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Alirocumab and chest pain after acute coronary syndrome: An analysis of ODYSSEY OUTCOMES

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ABSTRACT

Background: Patients with recent acute coronary syndrome (ACS) commonly experience chest pain, which affects quality of life even when not due to recurrence of ACS. This post hoc analysis of ODYSSEY OUTCOMES assessed the effect of alirocumab, a proprotein convertase subtilisin/kexin type 9 inhibitor, on the incidence of chest pain not due to recurrent ACS.

Methods: Patients with recent ACS (n = 18,894) and elevated atherogenic lipoprotein levels despite optimized statin therapy were randomized to subcutaneous alirocumab or matching placebo every 2 weeks. Alirocumab dose was adjusted to target low-density lipoprotein cholesterol (LDL-C) 25–50 mg/dL (0.6–1.3 mmol/L) and to avoid consecutive LDL-C <15 mg/dL (0.39 mmol/L). Non-hospitalized chest pain adverse events and chest pain events requiring hospitalization but negatively adjudicated for recurrent ACS were assessed.

Results: Chest pain not requiring hospitalization was reported as an adverse event in 1490 patients, including 7.5 % and 8.3 % of alirocumab and placebo groups, respectively. Hospitalization for chest pain negatively adjudicated for recurrent ACS occurred in 952 patients, including 4.8 % and 5.3 % of alirocumab and placebo groups, respectively. Adjusting for baseline covariates, alirocumab use was associated with 8.1 % lower risk of chest pain (either non-hospitalized or hospitalized events) versus placebo (HR: 0.919; 95 % CI: 0.845–0.998; P = 0.046); a landmark analysis at 7 months showed a larger, 11.7 % risk reduction (HR: 0.883; 95 % CI: 0.793–0.984; P = 0.024).

Conclusions: Alirocumab use is associated with reduced incidence of chest pain events after ACS, including those not requiring hospitalization and those requiring hospitalization but not adjudicated as recurrent ACS.

Trial registration: NCT01663402

1. Introduction

The ODYSSEY OUTCOMES trial investigated the effect of alirocumab, a proprotein convertase subtilisin/kexin type 9 inhibitor versus placebo on cardiovascular outcomes after an acute coronary syndrome (ACS) in patients receiving maximal statin therapy [1]. The primary endpoint was a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. The risk of recurrent ischemic cardiovascular events was lower among alirocumab-treated patients, with a composite primary endpoint event occurring in 9.5 % patients vs 11.1 % among placebo (hazard ratio [HR], 0.85; 95 % confidence interval [CI],

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0.78–0.93; $P < 0.001$) [2]. Among patients with ACS, complaints of chest pain are common and significantly affect quality of life even when not due to recurrent ACS [3]. This post hoc analysis of the ODYSSEY OUTCOMES trial investigated the effect of alirocumab on the incidence of treatment-emergent chest pain events, including those reported as adverse events (AE) that did not require hospitalization and events of chest pain requiring hospitalization that were negatively adjudicated as either unstable angina or myocardial infarction according to protocol definition.

2. Materials and methods

2.1. ODYSSEY OUTCOMES trial design

The ODYSSEY OUTCOMES trial design and primary results have been previously published [1,2]. Briefly, ODYSSEY OUTCOMES was a multicenter, double-blind, placebo-controlled trial that randomized patients with a recent ACS (defined as myocardial infarction or unstable angina) and who had elevated atherogenic lipids despite stable optimized statin therapy. Patients received either subcutaneous alirocumab 75 mg every 2 weeks or matching placebo. The dose of alirocumab was adjusted under blinded conditions to target an LDL-C level of 25–50 mg/dL (0.6–1.3 mmol/L) and to avoid consecutive LDL-C levels below 15 mg/dL (0.39 mmol/L). The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All sites obtained Institutional Review Board or Ethics Committee approval as per local and national guidelines. All patients provided written informed consent.

