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Alirocumab Reduces Fatal and Nonfatal Cardiovascular Events

ODYSSEY OUTCOMES Trial

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ABSTRACT

BACKGROUND The ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial compared alirocumab with placebo, added to high-intensity or maximum-tolerated statin treatment, after acute coronary syndrome (ACS) in 18,924 patients. Alirocumab reduced the first occurrence of the primary composite endpoint and was associated with fewer all-cause deaths.

OBJECTIVES This pre-specified analysis determined the extent to which alirocumab reduced total (first and subsequent) nonfatal cardiovascular events and all-cause deaths in ODYSSEY OUTCOMES.

METHODS Hazard functions for total nonfatal cardiovascular events (myocardial infarction, stroke, ischemia-driven coronary revascularization, and hospitalization for unstable angina or heart failure) and death were jointly estimated, linked by a shared frailty accounting for patient risk heterogeneity and correlated within-patient nonfatal events. An association parameter also quantified the strength of the linkage between risk of nonfatal events and death. The model provides accurate relative estimates of nonfatal event risk if nonfatal events are associated with increased risk for death.

RESULTS With 3,064 first and 5,425 total events, 190 fewer first and 385 fewer total nonfatal cardiovascular events or deaths were observed with alirocumab compared with placebo. Alirocumab reduced total nonfatal cardiovascular events (hazard ratio: 0.87; 95% confidence interval: 0.82 to 0.93) and death (hazard ratio: 0.83; 95% confidence interval: 0.71 to 0.97) in the presence of a strong association between nonfatal and fatal event risk.

CONCLUSIONS In patients with ACS, the total number of nonfatal cardiovascular events and deaths prevented with alirocumab was twice the number of first events prevented. Consequently, total event reduction is a more comprehensive metric to capture the totality of alirocumab clinical efficacy after ACS. (J Am Coll Cardiol 2018;■:■-■) © 2018 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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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CI = confidence interval

HR = hazard ratio

LDL-C = low-density lipoprotein cholesterol

In cardiovascular outcomes trials, the primary efficacy assessment is usually based on an intervention delaying the time to first occurrence of an event included in a composite of related nonfatal and fatal (i.e., death) events. In this setting, patients are typically encouraged to remain on randomized therapy after a first reported nonfatal event, such that treatment may continue to modify the risk of subsequent nonfatal and fatal events. Consequently, an analysis involving only the first event may not capture the totality of the clinical impact of an intervention. Furthermore, the burden of a disease process may be best assessed by all of the events experienced by a patient, as those occurring after the first add to morbidity, mortality, and health care expenditures.

Several reports have demonstrated the benefits of intensive statin therapy on reducing first and subsequent events in composites consisting of nonfatal cardiovascular events and all-cause or cause-specific death in patients with stable coronary heart disease or an acute coronary syndrome (ACS) (1–5); similar findings have been reported with other drug classes (6,7). In trials involving these patient populations, the majority of patients are censored due to surviving the follow-up period. An important additional source of censoring that may not be fully appreciated when evaluating the effect of an intervention on nonfatal events is the occurrence of death, which, unlike other types of censoring, prevents both the observation and occurrence of subsequent nonfatal events.

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If the risks of nonfatal events and death are unrelated to one another, censoring follow-up for nonfatal events due to death would be considered "non-informative," similar to censoring due to completing the follow-up period. However, if the risk of nonfatal events is positively associated with the risk of death,

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the occurrence of death may violate the non-informative censoring assumption that is integral to statistical methods typically used to analyze total events. This can lead to erroneous estimates of nonfatal event risk, and is especially problematic if there is an imbalance in the number of deaths between treatment groups.

As previously reported, when added to high-intensity or maximum-tolerated statin therapy after ACS, alirocumab reduced the first occurrence of the primary composite endpoint and was associated with fewer deaths relative to placebo in the ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial (8). To address the previously mentioned issues in the analysis of total events, we utilized a novel approach to jointly model total nonfatal cardiovascular and fatal events in a pre-specified analysis of the study, allowing for the possibility that patients may experience multiple related nonfatal events. The method formally quantifies the association between nonfatal events and death while accounting for competing deaths that prevent follow-up for nonfatal events, resulting in a more accurate relative estimate (i.e., hazard ratio [HR]) for nonfatal event risk. Our hypothesis was that alirocumab reduces total events following ACS.

