 2 MI were more likely than patients with Type 1 MI to have comorbidities including hypertension, heart failure, chronic obstructive pulmonary disease, diabetes, or malignancy. The rate of STEMI was relatively high in patients with Type 2 MI, but was similar to patients with Type 1 MI (28.1% vs. 26.9%). Reported rates of STEMI in patients with Type 2 MI have ranged from 3.4% to 9.7%.[11,13] Some of the patients in the present study with STEMI and Type 2 MI may have had plaque rupture with thrombus formation or embolization of thrombus, which may have been missed on angiography because of the low sensitivity for detecting thrombus, including beyond the plaque rupture in the proximal epicardial coronary vessel. Also, some of these patients may have had coronary artery spasm causing transmural ischaemia and STEMI.

The short- and long-term mortality rates for patients with Type 2 MI are generally higher than for Type 1 MI patients in most studies, due to an increased prevalence of comorbid conditions.[11–13,15–20] However, adjusted mortality may be similar.[13] Here, we found all-cause death to be more than twice as high after Type 2 than Type 1 MI.

The presence of significant CAD is a common finding in patients with Type 2 MI selected to undergo coronary angiography. The incidence of CAD depends on the population and how intensively they are studied. The presence of CAD in Type 2 MI ranges from 55% to 68%.[13,21,22] In general, patients with Type 2 MI and CAD have a worse prognosis than those without CAD.[18,20,22] As patients in the present study all had a recent ACS (within the past 1–12 months), it is likely that most had significant CAD and many would have benefited from lipid-lowering therapy through a decrease in plaque lipid content, and inflammatory cells perhaps leading to improved plaque stability and decreased progression of atherosclerosis. There are no data that statins or PCSK9 inhibitors modulate the risk associated with erosions. It is possible that Alirocumab by reducing LDL-C could improve coronary endothelial function.[23]

In the FOURIER trial, evolocumab reduced Type 4 MI ($n = 194$).[5] However, in this trial we found no effect of alirocumab on reducing Type 4 MI despite a similar number of events ($n = 225$) as in the FOURIER trial. Several small trials have suggested that statin loading before PCI may reduce the occurrence of Type 4 MI.[24] However, the recent large randomized SECURE-PCI trial showed that two loading doses of 80 mg atorvastatin before and 24 h after a planned PCI had no effect on a composite of death, MI, stroke, or unplanned coronary revascularization.[25] Our observations are consistent with the latter trial with no apparent effect of alirocumab on reducing Type 4a, 4b, or 4c MI, with 109 events occurring with alirocumab and 116 with placebo.

We pre-specified five geographic regions for the 57 participating countries (Supplementary material online, *Table S8*). Regional analysis showed that Type 2 MIs were relatively more frequent in North America (ratio of Type 2 to Type 1 MI 0.35) than in South America, Asia, and the rest of the world (ratio of Type 2 to Type 1 MI 0.16, 0.24, and 0.20, respectively). These findings could reflect regional differences in patient baseline characteristics or prevailing practice patterns influencing the ascertainment of electrocardiographic, biomarker or echocardiographic data to support MI diagnosis.

The prevalent use of therapies well-established to reduce the risk of recurrent MI were examined according to type of MI. Beta-blocker use at randomization was high and similar in patients who subsequently had Type 1 or Type 2 MI (86.5% vs. 85.1%, respectively). Large majorities of the patients with either Type 1 or Type 2 MI were treated with aspirin (94.5% and 89.3%, respectively).

Limitations

We did not specify study-specific adjudication algorithms to distinguish Type 1 and 2 MI. The trial did not mandate routine biomarker measurements following PCI or CABG to detect Type 4 and Type 5 MIs, and consequently there may have been under ascertainment of those events. The absence of any alirocumab treatment effect on the occurrence of Type 4 MI could represent Type 2 error, due to the relatively small number of these events. Classification of MI according to the development of Q-waves may have been limited because the protocol did not specify ECGs at fixed times in the study and there was no core ECG laboratory. We had no protocol-specified measurement of left ventricular function to ascertain the size of the MIs in addition to biomarker assessment. Finally, as pre-specified, we focused on first MI after randomization rather than analysing total MI events.[9]

Conclusion

In patients with ACS, alirocumab added to intensive statin therapy during 2.8 years of follow-up reduced the occurrence of both Type 1 and Type 2 MI. For Type 1 MIs, treatment benefit appeared to increase over time. The data indicate for the first time that a lipid-lowering therapy can attenuate the risk of Type 2 MI. Therefore, LDL-C lowering with alirocumab below levels achieved with statins may be an important preventive treatment for both Type 1 and Type 2 MI following ACS.

Supplementary material

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

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