Circulation: Cardiovascular Quality and Outcomes

ORIGINAL ARTICLE

Alirocumab Reduces Total Hospitalizations and Increases Days Alive and Out of Hospital in the ODYSSEY OUTCOMES Trial

BACKGROUND: In ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), alirocumab was compared with placebo, added to high-intensity or maximum tolerated statin treatment after acute coronary syndrome in 18 924 patients. Alirocumab reduced first occurrence of the primary composite end point—coronary heart disease death, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or hospitalization for unstable angina—as well as total nonfatal cardiovascular events and all-cause deaths. The present analysis determined whether alirocumab reduced total (first and subsequent) hospitalizations and death and increased days alive and out of hospital (DAOH) and percent DAOH in ODYSSEY OUTCOMES.

METHODS AND RESULTS: In prespecified analyses, hazard functions for total hospitalizations and death were jointly estimated by a semiparametric model, while in post hoc analyses, DAOH and percent DAOH were compared between treatment groups with Poisson regression and one-inflated beta regression, respectively. With 16 629 total hospitalizations and 726 deaths, 331 fewer hospitalizations, and 58 fewer deaths were observed with alirocumab compared with placebo, translating to 15.6 total hospitalizations or deaths avoided with alirocumab per 1000 patient-years of assigned treatment. Alirocumab reduced total hospitalizations (hazard ratio, 0.96 [95% CI, 0.92–1.00]; *P*=0.04) and increased DAOH relative to placebo (rate ratio, 1.003 [95% CI, 1.000–1.007]; *P*=0.05), primarily through a reduction in days dead (rate ratio, 0.847 [95% CI, 0.728–0.986]; *P*=0.03). Patients randomized to alirocumab were also more likely to survive to the end of the study without hospitalization (odds ratio, 1.06 [95% CI, 1.00–1.13]; *P*=0.03).

CONCLUSIONS: Alirocumab reduced total hospitalizations with corresponding small increases in DAOH and percent DAOH. These outcomes provide alternative patient-centered metrics to capture the totality of alirocumab clinical efficacy after acute coronary syndrome.

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WHAT IS KNOWN

- Analyses that account for total adjudicated nonfatal and fatal events measure the effect of an intervention on the total burden of a disease process.
- Central adjudication may not consider events other than particular study end points that nonetheless lead to hospitalization, and therefore have meaningful negative consequences to patients and contribute to their total disease burden.
- Total hospitalizations and death, days alive and out of hospital, and percent days alive and out of hospital are patient-centered outcomes that do not require adjudication and provide alternative metrics of the effect of an intervention on burden of disease.

WHAT THE STUDY ADDS

- On a background of high-intensity or maximum tolerated statin treatment, alirocumab, compared with placebo, reduced total hospitalizations, increased days alive and out of hospital, and increased the likelihood of survival without hospitalization in the ODYSSEY OUTCOMES trial.
- These outcomes provide alternative patient-centered metrics of the totality of alirocumab's effects, capturing benefits beyond first and total adjudicated events avoided.

Although the primary efficacy outcome in cardiovascular clinical trials is typically the time to first event in an adjudicated composite end point, events occurring after the first also contribute to morbidity, mortality, and healthcare costs. Consequently, the effect of a treatment on modifying the risk of total events may be more important to patients and to healthcare systems than considering only first events. Analyses that account for total adjudicated nonfatal and fatal events have accordingly been proposed as an alternative strategy to measure the effect of an intervention on the total burden of a disease process.[1–3]

A potential limitation with the analysis of total events is death removes a given patient from the risk set for subsequent nonfatal events, so that patients who die may experience fewer total events than patients who survive the duration of the trial. This can lead to inaccurate estimates of nonfatal event risk, and consequently total event risk, and is especially problematic if there is an imbalance in the number of deaths between treatment groups and patients at highest risk for nonfatal events are also at increased risk for death. Although methods have been proposed[4,5] and applied[6–8] to account for the association between nonfatal and fatal events, time to start of a narrowly defined set of events does not necessarily capture all consequences of a disease process that negatively impact patients' quality of life, motivating the adoption of more patient-centered outcomes to assess treatment benefit. In addition, the process of central adjudication, which is typical practice in cardiovascular clinical trials, has associated time and cost repercussions, and may not consider events other than particular study end points that nonetheless have meaningful negative consequences to patients and contribute to their total disease burden.

