Alirocumab in Patients With Polyvascular Disease and Recent Acute Coronary Syndrome

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ORIGINAL INVESTIGATIONS

Alirocumab in Patients With Polyvascular Disease and Recent Acute Coronary Syndrome

ODYSSEY OUTCOMES Trial

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ABSTRACT

BACKGROUND Patients with acute coronary syndrome (ACS) and concomitant noncoronary atherosclerosis have a high risk of major adverse cardiovascular events (MACEs) and death. The impact of lipid lowering by proprotein convertase subtilisin-kexin type 9 inhibition in such patients is undetermined.

OBJECTIVES This pre-specified analysis from ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) determined whether polyvascular disease influenced risks of MACEs and death and their modification by alirocumab in patients with recent ACS and dyslipidemia despite intensive statin therapy.

METHODS Patients were randomized to alirocumab or placebo 1 to 12 months after ACS. The primary MACEs endpoint was the composite of coronary heart disease death, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. All-cause death was a secondary endpoint.

RESULTS Median follow-up was 2.8 years. Of 18,924 patients, 17,370 had monovascular (coronary) disease, 1,405 had polyvascular disease in 2 beds (coronary and peripheral artery or cerebrovascular), and 149 had polyvascular disease in 3 beds (coronary, peripheral artery, cerebrovascular). With placebo, the incidence of MACEs by respective vascular categories was 10.0%, 22.2%, and 39.7%. With alirocumab, the corresponding absolute risk reduction was 1.4% (95% confidence interval [CI]: 0.6% to 2.3%), 1.9% (95% CI: −2.4% to 6.2%), and 13.0% (95% CI: −2.0% to 28.0%). With placebo, the incidence of death by respective vascular categories was 3.5%, 10.0%, and 21.8%; the absolute risk reduction with alirocumab was 0.4% (95% CI: −0.1% to 1.0%), 1.3% (95% CI: −1.8% to 4.3%), and 16.2% (95% CI: 5.5% to 26.8%).

CONCLUSIONS In patients with recent ACS and dyslipidemia despite intensive statin therapy, polyvascular disease is associated with high risks of MACEs and death. The large absolute reductions in those risks with alirocumab are a potential benefit for these patients. (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab [ODYSSEY OUTCOMES]: NCT01663402) (J Am Coll Cardiol 2019;74:1167-76)

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

ARR = absolute risk reduction

CAD = coronary artery disease

CeVD = cerebrovascular disease

CI = confidence interval

LDL-C = low-density lipoprotein cholesterol

MACE = major adverse cardiovascular event

PAD = peripheral artery disease

Patients with peripheral artery disease (PAD) or cerebrovascular disease (CeVD) have an elevated risk of major adverse cardiovascular events (MACEs) and death compared with patients without these conditions, irrespective of a concurrent history of coronary artery disease (CAD) (1-3). The risk of future MACEs and death also remains high among patients with an acute coronary syndrome (ACS), despite application of evidence-based secondary prevention measures including statins and dual antiplatelet therapy (4). When PAD or CeVD is concurrent with ACS, risk may be particularly elevated, warranting more intensive approaches to secondary prevention (5,6).

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Lowering of atherogenic lipoproteins, reflected in part by reduction of low-density lipoprotein cholesterol (LDL-C), favorably modifies the risks of MACEs and death (7). Accordingly, statin treatment is broadly recommended for patients with coronary atherosclerosis, PAD, or CeVD in the guidelines of the American College of Cardiology and American Heart Association, the American College of Cardiology and American Stroke Association, and the European Society of Cardiology and European Atherosclerosis Society (8-11).

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Jukema and Szarek are joint first authors and contributed equally to this work. †Drs. Schwartz and Steg are joint senior authors and contributed equally to this work. ‡A complete list of the ODYSSEY OUTCOMES Committee members, investigators, and contributors is provided in the Online Appendix. This study was supported by Sanofi, Regeneron Pharmaceuticals, Inc., and Fondation Assistance Publique-Hôpitaux de Paris. Dr. Jukema has received research grants from The Netherlands Heart Foundation, the Interuniversity Cardiology Institute of The Netherlands, and the European Community Framework KP7 Program; and has received other research support from Amgen, Astellas, AstraZeneca, Daiichi-Sankyo, Eli Lilly, Merck-Schering-Plough, Pfizer, Roche, and Sanofi. 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Dr. Bittner has received institutional research grants from Amgen, DalCor, Esperion, Sanofi, AstraZeneca, and Bayer Healthcare; has received honoraria from the American College of Cardiology, American Heart Association, and National Lipid Association; and has served as a consultant for and on the Advisory Board of Sanofi. Dr. Diaz has received grants, personal fees, and nonfinancial support from Sanofi during the conduct of the study; has received grants from DalCor, Population Health Research Institute, Duke Clinical Research Institute, TIMI Group, and Montreal Health Innovations Coordinating Center has received nonfinancial support from Lepetit; has received personal fees from AstraZeneca and Eli Lilly; and has received grants from Amgen. Dr. Edelberg was