2.2. Assessments / endpoints

This post hoc analysis evaluated chest pain events including non-hospitalized events reported as adverse events, and events requiring hospitalization that were negatively adjudicated as unstable angina or myocardial infarction. Analyses were performed for time from first study dose to first chest pain occurrence and included patients with complete first and last dose dates, grouped by treatment assignment. Safety population (those receiving ≥1 dose or part of dose) was assessed for chest pain events during the treatment-emergent adverse event (TEAE) period, defined for each patient as the interval between the first study dose and 70 days after the last study dose (or death if earlier).

2.3. Identification of chest pain

Chest pain events included those requiring hospitalization but negatively adjudicated for unstable angina or myocardial infarction according to protocol [1]. Also included in the analysis were non-hospitalized chest pain events identified from TEAEs under one of the preferred terms outlined in **Supplementary Table 1**, reviewed by a blinded expert investigator and confirmed by a second blinded expert investigator.

2.4. Statistical analysis

Kaplan-Meier cumulative incidence of chest pain events was assessed by study treatment. Cox regression model was conducted to evaluate the effect of alirocumab on chest pain incidence adjusting for baseline demographic covariates and medical history. Proportional hazard assumption was assessed globally and for each covariate, and the violation of the covariate proportionality assumption was resolved by stratification. Adjusted landmark analysis (≤7 months vs >7 months) was also conducted. The landmark of 7 months was empirically selected based on survival curves summarizing MACE endpoints from the main study results [2]. A sensitivity 1-year landmark analysis was also conducted. In addition, single and multiple chest pain events in the same individual were analyzed separately. The adjusted alirocumab effect was further evaluated by sex. Same analyses were applied for non-hospitalized chest pain and negatively adjudicated ACS requiring hospitalization individually. A supplementary analysis was performed using logistic regression to determine the occurrence of chest pain, after adjusting for the follow-up time of the patients. All analyses were done in R version 4.3.0.

3. Results

3.1. Baseline characteristics according to chest pain status

Overall, 18,894 participants from the safety population were included in the analysis (alirocumab, $n = 9451$; placebo, $n = 9443$). The median follow-up time was 2.6 (Q1: 2.1; Q3: 3.3) years for this analysis. During the study, 1490 patients reported chest pain as AE, and 952 patients were hospitalized for chest pain that subsequently was negatively adjudicated for ACS (**Supplementary Table 1**). A total of 211 patients experienced both types of events. Patients from Western Europe and North America reported a higher rate of chest pain AE than patients from the rest of the world. A higher proportion of patients who experienced chest pain during the study had prior (before index event) medical history of revascularization versus patients who did not experience chest pain (30.1 % vs 18.4 %) (**Supplementary Table 2**).

3.2. Incidence of chest pain by treatment group

In the alirocumab and placebo groups, respectively, 7.5 % and 8.3 % of patients reported chest pain as AE, and 4.8 % and 5.3 % were hospitalized with chest pain that was negatively adjudicated as ACS. The observed incidence of combined chest pain events was 11.2 % and 12.5 % for the alirocumab and placebo groups, respectively (Table 1). Kaplan-Meier estimated cumulative incidence of chest pain by treatment group is provided in the Central Illustration and **Supplementary Figure 1**. After adjusting for baseline covariates, the risk of having chest pain was 8.1 % lower (HR: 0.919; 95 % CI: 0.845–0.998; $P = 0.046$; Table 2) on alirocumab compared to placebo. When looking at the two types of events separately, the adjusted risk was reduced by 6.4 % for non-hospitalized chest pain (HR: 0.936; 95 % CI: 0.845–1.036; $P = 0.202$) and by 8.5 % for negatively adjudicated ACS requiring hospitalization (HR: 0.915; 95 % CI: 0.806–1.040; $P = 0.173$). A 7-month landmark analysis showed that the reduction in the risk of experiencing chest pain with alirocumab, compared to placebo, was 11.7 % (>7 months, HR: 0.883; 95 % CI: 0.793–0.984; $P = 0.024$; **Supplementary Table 3**). A sensitivity 1-year landmark analysis gave similar though non-significant results (HR: 0.901; 95 % CI: 0.792–1.026; $P = 0.116$). The incidence of chest pain requiring hospitalization and each individual preferred term for non-hospitalized chest pain are summarized in **Supplementary Table 1**. Irrespective of treatment group, most patients experienced a single chest pain event during the study (**Supplementary Table 4**). Kaplan-Meier estimated cumulative incidence by treatment group and sex is provided in **Supplementary Figure 2** and adjusted results are provided in Table 2. The incidence of chest pain by treatment group, the number of chest pain events and sex is summarized in **Supplementary Table 5**. The supplementary analysis model showed similar results, indicating that the odds of experiencing chest pain was 10 % lower for patients on alirocumab compared to those on a placebo (odds ratio: 0.899; 95 % CI: 0.822–0.984; $P = 0.020$). Interestingly, the rate of MACE was nearly double among those who experienced chest pain compared with those who did not (389/2231, or 17.4 % vs 1562/16663, or 9.4 %, respectively).

