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Triglyceride Levels, Alirocumab Treatment, and Cardiovascular Outcomes After an Acute Coronary Syndrome

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ABSTRACT

BACKGROUND It is unknown whether clinical benefit of proprotein convertase subtilisin/kexin type 9 inhibitors is associated with baseline or on-treatment triglyceride concentrations.

OBJECTIVES This study sought to examine relations between triglyceride levels and the effect of alirocumab vs placebo on cardiovascular outcomes using prespecified and post hoc analyses of the ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial.

METHODS Patients with recent acute coronary syndrome (ACS) (n = 18,924) and elevated atherogenic lipoproteins despite optimized statin therapy were randomized to alirocumab 75 to 150 mg or matching placebo every 2 weeks subcutaneously. Major adverse cardiovascular events (MACE) were examined in relation to continuous or dichotomous triglyceride concentrations.

RESULTS Median baseline triglyceride concentration was 129 mg/dL. In both treatment groups, a 10-mg/dL higher baseline concentration was associated with an adjusted MACE HR of 1.008 (95% CI: 1.003-1.013; $P < 0.005$). Baseline triglycerides ≥150 vs <150 mg/dL were associated with a HR of 1.184 (95% CI: 1.080-1.297; $P < 0.005$). Versus placebo, alirocumab reduced low-density lipoprotein cholesterol from baseline (average, 54.7%) and reduced MACE (HR: 0.85; 95% CI: 0.78-0.93). At month 4, triglyceride levels were reduced from baseline by median 17.7 mg/dL ($P < 0.001$) and 0.9 mg/dL (P = NS) with alirocumab and placebo, respectively. A 10-mg/dL decline from baseline in triglycerides was associated with lower subsequent risk of MACE with placebo (HR: 0.988; 95% CI: 0.982-0.995; $P < 0.005$) but not with alirocumab (HR: 0.999; 95% CI: 0.987-1.010; $P = 0.82$).

CONCLUSIONS Among patients with recent ACS on optimized statin therapy, baseline triglycerides was associated with cardiovascular risk. However, the reduction in triglycerides with alirocumab did not contribute to its clinical benefit. (ODYSSEY Outcomes: Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; NCT01663402) (*JACC*. 2024;84:994-1006) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Elevated circulating triglyceride levels, contained in the core of lipoprotein particles, are associated with increased cardiovascular risk.[1] Because elevated triglycerides often coexist with other metabolic derangements, notably insulin-resistant states, including type 2 diabetes, obesity, low levels of high-density lipoprotein cholesterol (HDL-C), and hypertension, it remains uncertain whether triglyceride-rich lipoproteins directly influence the risk of major adverse cardiovascular events (MACE). Analyses using genetic instrumental variables have shown an association between the levels of triglycerides or remnant cholesterol (calculated as cholesterol not contained in low- or high-density lipoproteins) and cardiovascular risk.[2-4] Trials of lipid-modifying therapies in patients with recent acute coronary syndrome (ACS) have shown an association between baseline triglyceride levels and the risk of MACE.[5,6] However, despite moderate triglyceride-lowering effects, trials of fibrates and omega-3 fatty acids have either failed to demonstrate a cardiovascular benefit[7-10] or have shown that such benefit is mostly unrelated to triglyceride reduction.[11]

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Monoclonal antibodies against proprotein convertase subtilisin/kexin type 9 (PCSK9), including evolocumab and alirocumab, produce a substantial reduction in low-density lipoprotein cholesterol (LDL-C) concentration with modest reductions in lipoprotein(a) (Lp[a]), and triglyceride concentrations,[12-15] as well as the cholesterol content of very low-density, intermediate-density, and remnant lipoproteins.[16] PCSK9 inhibitors reduce MACE in patients with chronic atherosclerotic cardiovascular disease or recent ACS, many of whom have elevated triglyceride levels.[17] However, it is unknown whether and to what extent the clinical benefit of PCSK9 inhibitors is associated with baseline triglyceride concentration and its reduction with treatment.

The ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial compared alirocumab with placebo in 18,924 patients with recent ACS.[17] During the ODYSSEY OUTCOMES trial, alirocumab reduced LDL-C from baseline by an average of 54.7% compared with placebo at 48 months, and reduced the risk of MACE compared with placebo (HR: 0.85; 95% CI: 0.78-0.93).[17] In prespecified and post hoc analyses, we examined the prognostic effect of baseline triglyceride levels and the relation between treatment-associated changes in triglyceride levels and subsequent risk of MACE.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

apoB = apolipoprotein B

BMI = body mass index

HDL-C = high-density lipoprotein cholesterol

LDL-C = low-density lipoprotein cholesterol

Lp(a) = lipoprotein(a)

MACE = major adverse cardiovascular event

PCSK9 = proprotein convertase subtilisin/kexin type 9

METHODS

The design of the ODYSSEY OUTCOMES trial has been previously reported.[17] Briefly, this was an international, randomized, double-blind, placebo-controlled trial in patients with a recent ACS and an LDL-C level ≥70 mg/dL, a non-HDL-C level ≥100 mg/dL, and/or an apolipoprotein B (apoB) level ≥80 mg/dL despite high-intensity or maximum-tolerated statin therapy. Fasting triglycerides >400 mg/dL were exclusionary. Patients who met entry criteria were randomly assigned to receive alirocumab 75 mg or matching placebo every 2 weeks by subcutaneous injection. Fasting lipid levels were obtained at randomization and at multiple time points during the trial; patients and investigators were blinded to the results. The dose of alirocumab was adjusted under blinded conditions to target an LDL-C level of 25 to 50 mg/dL and minimize the number of patients with sustained LDL-C levels <15 mg/dL. The primary outcome of MACE comprised death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. The median duration of follow-up was 2.8 years. The ODYSSEY OUTCOMES trial protocol and statistical analysis plan were approved by the responsible regulatory authorities and ethics committees. All patients provided written informed consent.