The advent of inhibitors of proprotein convertase subtilisin-kexin type 9 (PCSK9) provided an opportunity to lower LDL-C to levels not previously achievable with statins or ezetimibe. The FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial compared the PCSK9 inhibitor evolocumab with placebo in patients with established, stable atherosclerotic cardiovascular disease, including CAD, PAD, or CeVD. Evolocumab reduced MACEs, but not death. Benefits were particularly pronounced among patients with PAD at entry into the trial (12).

The ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial showed that MACEs were reduced with the PCSK9 inhibitor alirocumab compared with placebo in 18,924 patients with recent ACS and elevated atherogenic lipoproteins despite intensive statin therapy. In addition, fewer deaths occurred among patients treated with alirocumab. The aims of this prespecified analysis of the ODYSSEY OUTCOMES trial were to determine whether the benefits of alirocumab on MACE and death were influenced by the presence of polyvascular disease, defined as concomitant PAD, CeVD, or both, and thus to identify preferred candidates for alirocumab treatment.

METHODS

Details of the study design (13) and primary efficacy and safety results have been published (14). In brief, ODYSSEY OUTCOMES was a multicenter, double-blind, placebo-controlled trial in 18,924 patients at least 40 years of age who provided written informed consent and had been hospitalized with an ACS (defined as myocardial infarction or unstable angina) 1 to 12 months before randomization. Qualifying patients had a level of LDL-C of at least 70 mg/dl (1.81 mmol/l), non-high-density lipoprotein cholesterol at least 100 mg/dl (2.59 mmol/l), or apolipoprotein B at least 80 mg/dl, measured after a minimum of 2 weeks of stable treatment with atorvastatin 40 to 80 mg daily, rosuvastatin 20 to 40 mg daily, or the maximum tolerated dose of either statin (including no statin in case of documented intolerance). Patients were randomly assigned in a 1:1 ratio stratified by country to receive treatment with alirocumab 75 mg subcutaneously every 2 weeks or matching placebo.

CATEGORIES OF POLYVASCULAR DISEASE. In this analysis, 3 subgroups of patients with recent ACS were defined on the basis of the distribution of other evident vascular disease: 1) monovascular disease (CAD without known PAD or CeVD); 2) polyvascular disease in 2 vascular beds (CAD and either PAD or CeVD); and 3) polyvascular disease in 3 vascular beds

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TABLE 1 Baseline Characteristics by History of PAD or CeVD Category