4. Conclusions

Patients with recent ACS commonly experience chest pain, which affects quality of life [4–6]. This post hoc analysis of the ODYSSEY OUTCOMES trial provides evidence for a reduction in the incidence of

Table 1
Incidence of chest pain and number of chest pain events during the TEAE period by treatment group and overall

	Alirocumab (n = 9451)	Placebo (n = 9443)	Overall (N = 18,894)	Unadjusted relative risk alirocumab vs placebo
Combined[a]				
Total number of events (patients with events, n)	1439 (1055)	1554 (1176)	2993 (2231)	
Risk (95 % CI)	0.112 (0.105–0.118)	0.125 (0.118–0.131)	0.118 (0.114–0.123)	0.896
Non-hospitalized chest pain events as AE				
Total number of events (patients with events, n)	892 (710)	949 (780)	1841 (1490)	
Risk (95 % CI)	0.075 (0.070–0.080)	0.083 (0.077–0.088)	0.079 (0.075–0.083)	0.910
Hospitalized chest pain events negatively adjudicated for unstable angina or myocardial infarction				
Total number of events (patients with events, n)	547 (449)	605 (503)	1152 (952)	
Risk (95 % CI)	0.048 (0.043–0.052)	0.053 (0.049–0.058)	0.050 (0.047–0.054)	0.892

[a] Combined: Non-hospitalized chest pain events as AE or hospitalized chest pain events negatively adjudicated for unstable angina or myocardial infarction.
AE, adverse events; CI, confidence interval; TEAE, treatment-emergent adverse event.

chest pain among participants treated with alirocumab compared with placebo, which was particularly evident after 7 months in the study.

The primary endpoint of ODYSSEY OUTCOMES included positively adjudicated unstable angina requiring hospitalization. The treatment effect on unstable angina was significantly beneficial (HR: 0.61) even though the number of events was small (60 on placebo and 37 on treatment) and occurred in fewer than 1 % of the study cohort [2]. In this analysis, we focused on chest pain events that were not captured in the definition of MACE, and show that patients frequently experienced an adverse event of chest pain without hospitalization (alirocumab 7.5 % and placebo 8.3 %) or were hospitalized for chest pain that was then negatively adjudicated for ACS according to study protocol (alirocumab 4.8 % and placebo 5.3 %), and that lower rates occurred for those randomized to alirocumab versus those on placebo in each category.

Coronary microvascular dysfunction, often found in association with acute coronary syndrome [7], is identified more often in women than in men [8–10]. Lipid-lowering therapy with a PCSK9 inhibitor added to statin has not been shown to improve coronary microvascular dysfunction [11]. These observations raise the possibility that symptoms due to microvascular dysfunction, and therefore unresponsive to alirocumab, contributed to the numerically smaller treatment effect of alirocumab on chest pain in women versus men in the current study. The fact that alirocumab reduced chest pain events in parallel with reducing rates of acute myocardial infarction and hospitalization for unstable angina suggests that the beneficial effect on chest pain was not simply the result of a clinical downgrading of MACE. Finally, the nearly double rate of MACE among those reporting chest pain suggests the potential utility of this symptom in reducing cohort size and follow-up length to adequately power outcome trials in ACS. Overall, the effect of alirocumab on chest pain has the potential to benefit quality of life and may positively affect acceptance of, and adherence to, treatment.