An alternative outcome that avoids some of the limitations described above is total hospitalizations. If analyzed with methods that account for the possible association between hospitalizations and death, as well as for the fact that death removes a patient from the risk set for subsequent hospitalization, an accurate estimate of the impact of an intervention on this form of total events can be obtained. Additional metrics that integrate information on hospitalizations and death into a single patient-centered outcome are days alive and out of hospital (DAOH) and percent DAOH (PDAOH), end points that have been applied in previous trials in patients with heart failure or acute coronary syndrome (ACS)[9,10] as well as in cohort studies.[11,12]

In addition to allowing for multiple events in a patient, DAOH accounts for event severity in several ways. In studies with relatively long follow-up, death would be expected to result in a greater loss of DAOH than would hospitalization. DAOH further quantifies nonfatal event severity with days hospitalized rather than assuming all events have the same negative impact on a patient, regardless of duration from the start of the event until recovery. For these reasons, DAOH as an efficacy measure avoids several possible shortcomings of composite events: it recognizes patients' preference to avoid time in hospital, it weights longer hospitalizations with greater morbidity more than brief hospitalizations, and it amplifies the long-term consequences of modifying the risk of nonfatal cardiovascular events that are expected to result in multiple downstream hospitalizations and death.[10]

The ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) trial compared alirocumab, an inhibitor of PCSK9 (proprotein convertase subtilisin–kexin type 9), with placebo in patients with ACS and persistent dyslipidemia despite treatment with high-intensity or maximum tolerated statin therapy. Alirocumab reduced the first occurrence of the primary composite end point, a composite of coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, or hospitalization for unstable angina.[13] Total nonfatal cardiovascular events (total nonfatal primary end points plus hemorrhagic stroke, heart failure requiring hospitalization, and ischemia-driven coronary revascularization) and all-cause death were also reduced.[8]

In the present prespecified analyses of the trial, we evaluated the effect of alirocumab on total hos-

pitalizations and deaths. Joint modeling allowed for the possibility that patients may experience multiple hospitalizations quantified the association between hospitalizations and death and accounted for competing deaths that prevent follow-up for hospitalization, thereby resulting in a more accurate relative estimate (ie, hazard ratio [HR]) for hospitalization risk. We also compared DAOH and PDAOH between the alirocumab and placebo groups in post hoc analyses, accounting for both the incidence and duration of hospitalizations and deaths during the study. Our hypothesis was that alirocumab reduces total hospitalizations and death and extends DAOH after ACS.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Details of the study design,[14] primary efficacy and safety,[13] and total events results[8] have been published. Ethics committee approval was obtained at all participating institutions. 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 before randomization, and had either a LDL-C (low-density lipoprotein cholesterol) of ≥70 mg/dL (1.81 mmol/L), non-HDL-C (non–high-density lipoprotein cholesterol) of ≥100 mg/dL (2.59 mmol/L), or apolipoprotein B of ≥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 of 18924 patients in a 1:1 ratio to treatment with alirocumab 75 mg or matching placebo, stratified by country, was performed in patients meeting study entry criteria. All doses of study medication were given by subcutaneous injection every 2 weeks. All patients were eligible to be followed for ≥2 years, with the exception of patients enrolled in China. A CONSORT (Consolidated Standards of Reporting Trials) flow diagram for the study is provided in Figure I in the Data Supplement.

Hospitalization Assessments

Investigators reported all incidences and durations of admission to hospital or emergency department after randomization on a dedicated case report form, with a primary reason of (1) protocol efficacy end point, (2) adverse event other than protocol efficacy end point, or (3) elective reason that was not a protocol efficacy end point or adverse event. If the primary reason was protocol efficacy end point; the investigator was required to identify the corresponding event sent for central adjudication, while if the primary reason was an adverse event the investigator was required to specify the event. A text field was provided for investigators to specify the reason for elective hospitalizations; the most common elective reasons included coronary angiography and cardiac catheterization. Duration of hospitalization was determined from the dates of admission and discharge recorded by the investigators on the form; if a patient died in hospital, the hospitalization was ended on the date of death.