	Monovascular Disease	Disease in 2 Vascular Beds		Disease in 3 Vascular Beds	
	CAD Without PAD or CeVD (n = 17,370)	CAD and PAD (n = 610)	CAD and CeVD (n = 795)	CAD, PAD, and CeVD (n = 149)	p Value
Age, yrs	58 (51, 65)	62 (56, 68)	62 (56, 69)	66 (60, 71)	<0.0001
Age category					<0.0001
<65 yrs	12,956 (74.6)	368 (60.3)	456 (57.4)	60 (40.3)	
65 to <75 yrs	3,575 (20.6)	178 (29.2)	252 (31.7)	72 (48.3)	
≥75 yrs	839 (4.8)	64 (10.5)	87 (10.9)	17 (11.4)	
Female	4,298 (24.7)	163 (26.7)	264 (33.2)	37 (24.8)	<0.0001
Region					<0.0001
Western Europe	3,852 (22.2)	152 (24.9)	142 (17.9)	29 (19.5)	
Eastern Europe	4,993 (28.7)	189 (31.0)	215 (27.0)	40 (26.8)	
North America	2,513 (14.5)	134 (22.0)	170 (21.4)	54 (36.2)	
South America	2,413 (13.9)	64 (10.5)	101 (12.7)	10 (6.7)	
Asia	2,170 (12.5)	22 (3.6)	92 (11.6)	9 (6.0)	
Rest of world	1,429 (8.2)	49 (8.0)	75 (9.4)	7 (4.7)	
Index event					<0.0001
NSTEMI	8,300 (47.9)	342 (56.3)	439 (55.4)	94 (63.1)	
STEMI	6,080 (35.1)	195 (31.1)	227 (28.6)	34 (22.8)	
Unstable angina	2,963 (17.1)	71 (11.7)	127 (16.0)	21 (14.1)	
Time from index event to randomization, months	2.6 (1.7, 4.3)	3.0 (1.8, 5.4)	2.7 (1.7, 4.8)	3.0 (2.1, 3.9)	0.0003
Lipid-lowering therapy at randomization					<0.0001
High-dose atorvastatin or rosuvastatin	15,486 (89.2)	525 (86.1)	679 (85.4)	121 (81.2)	
Other LLT	1,734 (10.0)	75 (12.3)	102 (12.8)	24 (16.1)	
No LLT	150 (0.9)	10 (1.6)	14 (1.8)	4 (2.7)	
LDL-C, mg/dl	86 (73, 103)	91 (76, 108)	90 (75, 109)	95 (80, 115)	<0.0001
LDL-C ≥100 mg/dl	5,060 (29.1)	218 (35.7)	290 (36.5)	61 (40.9)	<0.0001
HDL-C, mg/dl	42 (36, 50)	42 (36, 50)	43 (36, 51)	43 (37, 51)	NS
Non–HDL-C, mg/dl	114 (99, 136)	121 (105, 143)	120 (103, 144)	124 (108, 143)	<0.0001
Triglycerides, mg/dl	128 (94, 181)	134 (99, 187)	136 (98, 190)	135 (94, 182)	0.002
Apolipoprotein B, mg/dl	79 (69, 93)	83 (72, 96)	83 (71, 96)	82 (75, 95)	<0.0001
Lipoprotein(a), mg/dl	20.8 (6.6, 59.4)	25.5 (7.5, 68.1)	23.0 (7.1, 61.7)	29.4 (9.4, 74.5)	0.004
C-reactive protein, mg/dl	0.16 (0.08, 3.73)	0.26 (0.11, 0.55)	0.22 (0.10, 0.48)	0.21 (0.11, 0.49)	<0.0001
Body mass index, kg/m^2	27.9 (25.2, 31.1)	27.7 (24.9, 31.0)	28.1 (25.4, 31.5)	27.7 (24.5, 30.7)	NS
Hemoglobin A_{1c}, %	5.8 (5.5, 6.3)	6.0 (5.6, 6.7)	6.1 (5.7, 7.0)	6.0 (5.7, 6.7)	<0.0001
eGFR, ml/min/1.73 m^2	78.5 (68.1, 90.4)	74.1 (61.6, 86.7)	72.9 (59.5, 85.8)	67.0 (52.2, 84.4)	<0.0001
eGFR <60 ml/min/1.73 m^2	2,139 (12.3)	135 (22.1)	206 (25.9)	59 (39.6)	<0.0001
Diabetes status					<0.0001
Diabetes	4,805 (27.7)	225 (36.9)	349 (43.9)	65 (43.6)	
Pre-diabetes	7,630 (43.9)	260 (42.6)	299 (37.6)	57 (38.3)	
Normoglycemia	4,935 (28.4)	125 (20.5)	147 (18.5)	27 (18.1)	
Smoking status					<0.0001
Current	4,181 (24.1)	189 (31.0)	147 (18.5)	43 (28.9)	
Former	7,095 (40.8)	302 (49.5)	335 (42.1)	79 (53.0)	
Never	6,093 (35.1)	119 (19.5)	313 (39.4)	27 (18.1)	
Medical history prior to index event					
Hypertension	10,930 (62.9)	489 (80.2)	694 (87.3)	136 (91.3)	<0.0001
Myocardial infarction	3,147 (18.1)	204 (33.4)	226 (28.4)	62 (41.6)	<0.0001
Stroke	0 (0.0)	0 (0.0)	526 (66.2)	85 (57.0)	<0.0001
Malignant disease	458 (2.6)	28 (4.6)	34 (4.3)	12 (8.1)	<0.0001
COPD	613 (3.5)	64 (10.5)	46 (5.8)	23 (15.4)	<0.0001
CABG	826 (4.8)	82 (13.4)	91 (11.4)	48 (32.2)	<0.0001
PAD	0 (0.0)	610 (100.0)	0 (0.0)	149 (100.0)	<0.0001
CeVD	0 (0.0)	0 (0.0)	795 (100.0)	149 (100.0)	<0.0001

