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

Harvey D White,¹ Ph Gabriel Steg,^{2,3} Michael Szarek,⁴ Deepak L Bhatt,⁵ Vera A Bittner,⁶ Rafael Diaz,⁷ Jay M Edelberg,⁸ Andrejs Erglis,⁹ Shaun G Goodman,^{10,11} Corinne Hanotin,¹² Robert A Harrington,¹³ J Wouter Jukema,¹⁴ Renato D Lopes,¹⁵ Kenneth W Mahaffey,¹⁶ Angele Moryusef,⁸ Robert Pordy,¹⁷ Matthew T Roe,¹⁵ Piyamitr Sritara,¹⁸ Pierluigi Tricoci,¹⁹ Andreas M Zeiher,²⁰ Gregory G Schwartz,²¹ and ODYSSEY OUTCOMES Investigators

¹Green Lane Cardiovascular Services, Auckland City Hospital, 5 Park Road, Grafton, Auckland, New Zealand

²FACT (French Alliance for Cardiovascular Trials), an F-CRIN network, Département Hospitalo-Universitaire FIRE, AP-HP, Hôpital Bichat, Université Paris-Diderot, Sorbonne Paris-Cité, INSERM U-1148, 46 rue Henri Huchard, Paris, France

³National Heart and Lung Institute, Imperial College, Royal Brompton Hospital, Sydney Street, London, UK

⁴Department of Epidemiology and Biostatistics, SUNY Downstate Medical Center School of Public Health, 450 Clarkson Avenue, Brooklyn, USA

⁵Brigham and Women's Hospital Heart and Vascular Center, Harvard Medical School, 75 Francis Street, Boston, USA

⁶Division of Cardiovascular Disease, University of Alabama at Birmingham, 701 19th Street South - LHRB 310, Birmingham, USA

⁷Estudios Cardiológicos Latinoamérica, Instituto Cardiovascular de Rosario, Paraguay 160, Rosario, Santa Fe, Argentina

⁸Sanofi, 55 Corporate Drive, Bridgewater, USA

⁹Latvian Centre of Cardiology, Pauls Stradins Clinical University Hospital, University of Latvia, Pilsonu Street 13, Riga, Latvia

¹⁰Canadian VIGOUR Centre, 2-132 Li Ka Shing Centre for Health Research Innovation University of Alberta, Edmonton, Alberta, Canada

¹¹St. Michael's Hospital, 30 Bond Street, University of Toronto, Toronto, ON, Canada

¹²Sanofi, 54-56 Rue la Boétie, Paris, France

¹³Stanford Center for Clinical Research, Department of Medicine, 300 Pasteur Drive, S-102, Stanford, CA, USA

¹⁴Department of Cardiology, Leiden University Medical Center, RC Leiden, The Netherlands

¹⁵Duke Clinical Research Institute, 200 Morris Street, Durham, NC, USA

¹⁶Department of Medicine, Stanford University School of Medicine, 300 Pasteur Drive, Grant S-102, Stanford, CA, USA

¹⁷Regeneron Pharmaceuticals, 777 Old Saw Mill River Road, Tarrytown, NY, USA

¹⁸Department of Medicine, Faculty of Medicine, Ramathibodi Hospital/Mahidol University, Rama VI Road, Thailand

¹⁹CSL Behring, 1100 N Miami Blvd Ste 613, Durham, NC, USA

²⁰Department of Medicine III, Goethe University, Theodor-Stern-Kai 7, Frankfurt am Main, Germany

²¹Division of Cardiology, University of Colorado School of Medicine, 1700 N. Wheeling Street, Aurora, CO, USA

The ODYSSEY OUTCOMES Committee members, investigators, and contributors are listed in [Supplementary material online](#).