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TABLE 1 Demographics and Baseline Characteristics by Baseline Triglyceride Group

	Triglycerides <150 mg/dL (n = 11,437)	Triglycerides ≥150 mg/dL (n = 7,085)	*P* Value
Age, y	59.1 ± 9.4	57.7 ± 9.2	<0.0001[a]
Age group 1			
<65 y	8,125 (71.0)	5,438 (76.8)	
65-<75 y	2,647 (23.1)	1,329 (18.8)	
≥75 y	665 (5.8)	318 (4.5)	<0.0001[b]
Age group 2			
<65 y	8,125 (71.0)	5,438 (76.8)	
≥65 y	3,312 (29.0)	1,647 (23.2)	<0.0001[b]
Sex			
Female	2,849 (24.9)	1,821 (25.7)	
Male	8,588 (75.1)	5,264 (74.3)	0.2278[b]
Race			
White	8,929 (78.1)	5,718 (80.7)	
Black or African American	345 (3.0)	123 (1.7)	
Asian	1,641 (14.3)	842 (11.9)	
Other	513 (4.5)	400 (5.6)	
Unknown	6 (0.1)	2 (0.0)	
Missing	3 (0.0)	0 (0.0)	<0.0001[b]
BMI, kg/m^2	27.9 ± 4.8	29.5 ± 4.9	<0.0001[a]
BMI group			
<30 kg/m^2	8,142 (71.2)	4,160 (58.7)	
≥30 kg/m^2	3,225 (28.2)	2,892 (40.8)	
Missing	70 (0.6)	33 (0.5)	<0.0001[b]
Country group			
North America	1,591 (13.9)	1,200 (16.9)	
South America	1,374 (12.0)	1,209 (17.1)	
Western Europe	2,670 (23.3)	1,301 (18.4)	
Eastern Europe	3,290 (28.8)	2,093 (29.5)	
Asia	1,515 (13.2)	766 (10.8)	
Rest of world	997 (8.7)	516 (7.3)	<0.0001[b]
Baseline laboratory parameters			
LDL-C, mg/dL	91.3 ± 27.4	94.3 ± 36.1	<0.0001[a]
Non-HDL-C, mg/dL	111.8 ± 28.5	139.5 ± 38.5	<0.0001[a]
Total cholesterol, mg/dL	158.1 ± 31.9	180.1 ± 40.9	<0.0001[a]
HDL-C, mg/dL	46.5 ± 11.7	40.6 ± 9.8	<0.0001[a]
Triglycerides, mg/dL	101.8 (80.5-123.0)	200.9 (171.7-252.2)	<0.0001[a]
Lp(a), mg/dL	24.7 (8.0-62.9)	15.6 (5.1-53.2)	<0.0001[a]
ApoB, mg/dL	76.9 ± 17.5	93.4 ± 23.3	<0.0001[a]
ApoA1, mg/dL	134.4 ± 24.2	132.6 ± 22.9	<0.0001[a]
Hemoglobin A1c, %	6.1 ± 1.1	6.4 ± 1.4	<0.0001[a]
Medications of interest received at randomization			
Aspirin and/or oral ADP receptor antagonists	11,298 (98.8)	7,009 (98.9)	0.3783[c]
Antidiabetic drugs	1,973 (17.3)	1,844 (26.0)	<0.0001[c]
Insulin	638 (5.6)	594 (8.4)	
Injectable (other than insulin)	21 (0.2)	21 (0.3)	
Oral	1,673 (14.6)	1,593 (22.5)	
ACE inhibitor or angiotensin receptor blocker	8,830 (77.2)	5,596 (79.0)	0.0046[c]
Beta-blocker	9,496 (83.0)	6147 (86.8)	<0.0001[c]
Calcium-channel blocker	1,605 (14.0)	1,084 (15.3)	0.0174[c]
Diuretics	2,422 (21.2)	1,810 (25.5)	<0.0001[c]
Nitrates	2,476 (21.6)	1,557 (22.0)	0.6003[c]

Continued on the next page

TABLE 1 Continued

	Triglycerides <150 mg/dL (n = 11,437)	Triglycerides ≥150 mg/dL (n = 7,085)	*P* Value
CAD before index ACS	3,630 (31.7)	2,663 (37.6)	<0.0001[c]
Prior myocardial infarction	2,025 (17.7)	1,529 (21.6)	
Prior coronary artery bypass graft surgery	553 (4.8)	452 (6.4)	
Prior percutaneous coronary intervention	1,751 (15.3)	1,416 (20.0)	
Hypertension	7,157 (62.6)	4,868 (68.7)	<0.0001[c]
Family history of CAD	4,020 (35.1)	2,575 (36.3)	<0.0001[c]
Type 1 or type 2 diabetes mellitus	2,360 (20.6)	2,202 (31.1)	<0.0001[c]
Congestive heart failure	1,685 (14.7)	1,109 (15.7)	0.0012[c]

Values are mean ± SD, n (%), or median (Q1-Q3). [a]Welch's *t* test. [b]Cochran-Mantel-Haenszel test. [c]Chi-square test.

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; ADP = adenosine diphosphate; apoA1 = apolipoprotein A1; apoB = apolipoprotein B; BMI = body mass index; CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a).

STATISTICAL ANALYSIS

PRESPECIFIED ANALYSES RELATED TO BASELINE TRIGLYCERIDE LEVELS. We examined the incidence of MACE in the aggregate trial population as well as in the alirocumab and placebo groups according to baseline triglyceride categories ≥150 vs <150 mg/dL and according to continuous baseline triglyceride concentration. For this purpose, proportional hazards models were constructed with adjustment for age, sex, geographical region, diabetes, coronary artery disease prior to index ACS event, hypertension, heart failure, peripheral arterial disease, cerebrovascular disease, body mass index (BMI), baseline LDL-C, and baseline Lp(a). The incidence of MACE for continuous vs median baseline triglyceride concentrations was evaluated using spline analysis with a natural cubic basis and 3 knots located at the 25th, 50th, and 75th percentiles.