METHODS

Details of the study design (9) and primary efficacy and safety results (8) have been published. Qualifying patients were ≥40 years of age, provided written informed consent, had been hospitalized with an ACS (myocardial infarction or unstable angina) 1 to 12 months prior to randomization, and had a low-density lipoprotein cholesterol (LDL-C) ≥70 mg/dl (1.81 mmol/l), non–high-density lipoprotein cholesterol ≥100 mg/dl (2.59 mmol/l), or apolipoprotein B ≥80 mg/dl, measured after ≥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). Randomization in a 1:1 ratio to treatment with alirocumab 75 mg or matching placebo, stratified by country, was performed with 18,924 patients meeting study entry criteria. All doses of study medication were given by subcutaneous injection every 2 weeks.

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TABLE 1 Categories of Nonfatal Cardiovascular Events

	Alirocumab (n = 9,462)	Placebo (n = 9,462)	Total (n = 18,924)
Myocardial infarction	866 (39.6)	994 (39.6)	1,860 (39.6)
Stroke	131 (6.0)	181 (7.2)	312 (6.6)
Unstable angina requiring hospitalization	37 (1.7)	64 (2.5)	101 (2.1)
Heart failure requiring hospitalization	283 (12.9)	276 (11.0)	559 (11.9)
Ischemia-driven coronary revascularization procedure	869 (39.8)	998 (39.7)	1,867 (39.7)
Total	2,186 (100.0)	2,513 (100.0)	4,699 (100.0)

Values are n (%).

The primary efficacy endpoint of the study was time to first occurrence of coronary heart disease death, nonfatal myocardial infarction, fatal and nonfatal ischemic stroke, or unstable angina requiring hospitalization. Nonfatal cardiovascular events recorded in the trial included nonfatal primary endpoints, hemorrhagic stroke, heart failure requiring hospitalization, and ischemia-driven coronary revascularization. Events included in the primary analysis of the present report were all-cause death and total nonfatal cardiovascular events as defined in the previous text. A sensitivity analysis restricted total nonfatal cardiovascular events to myocardial infarction, stroke (including hemorrhagic), or unstable angina requiring hospitalization. Given the previously reported observation that the absolute benefit of alirocumab on the study primary efficacy endpoint was greater among patients with higher LDL-C at study entry, a post hoc analysis examined possible heterogeneity in the treatment effect on total nonfatal cardiovascular events and deaths in subgroups defined by LDL-C at randomization (≥100 mg/dl vs. <100 mg/dl). All nonfatal cardiovascular events and deaths included in the analyses were adjudicated by an independent committee blinded to treatment assignment.

In this analysis, we applied a joint semiparametric model (sometimes referred to as a frailty model) that allows for multiple nonfatal cardiovascular events within a given patient, while simultaneously assessing and adjusting for possible informative censoring of the nonfatal event process by death. The model provides separate hazard functions for nonfatal events and fatal events, linked by a shared frailty (10). The frailty random effect accounts for patient risk heterogeneity and the correlation between nonfatal events within a patient and is also included in the fatal event function. In the latter case, the frailty random effect is multiplied exponentially by an association parameter that quantifies the strength of the relationship between the nonfatal and fatal event processes. Specifically, an association parameter value equal to 0 indicates that death is noninformative for nonfatal events, whereas a value greater than 0 indicates that patients at greater risk of nonfatal events are also at greater risk for death. Ignoring informative censoring by death has been shown to yield inaccurate estimates of nonfatal event risk over time, whereas this joint model has been shown to provide accurate relative estimates of nonfatal and fatal event risk if patients at greater risk of nonfatal events are also at increased risk for death (11). The Online Appendix provides additional details for the model.