Corresponding author. Tel: +64 9 630 9992, Fax: +64 9 630 9915, Email: harveyw@adhb.govt.nz

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Abstract

Aims

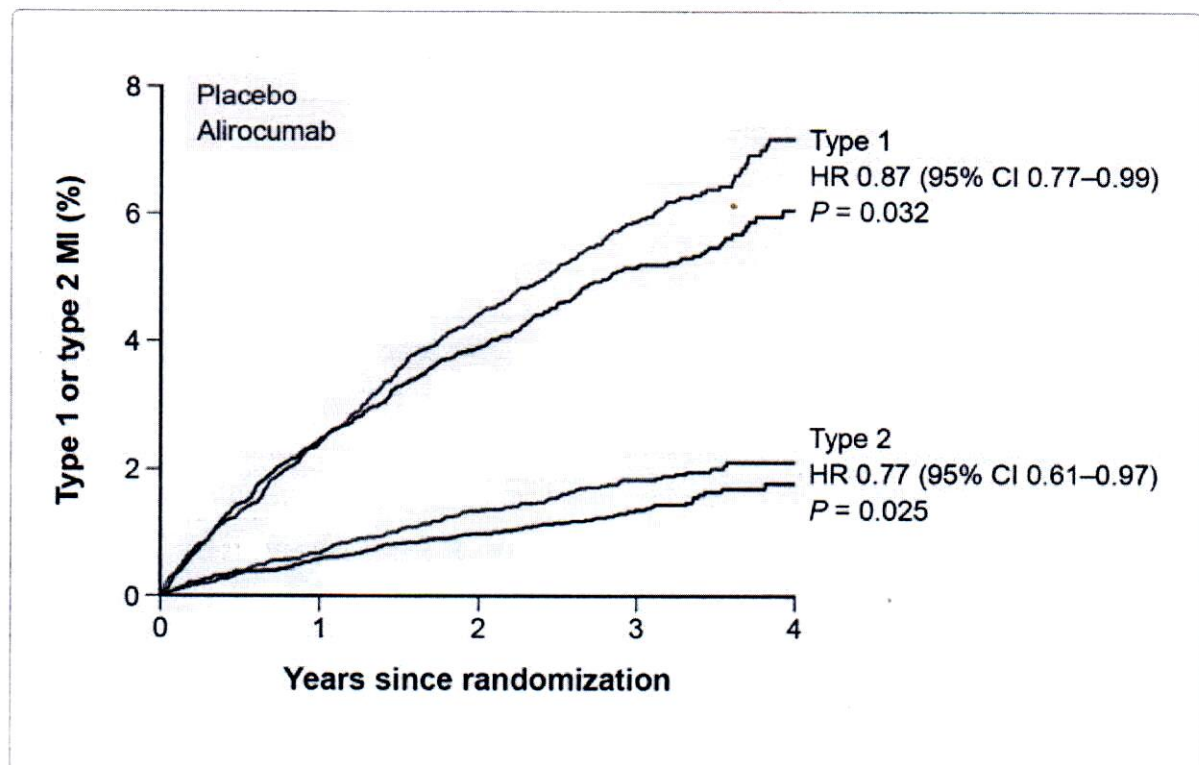
The third Universal Definition of Myocardial Infarction (MI) Task Force classified MIs into five types: Type 1, spontaneous; Type 2, related to oxygen supply/demand imbalance; Type 3, fatal without ascertainment of cardiac biomarkers; Type 4, related to percutaneous coronary intervention; and Type 5, 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.

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 design⁶ and primary results³ 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 Definition⁷ 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 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 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 ($P = 0.012$).

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

[Open in a separate window](#)

Data are represented as median (quartile 1–quartile 3) or *n* (%). Additional information on baseline characteristics is presented in [Supplementary material online, Table S5](#).

^aRank-based tests, comparing A vs. B vs. C.

^bRank-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.

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.

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

^aAnalysis of time to first Type 1, Type 2, or Type 4A, 4B, 4C MI by Cox proportional hazards models, stratified by geographical region.

^bSpontaneous.

^cSupply/demand imbalance.

^dCardiac death suggestive of MI without increased biomarkers.

^ePeri-percutaneous coronary intervention.

^fCorrespond to any Type 4 MI.

^gStent thrombosis.

^hRestenosis.

ⁱPeri-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.

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 ($P = 0.34$).