POST HOC ANALYSES RELATED TO ON-TREATMENT TRIGLYCERIDE LEVELS. Median levels of triglycerides and other lipids were determined at month 4 of assigned treatment along with their changes from baseline to month 4. If multiple values existed within an analysis window, the value nearest to the targeted time point was selected for analysis.

The relationship between the change in triglycerides from baseline to month 4 and the incidence of MACE after month 4 was examined using 3 proportional hazards models. Model 1 was unadjusted. Model 2 was adjusted for baseline triglyceride concentration. Model 3 was further adjusted for baseline characteristics associated with triglyceride levels or the risk of MACE (age, sex, race, geographical region, diabetes, BMI, smoking history, time from qualifying ACS event to randomization, HDL-C, LDL-C, and Lp(a)) and for the changes in LDL-C and Lp(a) from baseline to month 4. The incidence of MACE was assessed through spline analysis with a natural cubic basis and 3 knots positioned at 25th, 50th, and 75th percentiles, to compare continuous to median triglyceride change.

Among patients with baseline triglycerides ≥150 mg/dL in both treatment groups, we evaluated the risk of MACE after month 4 according to whether triglyceride levels at month 4 had decreased to <150 mg/dL or remained ≥150 mg/dL. For this purpose, the following proportional hazards models were constructed: 1) a model adjusted for treatment group; 2) a model additionally adjusted for baseline triglycerides, LDL-C, Lp(a), and HDL-C; and 3) a model additionally adjusted for the changes from baseline to month 4 in LDL-C and Lp(a). Time at risk was defined as the time from randomization to the earliest date of: 1) withdrawal from the trial; 2) first episode of the evaluated event; or 3) end of the trial.

We also assessed the risk of MACE in patients who achieved an LDL-C concentration <55 mg/dL at month 4 (consistent with recent guidelines and consensus statements)[1,18] according to whether baseline triglycerides were ≥150 or <150 mg/dL. For these subgroups, 3 proportional hazards models were constructed with adjustment variables as previously mentioned. No imputation was performed for missing data. *P* values <0.05 were considered nominally significant. Analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

At randomization, mean and median triglyceride levels in both treatment groups were 150 mg/dL and

129 mg/dL, respectively. Median triglycerides in patients with baseline levels ≥150 or <150 mg/dL were 200.9 mg/dL (Q1-Q3: 171.7-252.2 mg/dL) and 101.8 mg/dL (Q1-Q3: 80.5-123.0 mg/dL), respectively. Although patients with triglycerides >400 mg/dL at the qualifying visit were excluded, a few patients had triglycerides ≤400 mg/dL at the qualifying visit but >400 mg/dL at randomization. As shown in **Table 1**, patients with a baseline triglyceride level ≥150 mg/dL differed in many respects from those with a lower baseline value. The former category was younger, had a higher BMI, had higher prevalence of diabetes and hypertension, and more often had coronary artery disease prior to the qualifying ACS event. Patients in the higher triglyceride category also had higher baseline LDL-C, lower HDL-C, and substantially lower Lp(a) levels.

EFFECT OF BASELINE TRIGLYCERIDE LEVELS ON OUTCOME IN BOTH TREATMENT GROUPS. Considering both treatment groups in aggregate, patients with baseline triglyceride levels ≥150 mg/dL were more likely to experience MACE than patients with lower baseline triglycerides (HR: 1.184; 95% CI: 1.080-1.297) (Supplemental Table 1). Spline analysis of continuous baseline triglycerides and the HR for MACE (**Figures 1A and 1B**) indicated a relatively linear relationship between baseline triglyceride levels and the risk of MACE across treatment groups. When baseline triglyceride levels were examined as a continuous variable, the adjusted risk of MACE was significantly higher by about 1% for every 10-mg/dL higher triglyceride level (HR: 1.008; 95% CI: 1.003-1.013), with similar relationships observed in both treatment groups (Supplemental Table 2).

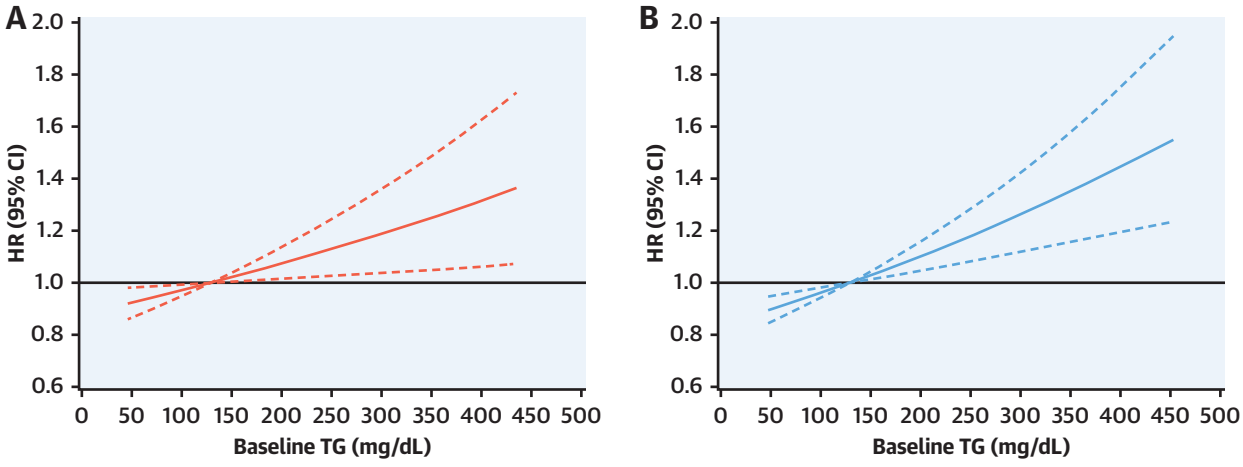
EFFECT OF ALIROCUMAB ON TRIGLYCERIDE LEVELS. Alirocumab significantly reduced triglyceride levels throughout the trial (**Figure 2**). The median absolute change in triglyceride levels between baseline and month 4 was −17.7 mg/dL in the alirocumab arm vs −0.9 mg/dL in the placebo arm ($P < 0.0001$). The reduction of LDL-C levels by alirocumab was similar among patients with an initial triglyceride level <150 mg/dL and ≥150 mg/dL (Supplemental Figure 1).