Continued on the next page

TABLE 1 Continued

	Monovascular Disease	Disease in 2 Vascular Beds		Disease in 3 Vascular Beds	
	CAD Without PAD or CeVD (n = 17,370)	CAD and PAD (n = 610)	CAD and CeVD (n = 795)	CAD, PAD, and CeVD (n = 149)	p Value
Revascularization for index event	12,596 (72.5)	436 (71.5)	540 (67.9)	105 (70.5)	0.04
Medications					
Aspirin	16,647 (95.8)	564 (92.5)	737 (92.7)	138 (92.6)	<0.0001
$P2Y_{12}$ antagonist	15,223 (87.6)	525 (86.1)	664 (83.5)	129 (86.6)	0.005
ACE inhibitor/ARB	13,444 (77.4)	494 (81.0)	655 (82.4)	123 (82.6)	0.0008
Beta-blocker	14,687 (84.6)	507 (83.1)	672 (84.5)	124 (83.2)	NS
Ezetimibe	473 (2.7)	38 (6.2)	30 (3.8)	13 (8.7)	<0.0001
Treatment variables among alirocumab-treated patients	8,683	302	406	71	
% switched to placebo	691 (8.0)	12 (4.0)	25 (6.2)	2 (2.8)	0.01

Values are median (quartile 1, quartile 3), n (%), or n. The p values reflect the statistical comparison among the 4 vascular disease subgroups (CAD without PAD or CeVD; CAD and PAD; CAD and CeVD; CAD PAD, and CeVD).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; CAD = coronary artery disease; CeVD = cerebrovascular disease; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; NS = not significant (p > 0.05); NSTEMI = non-ST-segment elevation myocardial infarction; PAD = peripheral artery disease; STEMI = ST-segment elevation myocardial infarction.

(CAD with both PAD and CeVD). Two additional sensitivity analyses were performed. The first considered 2 vascular disease categories: 1) monovascular disease (CAD without known PAD or CeVD); and 2) polyvascular disease (CAD with any combination of PAD or CeVD). The second analysis considered 4 subgroups of patients with ACS: 1) those with monovascular disease, as defined earlier; 2) all patients with PAD, with or without concurrent CeVD; 3) all patients with CeVD, with or without concurrent PAD; and 4) patients with disease in all 3 vascular beds, as defined earlier. PAD included arterial disease of the extremities or abdominal aortic aneurysm. CeVD was defined as a history of carotid endarterectomy, carotid stenting, prior stroke, or transient ischemic attack.

ENDPOINTS. The primary MACE endpoint was a composite of coronary heart disease death, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. All-cause death was a secondary endpoint.

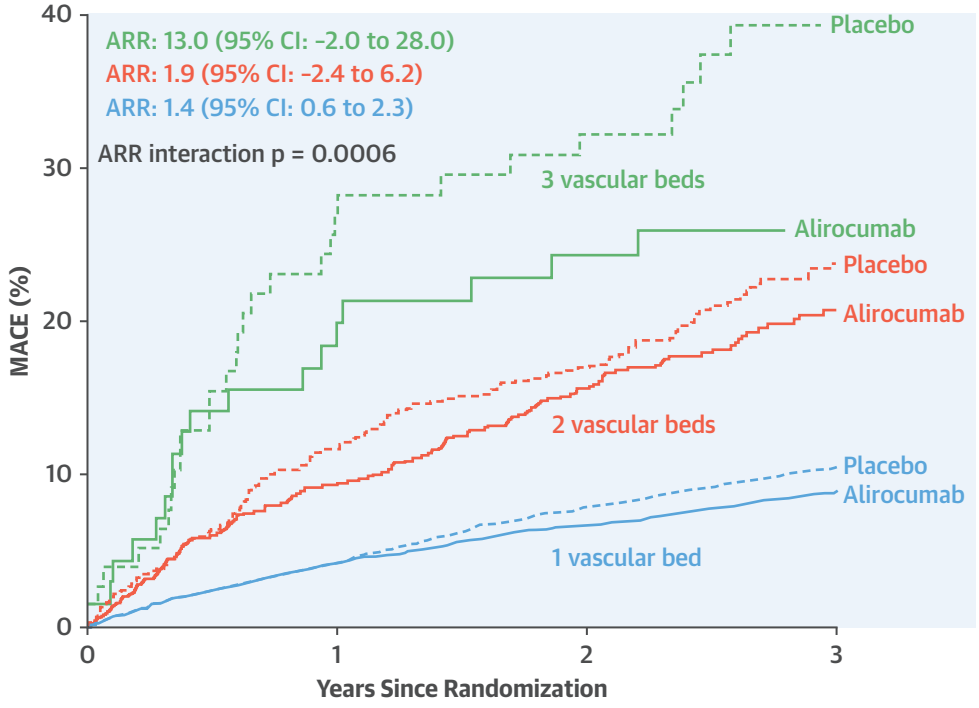
STATISTICAL CONSIDERATIONS. Analyses of clinical outcomes and LDL-C levels were performed according to the intention-to-treat principle, including all patients, events, and measurements from randomization to the common study end date (November 11, 2017). Hazard ratios and 95% confidence intervals (CIs) were estimated using a Cox proportional hazards model, stratified by geographic region; p values were determined using stratified log-rank tests. Endpoint rates were based on observed incidences. Alirocumab treatment effect heterogeneity by categories of polyvascular disease was assessed by Cox models with interaction terms for relative risk reduction and Gail-Simon tests for absolute risk reduction (ARR). Analyses were performed in SAS software version 9.4 (IBM Corp., Armonk, New York).