In its current application, the joint model estimates the effect of alirocumab relative to placebo on total adjudicated nonfatal cardiovascular events and separately on all-cause death, as well as the association between nonfatal cardiovascular events and death. A semiparametric penalized likelihood technique (11) was applied for parameter estimation, using splines with 10 knots to estimate baseline hazards, and the shared frailty was assumed to have a gamma distribution. Treatment effects on nonfatal and fatal events are summarized by HRs and corresponding 95% confidence intervals (CIs), with standard errors derived from the final Hessian matrix and p values for each estimated effect in the model from z-distributions. Point estimates and corresponding 95% CIs and p values were also calculated for the association parameters. Note that the estimated treatment HR and 95% CI for all-cause death from a joint analysis may differ numerically from that derived by other modeling strategies (e.g., Cox regression).

For model convergence purposes, for a given patient, a nonfatal event that occurred on the same day as death was excluded, and a maximum of 1 nonfatal event was allowed to occur on a given day. With these conventions, all nonfatal events and deaths within a given patient have distinct event times from randomization.

Nonparametric mean cumulative function curves were created for total nonfatal cardiovascular events. The mean cumulative function represents the expected (i.e., mean) cumulative number of events for a patient at a given point in time after randomization. For comparative purposes, Kaplan-Meier curves were also created for first nonfatal events and plotted with the mean cumulative function curves. Continuous variables are expressed as median (quartile 1, quartile 3), and categorical variables are expressed as counts and percentages. Comparisons of baseline demographics and clinical characteristics of patients grouped by categories of nonfatal and fatal

event frequencies were by Wilcoxon rank sum tests for continuous variables and chi-square and Fisher exact tests (where possible) for categorical variables. For all analyses, 2-tailed p values <0.05 were considered statistically significant, with no adjustment for multiple testing.

All analyses were conducted according to intention-to-treat, including all patients and events from randomization to the common study end date (November 11, 2017). Unless otherwise indicated, analyses were pre-specified prior to unblinding of the study database. Analyses were performed in SAS version 9.4 (IBM, Armonk, New York) and R version 3.5 (R Foundation, Vienna, Austria).

RESULTS

Patients were followed for survival for a median of 2.8 years (quartile 1, quartile 3: 2.3, 3.4 years), consisting of 27,014 patient-years for the alirocumab group and 26,915 patient-years for the placebo group. Ascertainment was complete for 99.1% and 99.8% of potential patient-years of follow-up for nonfatal cardiovascular events and survival, respectively. Exposure to randomized treatment as a percentage of follow-up for survival was 85.2% and 89.8% for the alirocumab and placebo groups, respectively; this excludes per-protocol blinded exposure to placebo in the alirocumab group following 2 consecutive LDL-C measurements below 15 mg/dl (9). Among 1,230 patients in the alirocumab group and 1,392 patients in the placebo group with an initial nonfatal cardiovascular event, 81.9% (excluding blinded placebo) and 84.6%, respectively, were receiving randomized treatment at the time of the event; all but 4 patients in the alirocumab group and 3 patients in the placebo group continued randomized treatment after the nonfatal event. Therefore, consistent with the intent of the study, patients continued their randomized treatment beyond their first nonfatal cardiovascular event, thus allowing treatment to potentially influence the occurrence of subsequent events.

Table 1 summarizes the types and counts of adjudicated nonfatal cardiovascular events after randomization. Myocardial infarction and coronary revascularization were the most common types of events, and the proportions of each event type within the treatment groups were similar. Patients randomized to alirocumab had numerically fewer nonfatal cardiovascular events of every type, except for heart failure requiring hospitalization.

Table 2 summarizes baseline characteristics by groups defined by event frequency categories. Patients with at least 1 event were older, had higher baseline LDL-C, and were more likely to have comorbidities than patients without an event during the study, including diabetes, hypertension, and myocardial infarction prior to the ACS index event. Comparing groups with at least 1 event, patients with multiple events or an only event of death had higher baseline LDL-C relative to patients with a single nonfatal event, and there were several differences in terms of comorbidities, including history of chronic obstructive pulmonary disease, coronary artery bypass graft, or peripheral artery disease.

The **Central Illustration** shows the Kaplan-Meier curves and mean cumulative function plots for first and total nonfatal cardiovascular events, respectively, according to treatment group. Based on the estimated proportions at 4 years, the risk in both groups and the absolute risk reduction with alirocumab was approximately double for total events versus first events. Accounting for total events therefore illustrates the high burden of ongoing disease in the study population and the diminution of that burden by alirocumab. Corresponding (post hoc) plots by baseline LDL-C subgroups are presented in Online Figures 1 and 2.