Definitions of DAOH and PDAOH

Total potential follow-up time for each patient was defined as the number of days from date of randomization until the patient's last assessment date within the study if the patient withdrew or was lost to follow-up, or the common study end date (November 11, 2017) if the patient completed follow-up or died. The total number of days spent in hospital was derived from the investigator reports. If a patient died, the number of days dead was calculated as the time interval between their date of death and the common study end date. DAOH was calculated by subtracting days in hospital and days dead from total potential follow-up time; if a patient survived without hospitalization, DAOH was equal to the potential follow-up time for that patient. To account for variation in duration of potential follow-up due to patients being randomized over the course of several years and late enrollment of patients from China, PDAOH was used in sensitivity analyses, calculated as DAOH divided by total potential follow-up time.

Statistical Methods

The primary analysis of total hospitalizations involved incident hospitalizations for any reason, while sensitivity analyses restricted total hospitalizations to those attributed to protocol efficacy end points. Causes of death were adjudicated by an independent committee blinded to treatment assignment. Given the previously reported observation that the absolute benefits of alirocumab on the study primary efficacy end point and total nonfatal cardiovascular events and death were greater among patients with higher LDL-C at study entry, post hoc analyses examined possible heterogeneity in the treatment effect on total hospitalizations, deaths, DAOH, and PDAOH in subgroups defined by LDL-C at randomization (≥100 mg/dL versus <100 mg/dL). To explore the possible effects of regional healthcare environments, additional post hoc analyses of DAOH and PDAOH were performed in subgroups defined by predefined geographic region (Western Europe, Eastern Europe, North America, South America, Asia, or Rest of World; the countries within each region are listed in the Data Supplement).

For the prespecified analysis of hospitalizations and death, we applied a joint semiparametric model that estimates the effect of alirocumab relative to placebo on total hospitalizations and separately on all-cause death, as well as the association between hospitalizations and death.[4,5] Treatment effects on hospitalizations and fatal events are summarized by HRs and corresponding 95% CIs and *P* values. Point estimates and corresponding 95% CIs and *P* values were also calculated for the association parameters. The Data Supplement provides additional details for the model. Note that unlike DAOH and PDAOH, the duration of each hospitalization was not included in the joint model; an event was only determined by when a given hospitalization began. In addition, the estimated treatment HR and CI for all-cause death from a joint model may differ numerically from that derived by other modeling strategies (eg, Cox regression).

To facilitate model convergence, for a given patient, a hospitalization that occurred on the same day as death was excluded, and a maximum of one hospitalization was allowed to occur on a given day. With these conventions, all

hospitalizations and deaths within a given patient had distinct event times from randomization.

Nonparametric mean cumulative function curves were created for total hospitalizations for any reason and total hospitalizations attributed to a protocol efficacy end point. The mean cumulative function represents the expected (ie, mean) cumulative number of hospitalizations for a patient at a given point in time after randomization, without consideration of the duration of each hospitalization.

DAOH, days dead, and days in hospital were compared post hoc between treatment groups by rate ratios (RRs) from Poisson regression with a log link function and Pearson χ^2 scaling of standard errors to account for potential overdispersion. In addition to treatment group, the logarithm of potential follow-up time was used as an offset variable in the model. Given the expectation that a substantial fraction of patients would survive without hospitalization until the end of follow-up (ie, PDAOH =100%), PDAOH was compared between treatment groups with one-inflated beta regression. In the current application, the model jointly estimates the treatment odds ratio (OR) of surviving until the end of the study without hospitalization (ie, PDAOH =100%), and the treatment OR of higher mean PDAOH among the subset of patients who died or had at least one hospitalization or died during follow-up (ie, PDAOH <100%).[15,16] The Data Supplement provides additional details for the one-inflated beta regression model.

All analyses were conducted according to intention-to-treat, including all patients and events from randomization to the common study end date. Continuous variables are expressed as mean (SD) or median (quartile 1, quartile 3) while categorical variables are expressed as counts and percentages. Unless otherwise indicated, analyses were prespecified before unblinding of the study database, and *P* values <0.05, 2-tailed, were considered statistically significant, with no adjustment for multiple testing. Analyses were performed in SAS 9.4 and R 3.5.