EFFECT OF ALIROCUMAB ON MACE ACCORDING TO TRIGLYCERIDE LEVELS. Compared with placebo, alirocumab reduced the risk of MACE consistently in both baseline triglyceride categories (HR: 0.87; 95% CI: 0.77-0.98; $P = 0.022$ in patients with baseline triglycerides <150 mg/dL; and HR: 0.82; 95% CI: 0.72-0.94; $P = 0.006$ in patients with baseline triglycerides ≥150 mg/dL) without treatment by baseline triglyceride interaction ($P_{interaction} = 0.820$) (Supplemental Table 3). However, the absolute reduction in the risk of MACE with alirocumab was greater in those with baseline triglycerides ≥150 vs <150 mg/dL (2.14% [95% CI: 0.67%-3.62%] vs 1.17% [95% CI: 0.09%-2.26%]).

RISK OF MACE AFTER MONTH 4 ACCORDING TO TRIGLYCERIDE LEVELS AT MONTH 4. Concentrations of triglycerides and other lipids at month 4 are shown in Supplemental Table 4. Overall, the median triglyceride levels were 108.0 mg/dL (Q1-Q3: 77.9-154.9 mg/dL) and 127.4 mg/dL (Q1-Q3: 91.2-184.1 mg/dL), while the LDL-C levels were 30.00 mg/dL (Q1-Q3: 20.08-46.72 mg/dL) and 87.26 mg/dL (Q1-Q3: 72.20-106.18 mg/dL) in the alirocumab and placebo groups, respectively. The relationship between triglyceride levels at month 4 and clinical outcomes after month 4 was evaluated among patients with baseline triglycerides ≥150 mg/dL according to whether triglyceride levels at month 4 were <150 or ≥150 mg/dL. Within the full cohort, patients who did not reach a triglyceride level <150 mg/dL at month 4 had higher baseline triglyceride levels (median 218.6 mg/dL vs 182.0 mg/dL) and lesser median change in triglycerides from baseline (−2.0 mg/dL vs −74.3 mg/dL) than those who did. Patients with month 4 triglycerides remaining at levels ≥150 mg/dL had a greater incidence of MACE after month 4 than patients reaching triglyceride levels <150 mg/dL (10.3% vs 7.5%; HR: 1.302; 95% CI: 1.089-1.556) with adjustment for treatment group. This association remained significant in adjusted model 2 (HR: 1.285; 95% CI: 1.064-1.551) and adjusted model 3 (HR: 1.314; 95% CI: 1.084-1.592) (Supplemental Table 5).

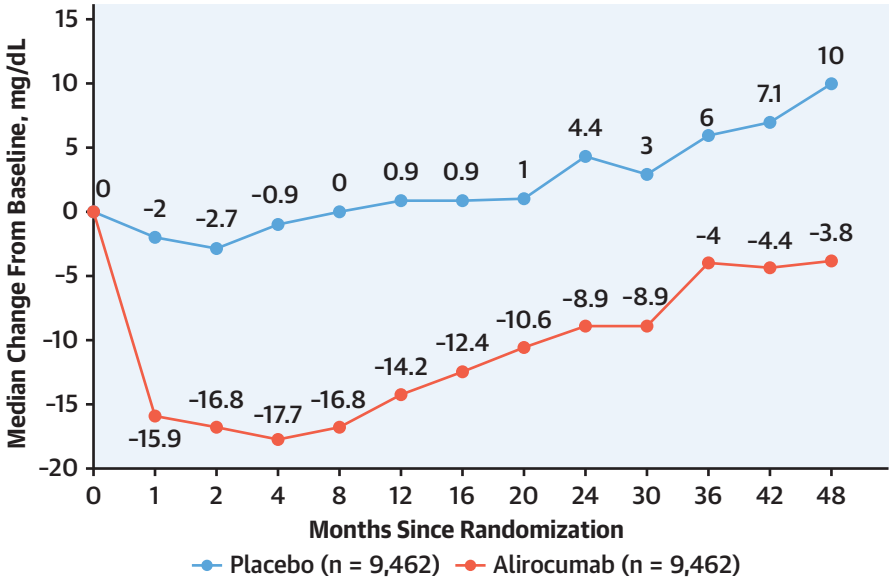
Among patients who achieved LDL-C <55 mg/dL at month 4, those with triglycerides ≥150 mg/dL at month 4 had a significantly higher incidence of MACE after month 4 than those with month 4 triglycerides <150 mg/dL (9.0% vs 6.4%; HR: 1.345; 95% CI: 1.010-1.791), adjusted for treatment group. This association remained significant in adjusted model 2 (HR: 1.383; 95% CI: 1.022-1.872) but was no longer significant in adjusted model 3 (HR: 1.235; 95% CI: 0.904-1.687) (Supplemental Table 6). In an additional analysis using triglycerides at month 4, treatment, and LDL-C change at month 4 as fixed covariates, stepwise selection identified baseline Lp(a) and change in HDL-C at month 4 as additional potentially relevant variables. In this model (model 4), among patients who achieved LDL-C <55 mg/dL at month 4, the risk of MACE after month 4 was higher when month 4 triglycerides were ≥150 mg/dL vs <150 mg/dL (HR: 1.347; 95% CI: 1.002-1.811) (Supplemental Table 6).