RESULTS

Of 18,924 randomized patients, 9,462 were assigned to the alirocumab group and 9,462 to the placebo group, with a median (quartile 1, quartile 3) follow-up of 2.8 years (2.3, 3.4 years). At baseline, 17,370 patients had monovascular disease (91.8%), 1,405 patients had polyvascular disease in 2 vascular beds (7.4%; 3.2% PAD and 4.2% CeVD), and 149 had polyvascular disease in 3 vascular beds (0.8%).

BASELINE CHARACTERISTICS. Table 1 summarizes the baseline characteristics of patients with monovascular (coronary) disease, polyvascular disease in 2 beds (split by PAD only and CeVD only), and polyvascular disease in 3 beds. Compared with patients with monovascular disease, those with CAD and PAD, CAD and CeVD, and polyvascular disease in 3 beds were older (median ages 58, 62, 62, and 66 years; p < 0.0001); patients with CAD and PAD or CAD and CeVD were more likely to be female (26.7% and 33.2%, respectively) than those with monovascular disease (24.7%; p < 0.0001). Of all patients with CeVD, 526 (66.2%) had a history of stroke. Patients with polyvascular disease in 3 beds had more comorbidities, including a history of hypertension, myocardial infarction, and coronary artery bypass

CENTRAL ILLUSTRATION **Alirocumab and Vascular Disease: Primary Major Adverse Cardiovascular Event Endpoint**



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Kaplan-Meier curves for primary major adverse cardiovascular event (MACE) endpoint in patients with arterial disease in, respectively, 1 (coronary artery disease [CAD] and no peripheral artery disease [PAD] or cerebrovascular disease [CeVD]), 2 (CAD and PAD or CeVD), or 3 (CAD and PAD and CeVD) vascular beds. ARR = absolute risk reduction; CI = confidence interval.

grafting, compared with patients with monovascular disease (all $p < 0.0001$). Furthermore, patients with polyvascular disease in 3 beds versus patients with monovascular disease had a higher prevalence of diabetes (43.6% vs. 27.7%; $p < 0.0001$) and were more likely to be current or former smokers (81.9% vs. 64.9%; $p < 0.0001$). More patients with polyvascular disease in 3 beds versus patients with monovascular disease had an estimated glomerular filtration rate of <60 ml/min/1.73 m^2 (39.6% vs. 12.3%) with median estimated glomerular filtration rates of 78.5, 74.1, 72.9, and 67.0 ml/min/1.73 m^2 in patients with monovascular disease, CAD and PAD, CAD and CeVD, and polyvascular disease in 3 beds, respectively ($p < 0.0001$).