RESULTS

Patients were followed for survival for a median of 2.8 (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 99.8% of potential patient-years of follow-up for survival.

Figure 1 summarizes the types and incidence of hospitalizations and deaths after randomization. Of 16 629 total hospitalizations, 5020 (30.2%) were attributed to protocol-defined efficacy end points, 10 259 (61.7%) were attributed to other adverse events, and 1342 (8.1%) were for elective reasons. Note that the total number of hospitalizations attributed to protocol efficacy end points is somewhat less than the total number of adjudicated nonfatal cardiovascular events (4699) and deaths (726) reported previously.[8] However, accounting for all hospitalizations greatly increases the number of events available for analysis.

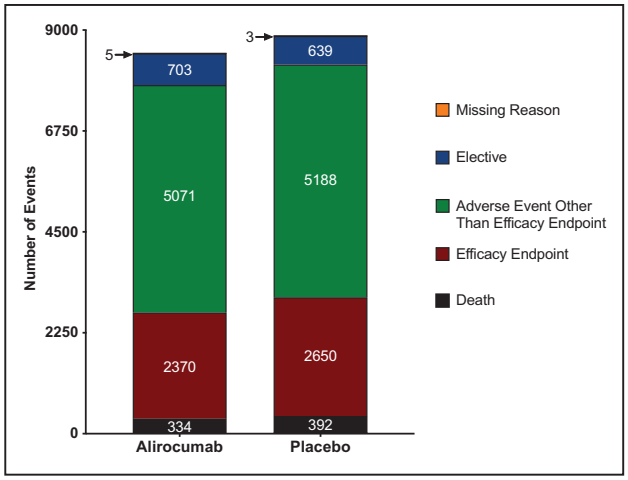

Figure 1. Incidence of death and hospitalizations by reason and treatment group.
There were 389 fewer total hospitalizations or deaths with alirocumab (8872 events for placebo, 8483 events for alirocumab), including 331 fewer hospitalizations and 58 fewer deaths.

There were 389 fewer total hospitalizations or deaths with alirocumab (8872 events for placebo, 8483 events for alirocumab), including 331 fewer hospitalizations and 58 fewer deaths; both of these reductions were statistically significant when jointly modeled, as described below. Normalizing for duration of follow-up, 13.4 total hospitalizations, and 15.6 total hospitalizations or deaths were avoided with alirocumab per 1000 patient-years of assigned treatment. Patients randomized to alirocumab had fewer deaths and hospitalizations attributed to efficacy end points or adverse events, while patients in the placebo group had fewer elective hospitalizations. The types and incidence of hospitalizations and deaths after randomization by baseline LDL-C subgroups are presented in Tables I and II in the Data Supplement.

Table 1 summarizes the distributions of deaths and hospitalizations by ordinal event. There were 17 355 total deaths or hospitalizations, 123% greater than if only the first death or hospitalization was considered (n=7768). Approximately 40% of patients experienced at least one hospitalization during the study, while ≈1% of patients died before experiencing a hospitalization. The mean cumulative function plots for total hospitalizations for any reason and the subset of total hospitalizations attributed to a protocol efficacy end point are shown in Figure 2. The functions exceeded 1 in both groups for hospitalizations, indicating that, on average, a patient would have expected to be hospitalized slightly more than once during the study. Given that a minority of patients actually experienced a hospitalization, however, this indicates the distribution of hospitalizations was skewed, with a relatively small fraction of patients experiencing multiple hospitalizations during follow-up.

Table 1. Distributions of Death and Hospitalizations by Event Number

	Alirocumab	Placebo
First Event, n/N (%)		
Hospitalization	3707/9462 (39.2)	3842/9462 (40.6)
Death	105/9462 (1.1)	114/9462 (1.2)
Second event, n/N (%)		
Hospitalization	1818/3707 (49.0)	1891/3842 (49.2)
Death	104/3707 (2.8)	112/3842 (2.9)
Third event, n/N (%)		
Hospitalization	936/1818 (51.5)	991/1891 (52.4)
Death	43/1818 (2.4)	63/1891 (3.3)
Fourth and additional event(s), n		
Hospitalization	1688	1756
Death	82	103
Total, n		
Hospitalization	8149	8480
Death	334	392