FIGURE 1 **Spline Analysis: Baseline TG and Risk of MACE in the Alirocumab and Placebo Groups**



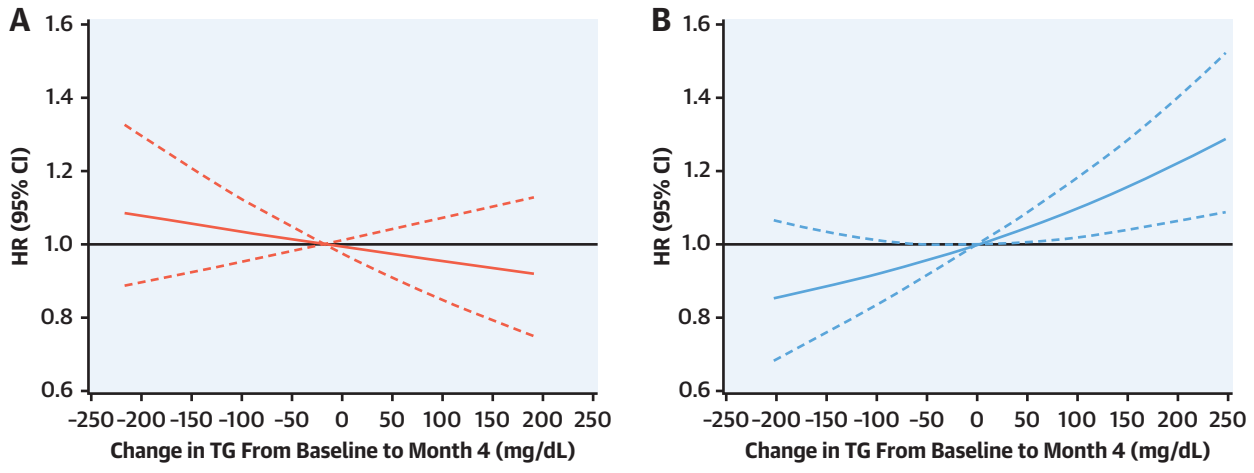
(A) Alirocumab. The x-axis represents the 1st to 99th percentiles of baseline TG in the alirocumab group. The HR was set to 1.0 at the overall baseline median (129.0 mg/dL) concentration of TG for the alirocumab group. $P < 0.0001$ for spline effect. This reflects a spline of degree 3 (piecewise cubic curve) with natural cubic basis and 3 knots, located at the overall 25th percentile (93.8 mg/dL), median (129.0 mg/dL), and 75th percentile (181.4 mg/dL). The *P* value for the spline effect is based on the score test. The red dotted lines indicate the upper and lower bounds of 95% CIs. (B) Placebo. The x-axis represents the 1st to 99th percentiles of baseline TG in the placebo group. The HR was set to 1.0 at the overall baseline median (129.2 mg/dL) concentration of TG for the placebo group. $P = 0.0008$ for spline effect. This reflects a spline of degree 3 (piecewise cubic curve) with natural cubic basis and 3 knots, located at the overall 25th percentile (94.7 mg/dL), median (129.2 mg/dL), and 75th percentile (183.0 mg/dL). The *P* value for the spline effect is based on the score test. The blue dotted lines indicate the upper and lower bounds of 95% CIs. MACE = major adverse cardiovascular events. TG = triglycerides.

FIGURE 2 **Median Change in Triglycerides to Month 48**



Alirocumab significantly reduced triglycerides throughout the trial ($P < 0.0001$ at month 4).

FIGURE 3 Spline Analysis: Change From Baseline in TG and Risk of MACE in the Alirocumab and Placebo Groups



(A) Alirocumab. The x-axis represents the 1st to 99th percentiles of change in TG from baseline at month 4 in the alirocumab group. The HR was set to 1.0 at the overall median change from baseline (−17.7 mg/dL) in TG levels at month 4 in the alirocumab group. $P = 0.7009$ for spline effect. This reflects a spline of degree 3 (piecewise cubic curve) with natural cubic basis and 3 knots, located at the overall 25th percentile (−49.6 mg/dL), median (−17.7 mg/dL), and 75th percentile (11.0 mg/dL). The *P* value for the spline effect is based on the score test. The red dotted lines indicate the upper and lower bounds of 95% CIs. (B) Placebo. The x-axis represents the 1st to 99th percentiles of change in TG from baseline at month 4 in the placebo group. The HR was set to 1.0 at the overall median change from baseline (−0.9 mg/dL) in TG levels at month 4 in the placebo group. $P = 0.0084$ for spline effect. This reflects a spline of degree 3 (piecewise cubic curve) with natural cubic basis and 3 knots, located at the overall 25th percentile (−31.9 mg/dL), median (−0.9 mg/dL), and 75th percentile (31.0 mg/dL). The *P* value for the spline effect is based on the score test. The blue dotted lines indicate the upper and lower bounds of 95% CIs. Abbreviations as in Figure 1.

EFFECT OF CONTINUOUS CHANGE IN TRIGLYCERIDE FROM BASELINE TO MONTH 4 ON RISK OF MACE AFTER MONTH 4. Spline analysis of continuous change in triglycerides from baseline at month 4 and the HR for MACE (Figures 3A and 3B) indicated a relatively linear relationship between the change from baseline triglyceride levels and the risk of MACE in the placebo group, but not in the alirocumab group. This finding was confirmed in unadjusted (model 1) and adjusted proportional hazards models (models 2 and 3). In the placebo group, a decline of 10 mg/dL in triglycerides from baseline to month 4 was associated with modestly lower risk of MACE after month 4 (HR: 0.988; 95% CI: 0.982-0.995; $P < 0.005$). In the alirocumab group, despite the systematic reduction of triglycerides levels on treatment, a 10-mg/dL decrease in triglycerides from baseline to month 4 was not associated with the subsequent risk of MACE (HR: 0.999; 95% CI: 0.987-1.010; $P = 0.82$) (Table 2, model 3).

DISCUSSION

We studied the relationship of triglyceride levels at baseline and on assigned randomized treatment with alirocumab or placebo to risk of MACE in a large cohort of patients with recent ACS receiving optimized statin therapy. Key findings were as follows (Central Illustration). First, baseline triglyceride levels predicted MACE, even after adjustment for covariates associated with triglyceride levels and risk of MACE, including diabetes and HDL-C. Second, in the placebo group, there was no overall change in triglyceride levels from baseline to month 4, but levels changed in individual patients. Lower triglyceride levels at month 4 compared with baseline associated with a lower subsequent risk of MACE. In the alirocumab group, despite the systematic reduction of triglyceride levels on treatment, the change in triglycerides from baseline to month 4 did not predict the subsequent risk of MACE. Third, among patients with baseline triglyceride levels ≥150 mg/dL, those with levels <150 mg/dL at month 4 had a lower adjusted risk of subsequent MACE than those whose levels remained ≥150 mg/dL. The association remained even when LDL-C at month 4 was <55 mg/dL.