LDL-C LOWERING. At baseline, median LDL-C (quartile 1, quartile 3) was higher in patients with polyvascular disease, with values of 86 mg/dl (73, 103 mg/dl) in patients with monovascular disease, 91 mg/dl (76, 108 mg/dl) in CAD and PAD, 90 mg/dl (75, 109 mg/dl) in CAD and CeVD, and 95 mg/dl (80, 115 mg/dl) in polyvascular disease in 3 beds ($p < 0.0001$). In the placebo group, LDL-C at 4 months was 87 mg/dl (72, 106 mg/dl) in patients with monovascular disease, 90 mg/dl (73, 108 mg/dl) in only PAD, 90 mg/dl (73, 115 mg/dl) in CeVD only, and 93 mg/dl (78, 118 mg/dl) in polyvascular disease in 3 beds. In patients treated with alirocumab, LDL-C at 4 months was 30 mg/dl (20, 47 mg/dl), 34 (23, 50 mg/dl), 34 mg/dl (21, 52 mg/dl), and 31 mg/dl (20, 42 mg/dl) in the same 4 vascular disease categories.

PRIMARY MACE ENDPOINT AND ALL-CAUSE DEATH. Overall in the ODYSSEY OUTCOMES trial, the incidence of MACE in the placebo and alirocumab groups was 11.1% and 9.5%, respectively, with a corresponding ARR of 1.6% (95% CI: 0.7% to 2.4%; $p = 0.0003$) (14). The **Central Illustration** and Online Figure 1 show that this overall efficacy reflects a

TABLE 2 Primary MACE Endpoint and All-Cause Death by History of PAD or CeVD Category

	Alirocumab	Placebo	HR* (95% CI)	HR Interaction p Value*	ARR (95% CI)	ARR Interaction p Value*
Primary composite						
Monovascular disease (CAD without PAD or CeVD)	740/8,683 (8.5)	866/8,687 (10.0)	0.85 (0.77 to 0.93)		1.4 (0.6 to 2.3)	
Disease in 2 vascular beds						
CAD and PAD	69/302 (22.8)	73/308 (23.7)	0.93 (0.67 to 1.30)	0.40	0.9 (−5.9 to 7.6)	0.0006
CAD and CeVD	75/406 (18.5)	82/389 (21.1)	0.87 (0.63 to 1.19)		2.6 (−2.9 to 8.2)	
Disease in 3 vascular beds (CAD, PAD, and CeVD)	19/71 (26.8)	31/78 (39.7)	0.64 (0.35 to 1.12)		13.0 (−2.0 to 28.0)	
All patients	903/9,462 (9.5)	1,052/9,462 (11.1)	0.85 (0.78 to 0.93)		1.6 (0.7 to 2.4)	
All-cause death						
Monovascular disease (CAD without PAD or CeVD)	268/8,683 (3.1)	305/8,687 (3.5)	0.88 (0.75 to 1.04)		0.4 (−0.1 to 1.0)	
Disease in 2 vascular beds						
CAD and PAD	28/302 (9.3)	27/308 (8.8)	1.03 (0.60 to 1.75)	0.06	−0.5 (−5.1 to 4.0)	0.002
CAD and CeVD	34/406 (8.4)	43/389 (11.1)	0.68 (0.44 to 1.08)		2.7 (1.4 to 6.8)	
Disease in 3 vascular beds (CAD, PAD, and CeVD)	4/71 (5.6)	17/78 (21.8)	0.23 (0.08 to 0.68)		16.2 (5.5 to 26.8)	
All patients	334/9,462 (3.5)	392/9,462 (4.1)	0.85 (0.77 to 0.98)		0.6 (0.1 to 1.2)	

Values are n/N (%) unless otherwise indicated. *HRs reflect stratification by geographic region in models with interaction between treatment and the 3 disease bed subgroups (monovascular disease, disease in 2 beds, and disease in 3 beds).

ARR = absolute risk reduction; CAD = coronary artery disease; CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiovascular event; other abbreviations as in Table 1.

gradient of absolute risk and ARR according to the number of diseased vascular beds. For patients in the placebo group with 1, 2, or 3 diseased vascular beds, the incidence of MACEs was 10.0%, 22.2%, and 39.7%, respectively. The corresponding ARR with alirocumab was 1.4% (95% CI: 0.6% to 2.3%), 1.9% (95% CI: −2.4% to 6.2%), and 13.0% (95% CI: −2.0% to 28.0%), with an interaction p = 0.0006.

For all-cause death in ODYSSEY OUTCOMES, the overall incidence of death in the placebo and alirocumab groups was 4.1% and 3.5%, respectively, with a corresponding ARR of 0.6% (95% CI: 0.2% to 1.2%) (14).