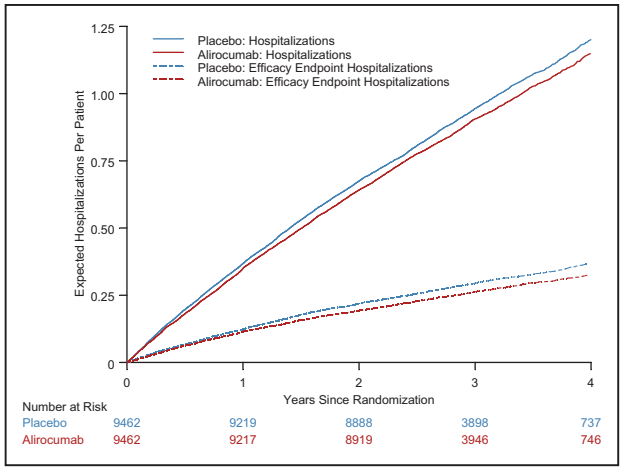

Figure 2. Mean cumulative functions, hospitalizations, and efficacy end point hospitalizations.
Mean cumulative function curves depict the expected total number of total hospitalizations and total protocol efficacy end point hospitalizations for a given patient in the placebo and alirocumab groups at a given time after randomization. At 4 y, the estimates are 1.20 and 1.15, respectively, for total hospitalizations, and 0.37 and 0.32, respectively, for total protocol efficacy end point hospitalizations. Alirocumab treatment reduced total hospitalizations (hazard ratio, 0.96 [95% CI, 0.92–1.00]; *P*=0.04) and total efficacy end point hospitalizations (hazard ratio, 0.89 [95% CI, 0.84–0.95]; *P*=0.0005).

Table 2 shows that when modeled using hospitalizations for any reason, alirocumab treatment reduced total hospitalizations (HR, 0.96 [95% CI, 0.92–1.00]; *P*=0.04) as well as death (HR, 0.83 [95% CI, 0.71–0.97]; *P*=0.02). Similarly, when modeled using hospitalizations attributed to a protocol efficacy end point, alirocumab reduced those events (HR, 0.89 [95% CI, 0.84–0.95]; *P*=0.0005), and death (HR, 0.83 [95% CI, 0.71–0.97]; *P*=0.02). Thus, the exclusion of hospitalizations not attributed to a protocol efficacy end point strengthened the relative effect of alirocumab. Furthermore, the parameters describing the estimated association between death and hospitalization were considerably >1, indicating that death is informative for the hospitalization rate. Specifically, conditional on treatment assignment, patients at the highest risk of death were also at elevated risk for hospitalization, so that death removed those patients at highest risk for hospitalizations from the risk set. Figure II in the Data Supplement displays the total hospitalizations and death joint model results for the overall study population and for LDL-C subgroups stratified at a baseline level of 100 mg/dL.

DAOH, days hospitalized, and days dead are summarized for the overall patient population in Table 3 and by subgroups defined by LDL-C and geographic region in Table III in the Data Supplement. The distribution of DAOH for the overall population is depicted in Figure III in the Data Supplement. The overall mean DAOH was 1039 days, corresponding to 97.6% of mean total potential follow-up days in the trial (1064 days). The median number of days hospitalized and days dead were both 0, confirming that the majority of patients were not hospitalized and survived until the end of the study. Specifically, 59.0% of patients survived the entire

Table 2. Joint Semiparametric Models

	Alirocumab, No. of Events	Placebo, No. of Events	HR (95% CI)	*P* Value	Association Parameter (95% CI)
Death and total hospitalizations for any reason					
Hospitalizations	8149	8480	0.96 (0.92–1.00)	0.04	
Death	334	392	0.83 (0.71–0.97)	0.02	
Association between hospitalizations and death				<0.0001	1.62 (1.48–1.77)
Death and total hospitalizations attributed to protocol efficacy end point					
Hospitalizations	2370	2650	0.89 (0.84–0.95)	0.0005	
Death	334	392	0.83 (0.71–0.97)	0.02	
Association between hospitalizations and death				<0.0001	1.80 (1.57–2.03)

Frailty variances were statistically significant (*P*<0.0001) in both models. HR indicates hazard ratio.