Whether triglyceride-rich lipoproteins are mediators or markers of risk, and hence whether they should be an independent target for treatment, remains a key unanswered question. Mendelian randomization analyses suggest that genetic instrumental variables associated with triglyceride or

TABLE 2 Relationship of Change in Triglycerides at Month 4 on MACE After Month 4

Model	Model Adjustments	Parameter	Treatment	HR (95% CI) per 10-mg/dL Decrease	*P* Value
1	None	Change in triglycerides from baseline at month 4	Placebo	0.991 (0.983-0.999)	0.0235
2	Baseline triglycerides	Change in triglycerides from baseline at month 4	Placebo	0.987 (0.981-0.994)	0.0002
3	Baseline triglycerides, baseline HDL-C, baseline LDL-C, change in LDL-C from baseline at month 4, baseline Lp(a), change in Lp(a) from baseline at month 4, age (years), sex, race, country, baseline BMI, smoking history, baseline diabetes, time from ACS event until randomization (months)	Change in triglycerides from baseline at month 4	Placebo	0.988 (0.982-0.995)	0.0008
1	None	Change in triglycerides from baseline at month 4	Alirocumab	1.004 (0.993-1.014)	0.4744
2	Baseline triglycerides	Change in triglycerides from baseline at month 4	Alirocumab	0.998 (0.989-1.007)	0.6219
3	Baseline triglycerides, baseline HDL-C, baseline LDL-C, change in LDL-C from baseline at month 4, baseline Lp(a), change in Lp(a) from baseline at month 4, age (years), sex, race, country, baseline BMI, smoking history, baseline diabetes, time from ACS event until randomization (months)	Change in triglycerides from baseline at month 4	Alirocumab	0.999 (0.987-1.010)	0.8150

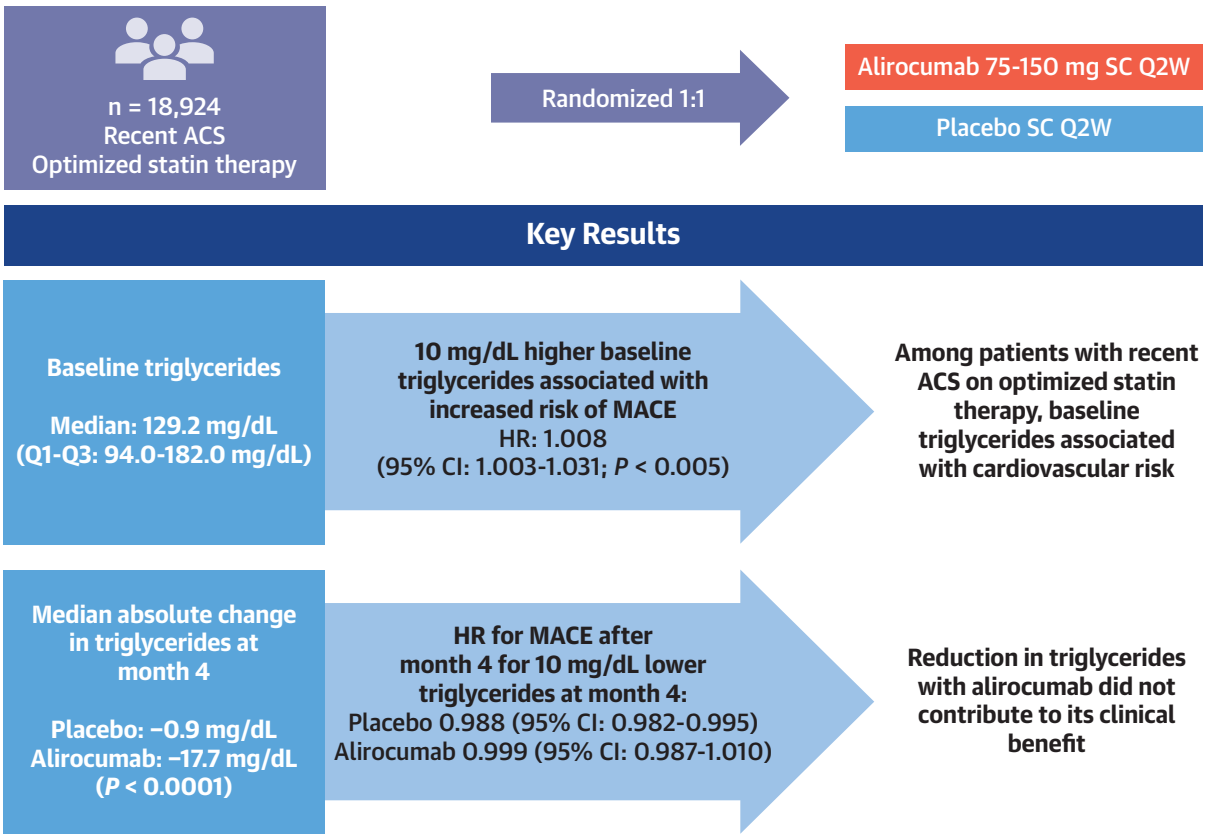
MACE = major adverse cardiovascular event; other abbreviations as in Table 1.