Study limitations, beyond those intrinsic to any post hoc analysis, include the observation period limited to treatment exposure, the incompleteness of adverse event reporting, and no formal adjudication for non-hospitalized chest pain events. However, it is reasonable to expect a low level of missingness and a high level of accuracy in the reporting of chest pain as adverse event, given that patients were in a study of cardiac protection and adverse events reporting was done by cardiovascular providers. To this point, it is important to note that the rate of MACE was nearly double among those who experienced chest pain compared with those who did not, supporting a clinically meaningful value of these adverse events in heralding the highest risk for the worst cardiovascular outcomes.

In conclusion, treatment with alirocumab reduced the rate of chest pain events among patients with recent ACS. These results are in line with the main effect of alirocumab on the rate of MACE.

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Disclosures

Sergio Fazio, Ruifeng Chen, Kasturi Talapatra, Gregory P Geba, Taylor Brackin, Kusha A Mohammadi, Robert Pordy and **Garen Manvelian** are all employees of and shareholders in Regeneron Pharmaceuticals, Inc.

David J Maron reports consulting fees from Regeneron Pharmaceuticals, Inc.

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Ph. Gabriel Steg reports grants and nonfinancial support (cochair 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; research grants and personal fees from Bayer (Steering Committee MARINER, grant for epidemiological study), Merck (speaker fees, grant for epidemiological studies), Sanofi (cochair of the ODYSSEY OUTCOMES trial; cochair of the SCORED trial; consulting, speaking), Servier (Chair of the CLARIFY registry; grant for

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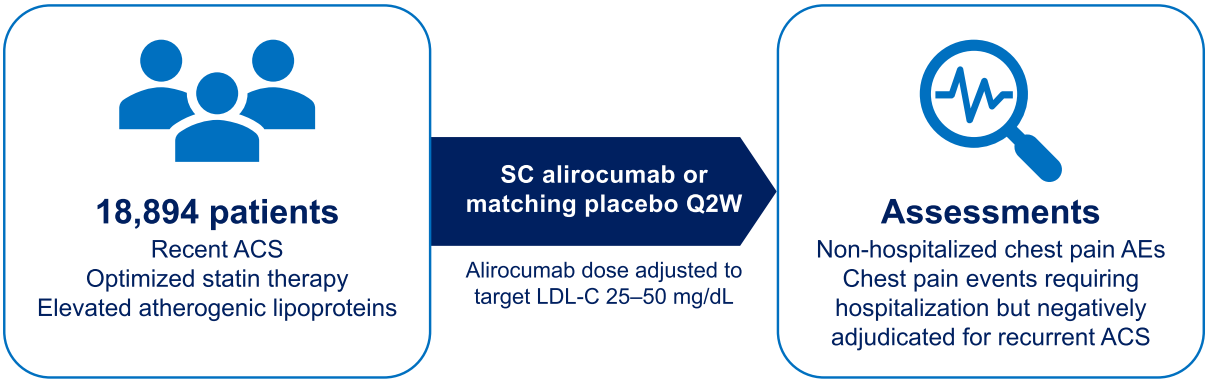
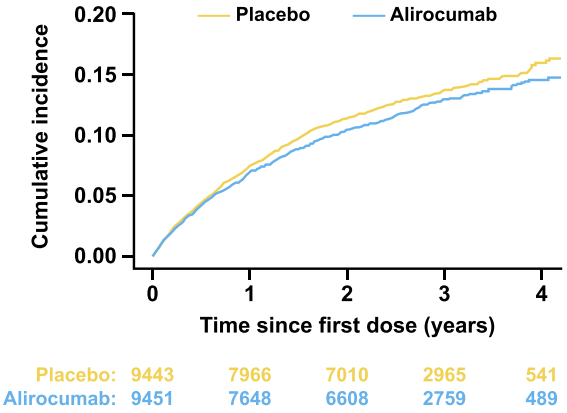