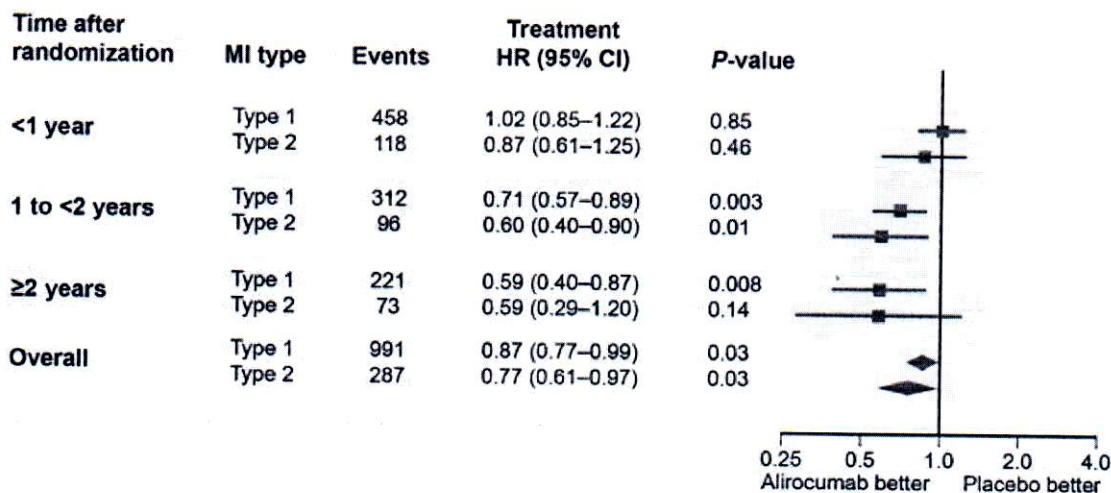
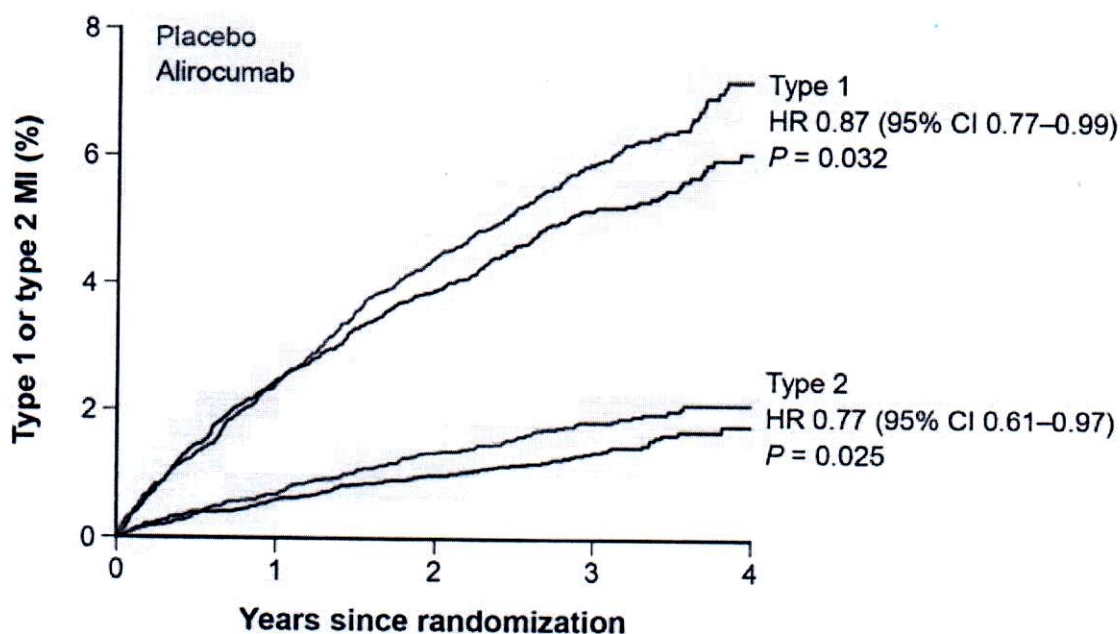


Figure 1

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.



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.

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.

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.

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.

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 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 trial⁵). Differences between the studies in the effects of treatment with a PCSK9 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

ehz299_Supplementary_Data

[Click here for additional data file.](#) (148K, docx)

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References

1. Cholesterol Treatment Trialists (CTT) Collaborators, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, Voysey M, Gray A, Collins R, Baigent C. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual

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- data from 27 randomised trials. *Lancet* 2012;380:581–590. [[PMC free article](#)] [[PubMed](#)] [[Google Scholar](#)]
2. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR, Fourier SCI. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376:1713–1722. [[PubMed](#)] [[Google Scholar](#)]
 3. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Quintero K, Roe MT, Sasiela WJ, Tamby JF, Tricoci P, White HD, Zeiher AM.; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;379:2097–2107. [[PubMed](#)] [[Google Scholar](#)]
 4. Thygesen K, Alpert JS, White HD.; on behalf of the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. *Eur Heart J* 2007;28:2525–2538. [[PubMed](#)] [[Google Scholar](#)]
 5. Wiviott SD, Giugliano RP, Morrow DA, De Ferrari GM, Lewis BS, Huber K, Kuder JF, Murphy SA, Forni DM, Kurtz C, Honarpour N, Keech AC, Sever PS, Pedersen TR, Sabatine MS. Characterization of types and sizes of myocardial infarction reduced with evolocumab in FOURIER. *Circulation* 2017;136:A16714. [[Google Scholar](#)]
 6. Schwartz GG, Bessac L, Berdan LG, Bhatt DL, Bittner V, Diaz R, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Mahaffey KW, Moryusef A, Pordy R, Roe MT, Rorick T, Sasiela WJ, Shirodaria C, Szarek M, Tamby JF, Tricoci P, White H, Zeiher A, Steg PG. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY outcomes trial. *Am Heart J* 2014;168:682–689. [[PubMed](#)] [[Google Scholar](#)]
 7. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Thygesen K, Alpert JS, White HD, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA, Chaitman BR, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Gabriel Steg P, Wijns W, Bassand J-P, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon J-L, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Ž, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Morais J, Aguiar C, Almahmeed W, Arnar DO, Barili F, Bloch KD, Bolger AF, Bøtker HE, Bozkurt B, Bugiardini R, Cannon C, de Lemos J, Eberli FR, Escobar E, Hlatky M, James S, Kern KB, Moliterno DJ, Mueller C, Neskovic AN, Pieske BM, Schulman SP, Storey RF, Taubert KA, Vranckx P, Wagner DR.; Writing Group on the Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction. Third universal definition of myocardial infarction. *Eur Heart J* 2012;33:2551–2567. [[PubMed](#)] [[Google Scholar](#)]
 8. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509. [[Google Scholar](#)]
 9. Szarek M, White HD, Schwartz GG, Alings M, Bhatt DL, Bittner VA, Chiang CE, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Kimura T, Kiss RG, Lecorps G, Mahaffey KW, Moryusef A, Pordy R, Roe MT, Tricoci P, Xavier D, Zeiher AM, Steg PG. ODYSSEY OUTCOMES Committees and Investigators. Alirocumab reduces total nonfatal cardiovascular and fatal events in the ODYSSEY OUTCOMES trial. *J Am Coll Cardiol* 2019;73:387–396. [[PubMed](#)] [[Google Scholar](#)]
 10. Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJ, Koenig W, Somaratne R, Kassahun H, Yang J, Wasserman SM, Scott R, Ungi I, Podolec J, Ophuis AO, Cornel JH, Borgman M, Brennan DM, Nissen SE. Effect of evolocumab on progression of coronary disease in statin-treated

patients: the GLAGOV randomized clinical trial. *JAMA* 2016;316:2373–2384. [[PubMed](#)] [[Google Scholar](#)]

11. Saaby L, Poulsen TS, Hosbond S, Larsen TB, Pyndt Diederichsen AC, Hallas J, Thygesen K, Mickley H. Classification of myocardial infarction: frequency and features of type 2 myocardial infarction. *Am J Med* 2013;126:789–797. [[PubMed](#)] [[Google Scholar](#)]

12. Cediël G, Gonzalez-del-Hoyo M, Carrasquer A, Sanchez R, Boqué C, Bardají A. Outcomes with type 2 myocardial infarction compared with non-ischaemic myocardial injury. *Heart* 2017;103:616–622. [[PubMed](#)] [[Google Scholar](#)]

13. Baron T, Hambraeus K, Sundstrom J, Erlinge D, Jernberg T, Lindahl B. TOTAL-AMI study group. Type 2 myocardial infarction in clinical practice. *Heart* 2015;101:101–106. [[PubMed](#)] [[Google Scholar](#)]

14. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD. ESC Scientific Document Group. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2019;40:237–269. [[PubMed](#)] [[Google Scholar](#)]

15. Shah AS, McAllister DA, Mills R, Lee KK, Churchhouse AM, Fleming KM, Layden E, Anand A, Fersia O, Joshi NV, Walker S, Jaffe AS, Fox KA, Newby DE, Mills NL. Sensitive troponin assay and the classification of myocardial infarction. *Am J Med* 2015;128:493–501.e3. [[PMC free article](#)] [[PubMed](#)] [[Google Scholar](#)]