remnant cholesterol levels are related to coronary events,[2,3,19-21] potentially through accompanying effects on apoB levels.[21] The Emerging Risk Factors Collaboration showed that triglyceride levels did not have incremental prognostic value beyond that of HDL, apolipoprotein A1, or apoB levels.[22] However, other observational data show that increasing triglyceride levels associate with higher risk of atherosclerotic events.[23] A meta-regression analysis of placebo-controlled trials with fibrates preceding the PROMINENT (Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes) trial[24] showed that the magnitude of cardiovascular risk reduction was associated with between-group difference in triglycerides and non-HDL-C. Another meta-regression analysis of randomized trials found that triglyceride lowering was associated with reduced risk of cardiovascular events, although to a lesser extent than that associated with LDL-C reduction.[25] The PESA (Progression of Early Subclinical Atherosclerosis) investigators showed that among apparently healthy persons at low-to-intermediate cardiovascular risk, triglyceride levels of >150 mg/dL were associated with subclinical atherosclerosis and inflammation, even in the presence of normal LDL levels.[26] Prior analyses have indicated an association of triglyceride levels with cardiovascular risk after ACS on a background of statin treatment.[5,6] The European Atherosclerosis Society concluded that evidence supports an independent role of triglyceride-rich lipoproteins in atherosclerosis.[27] Importantly, this risk is probably mediated through cholesterol contained in triglyceride-rich remnant particles.[28]

Other evidence points away from triglyceride-rich lipoproteins as a direct target of therapy. The REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention) trial showed that higher baseline triglycerides were associated with greater cardiovascular risk, but the effect of icosapent ethyl in reducing this risk was not attributable to triglyceride lowering.[11] Another large clinical trial of omega-3 fatty acids (STRENGTH [Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia])[29] and the PROMINENT trial of pemafibrate[10] failed to show cardiovascular benefits despite 18% and 26% reductions in triglyceride levels, respectively. Interestingly, in both of these trials only about one-fourth of treated patients reached a triglyceride level <150 mg/dL. In the PROMINENT trial, pemafibrate raised LDL-C and apoB levels by 12% and 5%, respectively, possibly accounting for the absence of clinical benefit. Conversely, a Mendelian randomization study has suggested that a benefit of triglyceride lowering, just like that of LDL-C lowering, is mediated and predicted by an accompanying reduction in apoB levels.[21]

The effect of alirocumab to reduce MACE was consistent across the range of baseline triglyceride levels. However, the relationship of change in triglycerides from baseline to month 4 to risk of MACE after month 4 appeared to differ between the placebo and alirocumab groups. In the placebo group, the

CENTRAL ILLUSTRATION **Relationship of Triglyceride Levels at Baseline or on Treatment With Alirocumab or Placebo to Cardiovascular Outcomes in Statin-Treated Patients With Recent Acute Coronary Syndrome**



Zahger D, et al. *JACC*. 2024;84(11):994-1006.

The ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial randomized statin-treated patients with recent ACS to alirocumab or placebo. A linear relationship between baseline triglyceride levels and the risk of MACE was indicated for both the alirocumab and placebo treatment groups using a spline analysis. However, a spline analysis of continuous change in triglyceride levels from baseline to month 4 and the HR for MACE indicated a relatively linear relationship between the change from baseline triglyceride levels and the risk of MACE in the placebo group but not in the alirocumab group. ACS = acute coronary syndrome; MACE = major adverse cardiovascular events; Q2W = every 2 weeks; SC = subcutaneous.

median change in triglycerides from baseline to month 4 was minimal (−0.9 mg/dL), and median LDL-C and apoB at month 4 were 87.3 and 80 mg/dL, respectively.[30] Despite no overall change in triglycerides from baseline, an improvement in triglyceride levels at month 4 in the placebo group was associated with lower risk of MACE after month 4. Among potential reasons for this association, a decline in triglycerides identified patients in the placebo group with good adherence to lifestyle modification and statin therapy, in turn reducing their cardiovascular risk. Alternatively, the findings may indicate that levels of triglyceride-rich lipoproteins affect subsequent cardiovascular risk in the presence of relatively high LDL-C and apoB levels.

In contrast, alirocumab produced a systematic reduction of triglycerides by a median 17.7 mg/dL from baseline to month 4 associated with median LDL-C and apoB levels of 30.0 and 39 mg/dL at month 4, respectively. However, the magnitude of triglyceride reduction with alirocumab from baseline to month 4 was not associated with subsequent risk of MACE. Thus, the clinical benefit of alirocumab was unrelated to its triglyceride-lowering effect, potentially indicating that levels of triglyceride-rich lipoproteins have little influence on cardiovascular risk when levels of LDL-C and apoB are very low.

Among patients who achieved LDL-C levels <55 mg/dL (the current recommended treatment goal in very high-risk patients) but had high

baseline triglycerides (≥150 mg/dL; average apoB of 93.4 mg/dL), those who achieved a triglyceride level <150 mg/dL had a lower risk of MACE than those whose triglycerides remained ≥150 mg/dL. These findings suggest that effective treatment of combined dyslipidemia (elevated triglycerides and LDL-C levels) may provide important cardiovascular benefit.

STUDY LIMITATIONS. First, it is conceivable that a reduction in triglyceride levels, even when adjusted for concurrent changes in LDL-C or achieved by those reaching a low LDL-C goal (<55 mg/dL), is a biomarker for changes in causal variables not measured in this trial, such as LDL particle size. Second, in patients with baseline triglycerides ≥150 mg/dL, a lower risk of MACE among those with on-treatment triglycerides <150 mg/dL compared with ≥150 mg/dL may be related to the fact that crossing a dichotomous boundary is more likely when baseline levels are closer to the boundary. Thus, patients with baseline triglycerides only slightly >150 mg/dL were at lower risk for MACE and more likely to achieve levels <150 mg/dL compared with those with very high baseline triglycerides, who were at higher risk for MACE but were less likely to achieve levels <150 mg/dL. Third, it is uncertain whether the current findings with alirocumab can be extrapolated to interventions that produce much larger reductions in triglycerides.[31] The effect of alirocumab on triglyceride levels was modest, and levels trended up over time in both treatment groups for reasons that may include loss of adherence to therapeutic lifestyle changes or statin therapy. In the alirocumab group, these reasons may also include discontinuation, nonadherence, or protocol-specified dose change. Finally, analyses of outcomes according to baseline triglycerides were prespecified but analyses according to achieved triglyceride levels were not.