Table 3. DAOH, Days Dead, Days Hospitalized, and PDAOH

	DAOH		Days Dead		Days Hospitalized		PDAOH	
	Mean (SD)	Median (Q1, Q3)	Mean (SD)	Median (Q1, Q3)	Mean (SD)	Median (Q1, Q3)	PDAOH=100%, n (%)	PDAOH Among Patients <100%, Mean (SD)
All patients (n=18924)	1039 (284)	1019 (846, 1244)	24 (134)	0 (0, 0)	5 (16)	0 (0, 4)	11157 (59.0)	94.5% (16.5%)

DAOH indicates days alive and out of hospital; and PDAOH, percent days alive and out of hospital.

follow-up period without hospitalization (ie, PDAOH =100%), while the mean PDAOH among patients who were hospitalized or died (ie, PDAOH <100%) was 94.5%. DAOH, the percent of patients with PDAOH of 100%, and the mean PDAOH among patients with <100% PDAOH were similar in both LDL-C subgroups. Relatively low DAOH in Asia reflects patient enrollment in China, and while the mean PDAOH among patients with <100% PDAOH was relatively consistent across geographic regions, the percent of patients with PDAOH =100% was more variable, ranging from 40.1% in North America to 70.3% in Asia.

The analysis of DAOH, days dead, and days in hospital by treatment group is summarized in Table 4. There was a small but statistically significant increase in DAOH in the alirocumab group compared with placebo with total hospitalizations for any reason (RR, 1.003 [95% CI, 1.000–1.007]; *P*=0.05), primarily through a significant reduction in days dead (RR, 0.847 [95% CI, 0.728–0.986]; *P*=0.03). Findings were similar when the treatment comparison was restricted to total hospitalizations attributed to protocol efficacy end point (RR, 1.003 [95% CI, 1.000–1.007]; *P*=0.06). Figure IV in the Data Supplement displays the DAOH model results for the overall study population and for LDL-C subgroups stratified at a baseline level of 100 mg/dL. These results suggest that the DAOH treatment difference observed in the overall study population was largely restricted to the subgroup with baseline LDL-C ≥100 mg/dL. The DAOH model for the overall study population and by geographic region is presented in Figure 5 in the Data Supplement. The results suggest heterogeneity in the treatment effect across geographic region, although despite the small interaction *P* values, there is substantial overlap in the CIs across the regions.

The analysis of PDAOH by treatment group is summarized in Table 5. There were statistically significant increases in the likelihood of patients randomized to alirocumab surviving the follow-up period without hospitalization, both for total hospitalizations for any reason (OR, 1.06 [95% CI, 1.00–1.13]; *P*=0.03) and total hospitalizations attributed to a protocol efficacy end point (OR, 1.11 [95% CI 1.03–1.19]; *P*=0.03). There were no significant differences, however, in mean PDAOH among patients who died or were hospitalized during the study. Figure VI in the Data Supplement displays the PDAOH model results for the overall study population and for LDL-C subgroups stratified at a baseline level of 100 mg/dL. These results suggest that while there was no significant heterogeneity in the likelihood of surviving until the end of the study without hospitalization, there was evidence of significant heterogeneity in the relative alirocumab treatment effect on the mean PDAOH in the subset of patients who had at least one hospitalization and died during follow-up, with the subgroup ≥100 mg/dL at randomization deriving greater relative benefit. The PDAOH model for the overall study population and by geographic region is presented in Figure VII in the Data Supplement. The results provide evidence of significant heterogeneity in the relative alirocumab treatment effect on the mean PDAOH in the subset of patients with PDAOH <100%, with patients from the North America and Rest of World regions deriving greater relative benefit.

Table 4. DAOH, Days Dead, and Days in Hospital by Treatment Group

	Alirocumab, Mean (SD)	Placebo, Mean (SD)	RR (95% CI)	*P* Value
Total hospitalizations for any reason				
DAOH	1040 (284)	1037 (284)	1.003 (1.000–1.007)	0.05
Days dead	22 (130)	26 (138)	0.847 (0.728–0.986)	0.03
Days in hospital	5 (16)	5 (17)	0.951 (0.866–1.044)	0.29
Total hospitalizations attributed to protocol efficacy end point				
DAOH	1043 (284)	1040 (284)	1.003 (1.000–1.006)	0.06
Days dead	22 (130)	26 (138)	0.847 (0.728–0.986)	0.03
Days in hospital	2 (7)	2 (6)	0.913 (0.811–1.028)	0.13

DAOH indicates days alive and out of hospital; and RR, rate ratio.