Cumulative incidence of chest pain (either non-hospitalized chest pain or chest pain requiring hospitalization but negatively adjudicated or recurrent ACS) by treatment group

- **Adjusting for baseline covariates, alirocumab use was associated with 8.1% lower risk of chest pain versus placebo**
  - **HR: 0.919; 95% CI: 0.845–0.998; *P*=0.046**
- **A landmark analysis at 7 months showed a larger risk reduction of 11.7% versus placebo**
  - **HR: 0.883; 95% CI: 0.793–0.984; *P*=0.024**



Alirocumab was associated with reduced incidence of chest pain events after acute coronary syndrome

Central Illustration. Cumulative incidence of chest pain event (either non-hospitalized chest pain or hospitalized chest pain negatively adjudicated for unstable angina or myocardial infarction) by treatment group using Kaplan-Meier estimation

epidemiological research), and Amarin (executive steering committee for the REDUCE-IT trial [Disease Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial]; consulting); and personal fees from Amgen, Bristol-Myers Squibb, Boehringer Ingelheim, Pfizer, Idorsia, Myokardia, Novo Nordisk, Novartis, Regeneron Pharmaceuticals, Inc., and AstraZeneca. He also has a European application number/patent number, issued on October 26, 2016 (no. 15712241.7), for a method for reducing cardiovascular risk, all royalties assigned to Sanofi.

Data sharing

Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing 1) once the product and indication has been approved by major health authorities (e.g., FDA, EMA, PMDA, etc) or development of the product has been discontinued globally for all indications on or after April 2020 and there

Table 2
Cox proportional hazard regression estimated[a] hazard ratio of incidence of chest pain between alirocumab and placebo

Types of chest pain events	Population	HR (95 % CI), *P*-value	*P*-value for interaction[c]
Combined[b]	Overall	0.919 (0.845–0.998), 0.046	
	Males	0.916 (0.830–1.011)	0.958
	Females	0.923 (0.790–1.078)	
Non-hospitalized chest pain events as AE	Overall	0.936 (0.845-1.036), 0.202	
	Males	0.924 (0.819–1.042)	0.698
	Females	0.969 (0.801–1.172)	
Hospitalized chest pain events negatively adjudicated for unstable angina or myocardial infarction	Overall	0.915 (0.806–1.040), 0.173	
	Males	0.921 (0.791–1.071)	0.851
	Females	0.895 (0.706–1.135)	

[a] Cox regression model adjusted covariates included age, sex, race, ethnicity, BMI, medical history of chest pain since qualifying ACS event and medical history of revascularization.
[b] Combined: Non-hospitalized chest pain events as AE or hospitalized chest pain events negatively adjudicated for unstable angina or myocardial infarction.
[c] *P*-value for testing the interaction between sex and treatment arms.
ACS, acute coronary syndrome AE, adverse events; BMI, body mass index; CI, confidence interval; HR, hazard

are no plans for future development 2) if there is legal authority to share the data and 3) there is not a reasonable likelihood of participant re-identification. Submit requests to https://vivli.org/.

CRediT authorship contribution statement

Gregory P. Geba: Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Ruifeng Chen:** Writing – review & editing, Formal analysis, Conceptualization. **Kasturi Talapatra:** Writing – review & editing, Formal analysis, Conceptualization. **Taylor Brackin:** Writing – review & editing, Formal analysis, Conceptualization. **Kusha A. Mohammadi:** Writing – review & editing, Formal analysis, Conceptualization. **Robert Pordy:** Writing – review & editing, Formal analysis, Conceptualization. **Garen Manvelian:** Writing – review & editing, Formal analysis, Conceptualization. **David J. Maron:** Writing – review & editing, Formal analysis, Conceptualization. **Gregory G. Schwartz:** Writing – review & editing, Formal analysis, Conceptualization. **Michael Szarek:** Writing – review & editing, Formal analysis, Conceptualization. **Ph. Gabriel Steg:** Writing – review & editing, Formal analysis, Conceptualization. **Sergio Fazio:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajpc.2024.100900.

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