16. Gupta S, Vaidya SR, Arora S, Bahekar A, Devarapally SR. Type 2 versus type 1 myocardial infarction: a comparison of clinical characteristics and outcomes with a meta-analysis of observational studies. *Cardiovasc Diagn Ther* 2017;7:348–358. [[PMC free article](#)] [[PubMed](#)] [[Google Scholar](#)]

17. Sandoval Y, Thygesen K. Myocardial infarction type 2 and myocardial injury. *Clin Chem* 2017;63:101–107. [[PubMed](#)] [[Google Scholar](#)]

18. Lambrecht S, Sarkisian L, Saaby L, Poulsen TS, Gerke O, Hosbond S, Diederichsen ACP, Thygesen K, Mickley H. Different causes of death in patients with myocardial infarction type 1, type 2, and myocardial injury. *Am J Med* 2018;131:548–554. [[PubMed](#)] [[Google Scholar](#)]

19. Chapman AR, Shah ASV, Lee KK, Anand A, Francis O, Adamson P, McAllister DA, Strachan FE, Newby DE, Mills NL. Long-term outcomes in patients with type 2 myocardial infarction and myocardial injury. *Circulation* 2018;137:1236–1245. [[PMC free article](#)] [[PubMed](#)] [[Google Scholar](#)]

20. Neumann JT, Sorensen NA, Rubsamen N, Ojeda F, Renne T, Qaderi V, Teltrop E, Kramer S, Quantius L, Zeller T, Karakas M, Blankenberg S, Westermann D. Discrimination of patients with type 2 myocardial infarction. *Eur Heart J* 2017;38:3514–3520. [[PubMed](#)] [[Google Scholar](#)]

21. Ambrose JA, Loures-Vale A, Javed U, Buhari CF, Aftab W. Angiographic correlates in type 1 and 2 MI by the universal definition. *JACC Cardiovasc Imaging* 2012;5:463–464. [[PubMed](#)] [[Google Scholar](#)]

22. Saaby L, Poulsen TS, Diederichsen AC, Hosbond S, Larsen TB, Schmidt H, Gerke O, Hallas J, Thygesen K, Mickley H. Mortality rate in type 2 myocardial infarction: observations from an unselected hospital cohort. *Am J Med* 2014;127:295–302. [[PubMed](#)] [[Google Scholar](#)]

23. Treasure CB, Klein JL, Weintraub WS, Talley JD, Stillabower ME, Kosinski AS, Zhang J, Boccuzzi SJ, Cedarholm JC, Alexander RW. Beneficial effects of cholesterol-lowering therapy on the coronary endothelium in patients with coronary artery disease. *N Engl J Med* 1995;332:481–487. [[PubMed](#)] [[Google Scholar](#)]

24. Patti G, Cannon CP, Murphy SA, Mega S, Pasceri V, Briguori C, Colombo A, Yun KH, Jeong MH, Kim JS, Choi D, Bozbas H, Kinoshita M, Fukuda K, Jia XW, Hara H, Cay S, Di Sciascio G. Clinical benefit of statin pretreatment in patients undergoing percutaneous coronary intervention: a collaborative patient-level meta-analysis of 13 randomized studies. *Circulation* 2011;123:1622–1632. [[PubMed](#)] [[Google Scholar](#)]

25. Berwanger O, Santucci EV, de Barros E, Jesuino IA, Damiani LP, Barbosa LM, Santos RHN, Laranjeira LN, Egydio FM, Borges de Oliveira JA, Dall Orto FTC, Beraldo de Andrade P, Bienert IRC, Bosso CE, Mangione JA, Polanczyk CA, Sousa A, Kalil RAK, Santos LM, Sposito AC, Rech RL, Sousa ACS, Baldissera F, Nascimento BR, Giraldez R, Cavalcanti AB, Pereira SB, Mattos LA, Armaganijan LV, Guimaraes HP, Sousa J, Alexander JH, Granger CB, Lopes RD. SECURE-PCI Investigators. Effect of loading dose of atorvastatin prior to planned percutaneous coronary intervention on major adverse cardiovascular events in acute coronary syndrome: the SECURE-PCI randomized clinical trial. JAMA 2018;319:1331–1340. [[PMC free article](#)] [[PubMed](#)] [[Google Scholar](#)]

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