CONCLUSIONS

In patients with recent ACS on high-intensity or maximum-tolerated statin therapy, baseline triglyceride levels independently predict the risk of MACE. Alirocumab significantly reduces triglyceride levels, with a relative treatment benefit for MACE that is consistent across triglyceride levels and absolute treatment benefit that increases with higher baseline triglycerides. Thus, patients with recent ACS and elevated triglycerides may warrant consideration for treatment with a PCSK9 inhibitor. A change in triglyceride levels from baseline to month 4 was associated with the risk of MACE after month 4 in the placebo group but not in the alirocumab group. However, alirocumab-treated patients with baseline triglycerides ≥150 mg/dL had nominally increased MACE risk if triglycerides did not decrease to <150 mg/dL. This suggests that when LDL-C and apoB levels are substantially lowered with a statin and a PCSK9 inhibitor, triglycerides and triglyceride-rich lipoproteins may no longer be markers or mediators of risk, except in patients with persistent hypertriglyceridemia.

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Dr Bhatt has served on the advisory board for Angiowave, Bayer, Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, High Enroll, Janssen, Level Ex, McKinsey, Medscape Cardiology, Merck, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences, and Stasys; has served on the Board of Directors for Angiowave (with stock options), Boston VA Research Institute, Bristol Myers Squibb (with stock), DRS.LINQ (with stock options), High Enroll (with stock), Society of Cardiovascular Patient Care, and TobeSoft; has served as the Inaugural Chair of the American Heart Association Quality Oversight Committee; has served as a consultant for Broadview Ventures and Hims; has served on the Data Monitoring Committee for Acesion Pharma, Assistance Publique-Hôpitaux de Paris, the Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), the Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi-Sankyo; for the ABILITY-DM trial, funded by Concept Medical), Novartis, the Population Health Research Institute, and Rutgers University (for the National Institutes of Health-funded MINT trial); has received honoraria from the American College of Cardiology (Senior Associate Editor, *Clinical Trials and News*, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, *Harvard Heart Letter*), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Cowen and Company, the Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor-in-Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Oakstone CME (Course Director, Comprehensive Review of Interventional Cardiology), Piper Sandler, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and U.S. national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees), Wiley (steering committee); has served as the Deputy Editor of *Clinical Cardiology*; has served as the Chair of the NCDR-ACTION Registry Steering Committee and the VA CART Research and Publications Committee; holds a patent for sotagliflozin (named on a patent for sotagliflozin assigned to Brigham and Women's Hospital who assigned to Lexicon; neither Dr Bhatt nor Brigham and Women's Hospital receives any income from this patent); has received research funding from Abbott, Acesion Pharma, Afimmune, Aker Biomarine, Amarin, Amgen, AstraZeneca, Bayer, Beren, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CinCor, Cleerly, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Javelin, Lexicon, Eli Lilly and Company, Medtronic, Merck, Moderna, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Owkin, Pfizer, PhaseBio, PLx Pharma, Recardio, Regeneron Pharmaceuticals, Inc, Reid Hoffman Foundation, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, Youngene, and 89Bio; has received royalties from Elsevier (Editor, *Braunwald's Heart Disease*); has served as a site co-investigator for Abbott, Biotronik, Boston Scientific, CSI, Endotronix, St. Jude Medical (now Abbott), Philips, SpectraWAVE, Svelte, and Vascular Solutions; is a trustee of the American College of Cardiology; and conducted unfunded research for FlowCo and Takeda. 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from CSL Behring, for the SCORED trial and the SOLOIST-WHF trial from Sanofi Australia Pty Ltd, and for the CLEAR Outcomes Study from Esperion Therapeutics Inc; and has served on the advisory board for CSL Behring and Genentech (an affiliate of F. Hoffmann-La Roche Ltd, "Roche"; Lytics Post-PCI Advisory Board at European Society of Cardiology). Dr Zeiher has received fees for serving on a steering committee for the ODYSSEY OUTCOMES trial from Sanofi; and has received advisory board and speaker fees from Sanofi, Amgen, Boehringer Ingelheim, Bayer, Novartis, Pfizer, AstraZeneca, and Vifor. Dr Steg has received grants and nonfinancial support (co-Chair of the ODYSSEY OUTCOMES trial; as such, he received no personal fees, but his institution has received funding for the time he has devoted to trial coordination, and he has received support for travel related to trial meetings) from Sanofi; has received research grants and personal fees from Bayer (Steering Committee MARINER, grant for epidemiological study), Merck (speaker fees, grant for epidemiological studies), Sanofi (co-Chair of the ODYSSEY OUTCOMES trial; co-Chair of the SCORED trial; consulting; speaking), Servier (Chair of the CLARIFY registry; grant for epidemiological research), and Amarin (executive steering committee for the REDUCE-IT trial [Disease Reduction of Cardiovascular Events With Icosapent Ethyl-Intervention Trial]; consulting); has received personal fees from Amgen, Bristol Myers Squibb, Boehringer Ingelheim, Pfizer, Idorsia, MyoKardia, Novo Nordisk, Novartis, Regeneron Pharmaceuticals, Inc, and AstraZeneca; and has a European application number/patent number, issued on October 26, 2016 (no. 15712241.7), for a method for reducing cardiovascular risk, with all royalties assigned to Sanofi. Dr Kiss has reported that he has no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with ACS on statin treatment, blood triglyceride levels correlate with cardiovascular risk, but lowering triglycerides with alirocumab does not account for the clinical benefit of PCSK9 inhibition.

TRANSLATIONAL OUTLOOK: Further research is needed to clarify the mechanisms by which high or low levels of triglyceride-rich lipoproteins affect cardiovascular risk in relation to the levels of other atherogenic lipids, such as LDL-C and apoB, and how these pathways are modified by various combinations of lipid-lowering drugs.

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KEY WORDS cardiovascular risk, clinical trial, lipids, proprotein convertase subtilisin/kexin type 9 inhibitor

APPENDIX For supplemental tables and a figure, please see the online version of this paper.