Table 3 summarizes the distributions of deaths and nonfatal cardiovascular events by ordinal event. There were 5,425 total deaths or nonfatal cardiovascular events, 77% greater than first events ($n = 3,064$). The number of patients with a first event includes 1,955 that experienced a primary efficacy endpoint of the study and 1,109 that experienced a nonfatal cardiovascular or fatal event that was not a component of the primary efficacy composite. Furthermore, while a majority of patients did not experience an event during the study, a sizable subset of patients experienced more than 1 event (1,261 patients). Among patients at risk for a first event in the alirocumab and placebo groups, death occurred as a first event in 2.2% and 2.5%, respectively. Notably, conditional on having a first nonfatal cardiovascular event, the risk of subsequent death was greater. After a first nonfatal cardiovascular event occurring an overall median of 1.0 year (quartile 1, quartile 3: 0.4, 1.7 years) after randomization, death occurred as a second event in 5.7% and 5.0%, respectively, of the patients in the alirocumab and placebo groups. Similarly, after a second nonfatal cardiovascular event occurring an overall median of 1.2 years (quartile 1, quartile 3: 0.6, 2.0 years) after randomization, death occurred as a third event in 6.2% and 6.6%, respectively, of the patients in the alirocumab and placebo groups. Qualitatively, these data suggest that each successive prior nonfatal cardiovascular event is associated with an increased subsequent risk

TABLE 2 Baseline Characteristics of Patients by Category of Number of Nonfatal Cardiovascular and Fatal Events