TABLE 3 Safety Endpoints

	Monovascular Disease		Disease in 2 Vascular Beds				Disease in 3 Vascular Beds	
	CAD Without PAD or CeVD		CAD and PAD		CAD and CeVD		CAD, PAD, and CeVD	
	Alirocumab (n = 8,672)	Placebo (n = 8,668)	Alirocumab (n = 302)	Placebo (n = 308)	Alirocumab (n = 406)	Placebo (n = 389)	Alirocumab (n = 71)	Placebo (n = 78)
Any adverse event	6,532 (75.3)	6,619 (76.4)	250 (82.8)	262 (85.1)	321 (79.1)	328 (84.3)	62 (87.3)	73 (93.6)
Serious adverse event	1,905 (22.0)	2,012 (23.2)	124 (41.1)	142 (46.1)	136 (33.5)	151 (38.8)	37 (52.1)	45 (57.7)
Adverse event that led to death	143 (1.6)	175 (2.0)	15 (5.0)	15 (4.9)	22 (5.4)	24 (6.2)	1 (1.4)	8 (10.3)
Adverse event that led to treatment discontinuation	298 (3.4)	285 (3.3)	21 (7.0)	15 (4.9)	19 (4.7)	18 (4.6)	5 (7.0)	6 (7.7)
Local injection-site reaction	339 (3.9)	185 (2.1)	8 (2.6)	4 (1.3)	9 (2.2)	11 (2.8)	4 (5.6)	3 (3.8)
General allergic reaction	670 (7.7)	643 (7.4)	31 (10.3)	38 (12.3)	41 (10.1)	45 (11.6)	6 (8.5)	10 (12.8)
Diabetes worsening or diabetic complication in patients with diabetes at baseline	444/2,369 (18.7)	521/2,427 (21.5)	23/99 (2.3)	28/126 (22.2)	29/188 (15.4)	32/161 (19.9)	10/32 (31.3)	2/33 (6.1)
New-onset diabetes among patients without diabetes at baseline*	595/6,303 (9.4)	617/6,241 (9.9)	26/203 (12.8)	22/182 (12.1)	24/218 (11.0)	32/228 (14.0)	3/39 (7.7)	5/45 (11.1)
Neurocognitive disorder	120 (1.4)	143 (1.6)	6 (2.0)	10 (3.2)	9 (2.2)	10 (2.6)	8 (11.3)	4 (5.1)
Hepatic disorder	450 (5.2)	493 (5.7)	19 (6.3)	18 (5.8)	24 (5.9)	21 (5.4)	7 (9.9)	2 (2.6)
Cataracts	99 (1.1)	117 (1.3)	8 (2.6)	9 (2.9)	10 (2.5)	5 (1.3)	3 (4.2)	3 (3.8)
Hemorrhagic stroke, adjudicated (fatal and nonfatal)	10 (0.1)	13 (0.1)	1 (0.3)	1 (0.3)	2 (0.5)	3 (0.8)	0 (0.0)	0 (0.0)

Values are n (%) or n/N (%). *New-onset diabetes was defined according to the presence of 1 or more of the following, with confirmation of the diagnosis by blinded external review by experts in the field of diabetes: an adverse event report, a new prescription for diabetes medication, a glycated hemoglobin level of ≥6.5% on 2 occasions (and a baseline level of <6.5%), or a fasting serum glucose level of ≥126 mg/dl (7.0 mmol/l) on 2 occasions (and a baseline level of <126 mg/dl).

Abbreviations as in Table 1.

Similar to MACEs, there was a gradient of absolute risk and ARR with alirocumab. In the placebo group, the incidence of death in patients with 1, 2, or 3 diseased vascular beds was 3.5%, 10.0%, and 21.8%, respectively. With alirocumab, the corresponding ARR was 0.4% (95% CI: −0.1% to 1.0%), 1.3% (95% CI: −1.8% to 4.3%), and 16.2% (95% CI: 5.5% to 26.8%), with an interaction $p = 0.002$.

Details of the primary MACE endpoint and all-cause death are shown in **Table 2**, including the total number of events with corresponding hazard ratio and ARR of alirocumab versus placebo for primary endpoint and all-cause death for patients with monovascular disease, polyvascular disease in 2 or 3 beds, polyvascular disease in 2 beds (split by PAD or CeVD), and polyvascular disease in 3 beds. Online Tables 1 and 2 show these details for both sensitivity analyses (monovascular vs. polyvascular and the 4 overlapping vascular groups on the basis of PAD or CeVD).