Table 5. PDAOH by Treatment Group

	PDAOH =100%				PDAOH Among Patients <100%			
	Alirocumab, n (%)	Placebo, n (%)	OR (95% CI)	*P* Value	Alirocumab, Mean (SD), %	Placebo, Mean (SD), %	OR (95% CI)	*P* Value
Total hospitalizations for any reason	5650 (59.7)	5507 (58.2)	1.06 (1.00–1.13)	0.03	94.7 (16.3)	94.3 (16.7)	1.05 (0.97–1.13)	0.20
Total hospitalizations attributed to protocol efficacy end point	7697 (81.3)	7544 (79.7)	1.11 (1.03–1.19)	0.005	90.1 (22.7)	89.7 (22.6)	1.01 (0.91–1.12)	0.83

OR indicates odds ratio; and PDAOH, percent days alive and out of hospital.

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, as well as total nonfatal cardiovascular events and death, compared with placebo.[8,13] The present analysis extends those findings by establishing a favorable effect of alirocumab on patient-centered outcomes, reducing total hospitalizations and death when jointly modeled, and extending DAOH.

Given that a minority of hospitalizations were attributed by the investigators to a protocol efficacy end point, one might not expect a treatment effect on total hospitalizations for any reason. While hospitalizations attributed to efficacy end points were reduced more than total hospitalizations for any reason, the reduction in the later was nonetheless statistically significant. This suggests that prevention of cardiovascular end point events by alirocumab may have prevented disability and physiological frailty, in turn diminishing the total number of downstream hospitalizations. The present results indicating that the effect of alirocumab on total hospitalizations is more pronounced among patients with higher baseline LDL-C is aligned with other outcomes results from the trial, including the previously reported analysis of total nonfatal cardiovascular and fatal events.[8]

Although DAOH and PDAOH were significantly greater in the alirocumab group, the differences between treatment groups were small because the majority of patients in both groups survived to the end of the study without hospitalization. The treatment differences in DAOH and PDAOH were driven by a subset of patients with relatively high days hospitalized and dead, which occurred more frequently in the placebo group. Akin to the joint semiparametric model results, treatment effects on DAOH and PDAOH stemming from total hospitalizations for any reason and for total hospitalizations attributed to a protocol primary end point were more pronounced among patients with higher baseline LDL-C.

Despite the fact that a relatively low percentage of patients died during the study, the treatment difference in DAOH primarily reflected a difference in days dead. Furthermore, because a proportion of hospitalizations were not directly related to the disease process under study in the trial, it is not surprising that the HRs for total hospitalizations, RRs for DAOH, and ORs for PDAOH were closer to 1.0 than those for the study primary end point and total nonfatal cardiovascular events.[8,13]

A possible limitation of total hospitalizations and DAOH is that the analyses relied on investigator reports of hospitalizations on a dedicated case report form. While this had the benefit of allowing investigators to provide a primary reason for a given hospitalization, there may have been additional hospitalizations that either was not recorded on this form or were unknown to the investigators, resulting in an underreporting of hospitalizations. In addition, attribution to protocol efficacy end point on the form did not distinguish primary from secondary end point events.

CONCLUSIONS

Over a median 2.8 years of follow-up in patients with ACS, alirocumab reduced death and total hospitalizations, with 15.6 total hospitalizations or deaths avoided with alirocumab per 1000 patient-years of assigned treatment. Alirocumab, relative to placebo, also extended DAOH and increased the likelihood of surviving until the end of the study without hospitalization. These outcomes provide alternative patient-centered metrics to capture the totality of alirocumab clinical efficacy after ACS, indicating benefits in addition to first and total adjudicated end point events avoided.

ARTICLE INFORMATION

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*A complete list of the ODYSSEY OUTCOMES Committee members, investigators, and contributors is provided in the Data Supplement.

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