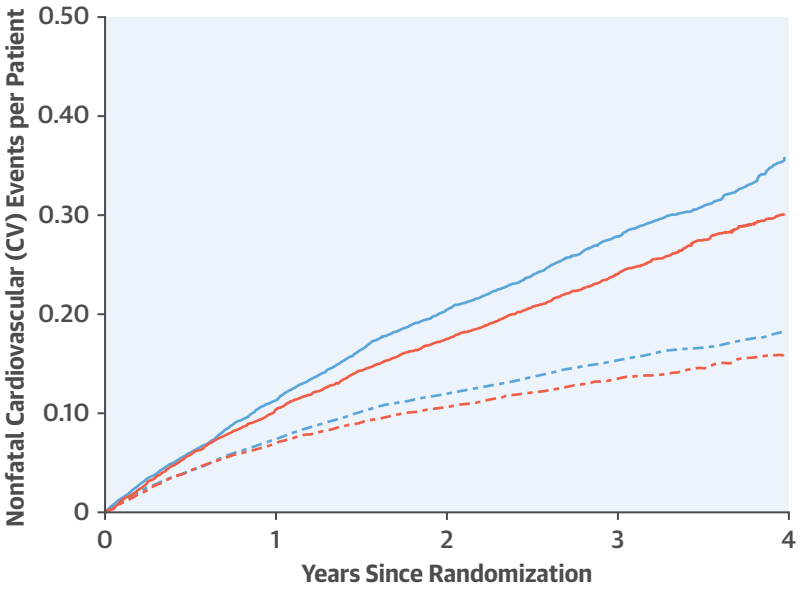
	(A) No Events (n = 15,860)	(B) Only Event = Death (n = 442)	(C) Only Event = Nonfatal CV (n = 1,361)	(D) Multiple Events (n = 1,261)	p Value			
					(A) vs. (B)+(C)+(D)	(B) vs. (C)	(C) vs. (D)	(B) vs. (D)
Age, yrs	58 (51-65)	63 (56-70)	59 (52-66)	61 (54-68)	<0.0001	<0.0001	0.0004	<0.0001
Age category					<0.0001	<0.0001	0.0003	0.01
<65 yrs	74.5	56.3	71.1	64.2				
65 to <75 yrs	20.8	31.5	22.5	26.6				
≥75 yrs	4.7	12.2	6.4	9.2				
Female sex	24.9	25.1	27.9	26.1	0.03	NS	NS	NS
Region					<0.0001	<0.0001	0.0001	<0.0001
Western Europe	22.3	11.3	22.6	22.1				
Eastern Europe	29.3	36.0	25.2	22.5				
North America	13.8	12.9	20.9	27.4				
South America	13.9	20.6	12.3	10.6				
Asia	12.8	10.4	9.6	6.3				
Rest of world	7.9	8.8	9.4	11.1				
Index event					<0.0001	0.005	0.02	0.01
NSTEMI	47.4	52.6	52.8	57.8				
STEMI	35.6	26.5	32.3	27.2				
Unstable angina	17.0	20.8	14.9	15.0				
Time from index event to randomization, months	2.7 (1.7-4.4)	2.5 (1.7-3.6)	2.6 (1.7-4.2)	2.4 (1.6-3.9)	<0.0001	NS	0.03	NS
Lipid-lowering therapy at randomization					<0.0001	NS	0.003	0.004
High dose atorvastatin/ rosuvastatin	89.3	88.7	86.5	85.9				
Other LLT	10.0	9.9	12.1	11.2				
No LLT	0.7	1.4	1.4	2.9				
LDL-C, mg/dl	86 (73-103)	91 (74-109)	88 (73-107)	92 (76-113)	<0.0001	NS	0.0007	NS
LDL-C ≥100 mg/dl	28.6	37.3	32.0	39.3	<0.0001	0.04	<0.0001	NS
Diabetes status					<0.0001	<0.0001	NS	<0.0001
Diabetes	26.8	44.8	33.4	43.4				
Pre-diabetes	44.6	34.4	42.0	36.0				
Normoglycemia	28.7	20.8	24.5	20.6				
Smoking status					0.02	NS	NS	NS
Current	24.0	22.9	24.5	25.5				
Former	41.0	41.6	42.1	44.2				
Never	35.0	35.5	33.4	30.4				
Medical history prior to index event								
Hypertension	62.4	77.2	73.2	80.7	<0.0001	NS	<0.0001	NS
Myocardial infarction	16.8	28.5	25.8	39.7	<0.0001	NS	<0.0001	<0.0001
Stroke	2.6	7.5	5.7	6.8	<0.0001	NS	NS	NS
Malignant disease	2.6	3.2	3.7	4.9	<0.0001	NS	NS	NS
COPD	3.1	11.3	5.5	10.6	<0.0001	<0.0001	<0.0001	NS
CABG	4.2	9.3	8.8	17.0	<0.0001	NS	<0.0001	<0.0001
PAD	3.1	8.4	6.6	10.5	<0.0001	NS	0.0003	NS
GFR, ml/min per 1.73 m^2	78.8 (68.3-90.6)	73.2 (59.9-87.3)	76.6 (64.9-88.6)	74.5 (60.0-87.3)	<0.0001	NS	<0.0001	NS
GFR <60 ml/min per 1.73 m^2	11.9	25.3	17.0	24.6	<0.0001	0.0002	<0.0001	NS

Values are median (quartile 1, quartile 3) or column %. NS: $p > 0.05$.

CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; GFR = glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; NSTEMI = non-ST-segment elevation myocardial infarction; PAD = peripheral artery disease; STEMI = ST-segment elevation myocardial infarction.

for death. The joint model (Table 4) confirms this observation with an association parameter of 2.04 (95% CI: 1.78 to 2.29), linking the risks of nonfatal cardiovascular events and death. An even stronger association (parameter estimate 3.29; 95% CI: 2.86 to 3.72) was found between death and nonfatal events limited to myocardial infarction, stroke, or unstable angina requiring hospitalization.

CENTRAL ILLUSTRATION **Mean Cumulative Functions and Kaplan-Meier Curves for Nonfatal Cardiovascular Events**



Number at Risk					
Placebo	9,462	9,219	8,888	3,898	737
Alirocumab	9,462	9,217	8,919	3,946	746

Placebo: Total Nonfatal CV
Alirocumab: Total Nonfatal CV
Placebo: First Nonfatal CV
Alirocumab: First Nonfatal CV

Szarek, M. et al. J Am Coll Cardiol. 2018;■(■):■-■.

Mean cumulative function curves depict the expected total number of nonfatal cardiovascular (CV) events for a given patient in the placebo and alirocumab groups at a given time after randomization. At 4 years, the estimates are 0.357 and 0.301, respectively. In contrast, the expected proportions of patients with a first nonfatal CV event in the placebo and alirocumab groups were 0.183 and 0.160, respectively.