SAFETY OUTCOMES. Overall, there were no differences in the incidence of adverse events or laboratory abnormalities between alirocumab and placebo groups, with the exception of local injection-site reactions, which occurred more often in the alirocumab group (14). **Table 3** shows all safety endpoints for alirocumab versus placebo for patients with monovascular disease, polyvascular disease in 2 beds (categorized as PAD or CeVD), and polyvascular disease in 3 beds. No major differences were observed among the groups.

DISCUSSION

In patients with recent ACS and dyslipidemia despite intensive statin therapy and high rates of guideline-directed medical therapy, polyvascular disease is associated with high risks of MACEs and death. The large absolute reductions in both MACEs and death with alirocumab therapy are a potential benefit for this group of patients.

This analysis of ODYSSEY OUTCOMES defines easily identifiable subsets of patients with ACS with high absolute risk and marked absolute benefit of PCSK9 inhibition with alirocumab. Identification of patient subsets likely to derive large absolute benefit is important (15,16).

Increasing risks of MACEs and death in patients with an increasing number of affected vascular beds have been described previously in large cohorts such as the REACH (Reduction of Atherothrombosis for Continued Health), CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines), and the American Heart Association Get With the Guidelines registries (2,5,17), but they remain a therapeutic challenge. It is likely that the elevated cardiovascular risk associated with polyvascular disease is the result in part of clustering of risk factors known to affect prognosis, including older age and more frequent history of hypertension, diabetes, prior myocardial infarction, coronary artery bypass surgery, and chronic kidney disease, as was observed in the present analysis. Dyslipidemia, including higher levels of LDL-C and lipoprotein(a), was also more pronounced in patients with polyvascular disease than in patients with monovascular (coronary) disease (**Table 1**). Studies have shown that high-intensity compared with low- to moderate-intensity statin therapy reduces MACEs and death in patients with polyvascular disease, including trials with ACS, but also PAD and CeVD (7,18,19). Our findings reinforce and extend this concept with reduction of LDL-C to less than levels achievable with statins by using alirocumab. Although alirocumab produced a similar degree of LDL-C lowering in each vascular category, a particularly pronounced absolute reduction of MACEs and death was observed in patients with ACS and concurrent disease in other vascular beds. Similar conclusions regarding MACEs were drawn from an analysis of the FOURIER trial, using the PCSK9 inhibitor evolocumab added to statin in patients with stable, established atherosclerotic cardiovascular disease (12). In that analysis, evolocumab reduced the risk of cardiovascular-related events in patients with PAD. Of note, because of trial selection criteria, patients with PAD comprised 13.2% of the FOURIER cohort, compared with 3.2% in ODYSSEY OUTCOMES (12). However, some patients in FOURIER with PAD or CeVD had monovascular disease in those territories. Conversely, because qualification for ODYSSEY OUTCOMES required ACS, all patients with PAD or CeVD had disease in at least 2 vascular beds.

STUDY LIMITATIONS. A substantial fraction of the patients categorized as having monovascular (coronary) disease may have had undetected PAD or CeVD, given that they were not systematically evaluated for those conditions at baseline. However, the classification used in the present analysis is representative of daily clinical practice and decision making because patients with ACS are not routinely screened for polyvascular disease (20).

CONCLUSIONS

The present findings indicate that patients with polyvascular disease comprise an easily identifiable subgroup of patients with recent ACS with a high absolute risk of MACEs and death. The large absolute benefit of PCSK9 inhibition with alirocumab, when added to high-intensity statin therapy, is a potential benefit for this group of patients. However, further studies are needed to guide the selection of patients with ACS for treatment with a PCSK9 inhibitor in the context of other established and evolving therapies in atherosclerosis, so that efficacy and efficiency are optimized (21–23).

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Patients with polyvascular disease and ACS gain considerable absolute benefit from PCSK9 inhibition with alirocumab.

TRANSLATIONAL OUTLOOK: Further studies are needed to identify other subgroups of patients with atherosclerosis who stand to gain substantial benefit from PCSK9 inhibition.

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KEY WORDS acute coronary syndrome, alirocumab, cerebrovascular disease, death, major adverse cardiac events, peripheral artery disease

APPENDIX For supplemental tables and a complete list of the ODYSSEY OUTCOMES committees and investigators, please see the online version of this paper.