As depicted in Figure 1, there were 385 fewer total nonfatal cardiovascular or death events with alirocumab (2,905 events for placebo, 2,520 events for alirocumab), including 190 fewer first nonfatal cardiovascular or death events (1,627 events for placebo, 1,437 events for alirocumab) and an additional 195 fewer events among the 2,622 patients with a first nonfatal cardiovascular event. Normalizing for duration of follow-up, 7.2 first events and 14.6 total events were avoided with alirocumab per 1,000 patient-years of assigned treatment. Thus, analysis of first events reflects only about one-half of the total event reduction associated with alirocumab treatment over a median of 2.8 years.

Table 4 shows that when modeled using total nonfatal cardiovascular events, alirocumab treatment reduced total nonfatal events (HR: 0.87; 95% CI: 0.82 to 0.93) as well as death (HR: 0.83; 95% CI: 0.71 to 0.97). Similarly, when modeled using total nonfatal myocardial infarction, stroke, and unstable angina, alirocumab reduced those events (HR: 0.84; 95% CI: 0.77 to 0.91) and death (HR: 0.82; 95% CI: 0.68 to 0.99). Thus, the inclusion or exclusion of ischemia-driven coronary revascularization and hospitalization for congestive heart failure had minimal impact on the estimated relative effects of alirocumab.

The estimated association parameters were considerably greater than 1, indicating that death is informative for the nonfatal cardiovascular event rate. Specifically, conditional on treatment assignment, patients at the highest risk of death were also at elevated risk for nonfatal events, so that death removed those patients at highest risk for nonfatal events from the risk set. To determine if this association would be altered by including additional baseline characteristics of patients expected to be

TABLE 3 Distributions of Death and Adjudicated Nonfatal Cardiovascular Events by Event Number

	Alirocumab		Placebo	
		Median Event Time*		Median Event Time*
First event				
Nonfatal cardiovascular	1,230/9,462 (13.0)	0.9 (0.4, 1.7)	1,392/9,462 (14.7)	1.0 (0.4, 1.8)
Death	207/9,462 (2.2)	1.5 (0.7, 2.4)	235/9,462 (2.5)	1.5 (0.8, 2.3)
Second event				
Nonfatal cardiovascular	513/1,230 (41.7)	1.2 (0.6, 2.0)	608/1,392 (43.7)	1.3 (0.6, 2.0)
Death	70/1,230 (5.7)	1.4 (0.7, 2.4)	70/1,392 (5.0)	1.6 (1.0, 2.4)
Third event				
Nonfatal cardiovascular	188/513 (36.7)	1.6 (1.0, 2.3)	245/608 (40.3)	1.5 (0.9, 2.4)
Death	32/513 (6.2)	1.4 (1.0, 2.7)	40/608 (6.6)	1.4 (0.7, 2.4)
Fourth and additional event(s)				
Nonfatal cardiovascular	255		268	
Death	25		47	
Total				
Nonfatal cardiovascular	2,186		2,513	
Death	334		392	

Values are n/N (%), median (quartile 1, quartile 3), or n. *Median event time is expressed as years since randomization.

prognostic for survival, a post hoc joint model was fit with total nonfatal cardiovascular events and death with inclusion of treatment assignment, age category (<65, 65 to <75, or ≥75 years), diabetes status (diabetes, prediabetes, or normoglycemia), history of myocardial infarction prior to the index ACS event, history of chronic obstructive pulmonary disorder, history of malignant disease, history of coronary artery bypass graft, history of peripheral artery disease, glomerular filtration rate <60 ml/min per 1.73 m^2, and baseline LDL-C group (<100 or ≥100 mg/dl) in both hazard functions. Each additional factor was significantly related ($p < 0.05$) to risk of nonfatal and/or fatal events, and the resulting estimated association parameter of 1.70 (95% CI: 1.44 to 1.96) indicates the linkage between risk of nonfatal and fatal events persists even when taking these additional factors into account. Note that geographic region, smoking status, and history of hypertension could not be entered into the adjusted post hoc model due to convergence issues. However, in separate post hoc models with treatment assignment, the estimated association parameters for the models with these additional characteristics were 2.35 (95% CI: 2.03 to 2.66), 2.03 (95% CI: 1.78 to 2.29), and 1.97 (95% CI: 1.72 to 2.22), respectively.

TABLE 4 Joint Semiparametric Models

	HR (95% CI)	p Value
Death and total nonfatal cardiovascular events (n = 5,425)		
Alirocumab: placebo HR for nonfatal cardiovascular events (n = 2,186 vs. n = 2,513)	0.87 (0.82-0.93)	<0.0001
Alirocumab: placebo HR for fatal events (n = 334 vs. n = 392)	0.83 (0.71-0.97)	0.02
Association between nonfatal cardiovascular and fatal events 2.04 (95% CI: 1.78-2.29)	-	<0.0001
Death and total nonfatal MI, stroke, or UA events (n = 2,999)		
Alirocumab: placebo HR for nonfatal myocardial infarction, stroke, or unstable angina (n = 1,034 vs. n = 1,239)	0.84 (0.77-0.91)	<0.0001
Alirocumab: placebo HR for fatal events (n = 334 vs. n = 392)	0.82 (0.68-0.99)	0.04
Association between nonfatal and fatal events 3.29 (95% CI: 2.86-3.72)	-	<0.0001

Frailty variances were statistically significant ($p < 0.0001$) in both models.
CI = confidence interval; HR = hazard ratio.

Online Figure 3 displays the total nonfatal cardiovascular and death joint model results for the overall study population and for LDL-C subgroups stratified at a baseline level of 100 mg/dl. Among 5,629 patients with baseline LDL-C ≥100 mg/dl, there were 255 fewer total nonfatal cardiovascular and fatal events with alirocumab compared with placebo. Among 13,295 patients with baseline LDL-C <100 mg/dl, there were 130 fewer such events with alirocumab than with placebo. Put another way, 66% of the absolute event reduction with alirocumab was observed in 30% of the study population defined by baseline LDL-C ≥100 mg/dl.

DISCUSSION

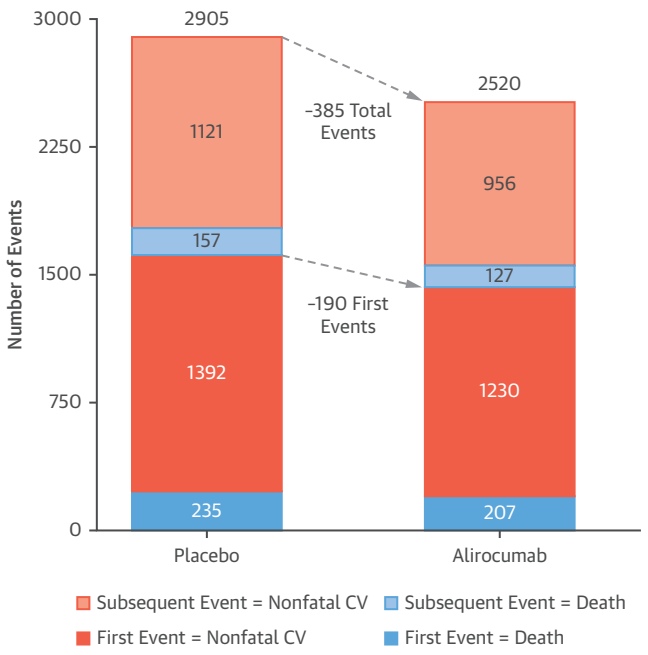
The ODYSSEY OUTCOMES trial demonstrated that adding the PCSK9 monoclonal antibody alirocumab to intensive statin therapy decreases the first occurrence of major adverse cardiovascular events compared with placebo (8). The present analysis illustrates that this treatment effect is magnified when total nonfatal cardiovascular events and death are considered, with approximately twice as many total as first events prevented. Therefore, while the efficacy of alirocumab treatment after ACS was established on analysis of time to first primary endpoint event, the efficiency of the intervention to reduce morbidity and mortality after ACS, and its benefit to reduce the total burden of disease and health care costs, are best reflected by an analysis of total events. These findings mirror the pattern observed in prior trials of statins or ezetimibe in patients with coronary heart disease or ACS (1-5), indicating the value of evaluating any long-term lipid-lowering therapy on the basis of total event modification.

There were more deaths in the placebo group than in the alirocumab group. It can be inferred from the distributions of death and nonfatal cardiovascular events by ordinal event number that experiencing a nonfatal cardiovascular event was associated with an increased risk of death, since the incidence of death as a second or later event was greater than as a first event. Furthermore, the joint models demonstrated a strong statistical association between nonfatal cardiovascular events and death, which was not meaningfully attenuated after accounting for multiple factors that were prognostic for nonfatal and fatal events. Thus, a greater number of "frail" patients in the placebo group than the alirocumab were taken out of the risk set for nonfatal events over time due to the occurrence of death. This includes a greater number of patients in the placebo group (n = 235) than in the alirocumab group (n = 207) that died prior to any observed nonfatal events a median of 1.5 years after randomization. Consequently, the relationship between nonfatal and fatal events is an important consideration when interpreting the absolute treatment effect on the first event in a composite endpoint that excludes certain causes of death, as well as the absolute treatment effect on total events.

In the previously reported primary analysis of the study data (8), the observed 15% hazard reduction in all-cause death with alirocumab, with p = 0.026 by a stratified log-rank test, was considered nominally significant due to the pre-specified testing sequence of secondary endpoints. The joint models demonstrated significant relative reductions in both total nonfatal cardiovascular events and death by alirocumab. This complementary modeling strategy therefore supports the observation that alirocumab reduced all-cause death in the trial.

STUDY LIMITATIONS. A limitation of the present analysis is the possibility that the apparent relationship between nonfatal cardiovascular events and death could be explained by other baseline patient characteristics that were not included in the prespecified or post hoc models. In addition, one might expect the association between nonfatal cardiovascular and fatal events would be restricted to cause-specific deaths (i.e., deaths from cardiovascular causes, but not noncardiovascular causes). However, the association parameters in separate models adjusted for baseline prognostic factors were statistically significant when fatal events were restricted to cardiovascular deaths or noncardiovascular deaths. Regarding the results for baseline LDL-C subgroups, it should be noted that patients with baseline LDL-C ≥100 mg/dl at randomization were less likely to be blindly switched to placebo due to low on-treatment LDL-C (2.3%) than patients with LDL-C <100 mg/dl at randomization (10.0%). This may, in part, explain the apparent heterogeneity in the relative treatment effects on total nonfatal cardiovascular events and death. In addition, the baseline LDL-C subgroup analyses did not involve adjustment for other factors that may be prognostic for nonfatal cardiovascular events or death.

FIGURE 1 First, Subsequent, and Total Nonfatal CV Events and Death by Treatment Group



There were 385 fewer total nonfatal cardiovascular (CV) or death events with alirocumab (2,905 events for placebo, 2,520 events for alirocumab) versus 190 fewer first nonfatal CV or death events (1,627 events for placebo, 1,437 events for alirocumab).

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CONCLUSIONS

Over a median of 2.8 years of follow-up in patients with ACS, the total number of nonfatal cardiovascular events and deaths prevented with alirocumab was twice the number of first events prevented. The present analysis also demonstrated a strong association between the risks of nonfatal and fatal events during the study. This finding together with the relative reductions in total nonfatal and fatal events support the previously reported observation that alirocumab treatment reduced the first occurrence of the primary composite endpoint and was associated with a

reduced risk of all-cause death. Given these observations, reduction in total nonfatal and fatal events may be viewed as a preferred metric to summarize the clinical benefit and efficiency of treatment with alirocumab.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Compared with placebo, the PCSK9 inhibitor alirocumab, when added to high-intensity statin therapy after an ACS, reduced first and subsequent nonfatal cardiovascular events and all-cause mortality over a median of 2.8 years of follow-up.

TRANSLATIONAL OUTLOOK: Further studies are needed to quantify the broader socioeconomic implications of interventions that reduce the total burden of fatal and nonfatal cardiovascular and noncardiovascular events in high-risk patient populations that accumulate frailty over time.

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KEY WORDS acute coronary syndrome, alirocumab, total events

APPENDIX For an expanded Methods section, supplemental figures, and a complete list of investigators, please see the online version of this paper.