Journal of Clinical Lipidology (2024) 000, 1–14

Journal of Clinical Lipidology

Original Research

Alirocumab and cardiovascular outcomes according to sex and lipoprotein(a) after acute coronary syndrome: a report from the ODYSSEY OUTCOMES study

Vera A. Bittner, MD, MSPH*, Gregory G. Schwartz, MD, PhD, Deepak L. Bhatt, MD, MPH, Terrance Chua, MD, H. Asita De Silva, MD, Rafael Diaz, MD, Shaun G. Goodman, MD, Robert A. Harrington, MD, J. Wouter Jukema, MD, PhD, Jennifer McGinniss, PhD, Robert Pordy, MD, Genevieve Garon, BS Micr, MBA, Michel Scemama, MD, Harvey D. White, DSc, Ph. Gabriel Steg, MD, Michael Szarek, PhD, for the ODYSSEY OUTCOMES Investigators†

Division of Cardiovascular Disease, University of Alabama at Birmingham, Birmingham, UK (Dr Bittner); Division of Cardiology, University of Colorado School of Medicine, Aurora, CO (Dr Schwartz); Mount Sinai Heart, Icahn School of Medicine at Mount Sinai Health System, New York, NY, USA (Dr Bhatt); National Heart Centre, Singapore (Dr Chua); Clinical Trials Unit, Department of Pharmacology, Faculty of Medicine, University of Kelaniya, Sri Lanka (Dr De Silva); Estudios Cardiológicos Latino América, Instituto Cardiovascular de Rosario, Rosario, Argentina (Dr Diaz); Canadian VIGOUR Centre, University of Alberta, Edmonton, Alberta, Canada (Dr Goodman); St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada (Dr Goodman); Stanford Center for Clinical Research, Department of Medicine, Stanford University, Stanford, CA (Dr Harrington); Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands (Dr Jukema); Netherlands Heart Institute, Utrecht, the Netherlands (Dr Jukema); Regeneron Pharmaceuticals, Inc, Tarrytown, NY, USA (Dr McGinniss, Pordy); Sanofi, Montreal, Canada (Ms Garon); Sanofi Research and Development, Paris, France (Dr Scemama); Green Lane Cardiovascular Research Unit, Te Whatu Ora – Health New Zealand, Te Toka Tumai, and University of Auckland, Auckland, New Zealand (Dr White); Université Paris-Cité, Institut Universitaire de France, Assistance Publique-Hôpitaux de Paris, Hôpital Bichat, FACT (French Alliance for Cardiovascular Trials), and INSERM U1148, Paris, France (Dr Steg); CPC Clinical Research and Division of Cardiology, University of Colorado School of Medicine, Aurora, CO (Dr Szarek); State University of New York, Downstate Health Sciences University, Brooklyn, NY (Dr Szarek)

Abbreviations: ACS, Acute coronary syndrome; ARR, Absolute rate reduction; CHD, Coronary heart disease; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; MACE, Major adverse cardiovascular events; NSTEMI, Non-ST-segment elevation myocardial infarction; Non-HDL-C, Non-high-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; STEMI, ST-segment elevation myocardial infarction.

* Corresponding author. University of Alabama at Birmingham, 521 19th Street South – GSB 444, Birmingham, AL 35233.
E-mail address: vbittner@uab.edu (V.A. Bittner).

Submitted November 23, 2023. Accepted for publication April 6, 2024.

Social media: (V.A. Bittner)

† The ODYSSEY OUTCOMES Committee members, investigators, and contributors are listed in the Suppl. Appendix.

https://doi.org/10.1016/j.jacl.2024.04.122

Please cite this article as: Bittner et al, Alirocumab and cardiovascular outcomes according to sex and lipoprotein(a) after acute coronary syndrome: ODYSSEY OUTCOMES, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2024.04.122

KEYWORDS
Acute coronary syndrome;
Sex;
Alirocumab;
PCSK9 inhibition;
Cholesterol;
Cardiovascular outcomes;
Lipoprotein(a)

Abstract:

Background: The ODYSSEY OUTCOMES trial (NCT01663402) compared the effects of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab with placebo on major adverse cardiovascular events (MACE) in patients with recent acute coronary syndrome (ACS).

Objective: We assessed efficacy and safety of alirocumab versus placebo according to sex and lipoprotein(a) level.

Methods: This prespecified analysis compared the effects of alirocumab versus placebo on lipoproteins, MACE (coronary heart disease death, non-fatal myocardial infarction, fatal/non-fatal ischemic stroke, unstable angina requiring hospitalization), death, total cardiovascular events, and adverse events in 4762 women and 14,162 men followed for a median of 2.8 years. In post-hoc analysis, we evaluated total cardiovascular events according to sex, baseline lipoprotein(a), and treatment.

Results: Women were older, had higher baseline LDL-C levels (89.6 vs 85.3 mg/dL) and lipoprotein(a) (28.0 vs 19.3 mg/dL) and had more co-morbidities than men. At 4 months, alirocumab lowered LDL-C by 49.4 mg/dL in women and 54.0 mg/dL in men and lipoprotein(a) by 9.7 and 8.1 mg/dL, respectively (both $p < 0.0001$). Alirocumab reduced MACE, death, and total cardiovascular events similarly in both sexes. In the placebo group, lipoprotein(a) was a risk factor for total cardiovascular events in women and men. In both sexes, reduction of total cardiovascular events was greater at higher baseline lipoprotein(a), but this effect was more evident in women than men ($p_{interaction}$=0.08). Medication adherence and adverse event rates were similar in both sexes.

Conclusions: Alirocumab improves cardiovascular outcomes after ACS irrespective of sex. Reduction of total cardiovascular events was greater at higher baseline lipoprotein(a).

Introduction

Women are often underrepresented in clinical trials, leading to uncertainty in subgroup analyses by sex and lower quality data to guide evidence-based therapy.[1,2] While many individual trials are inconclusive, patient-level meta-analyses show that women with established cardiovascular disease benefit from statin therapy to the same degree as men.[3] However, sex-specific data for non-statin lipid-lowering therapies are sparse.[2] A recent statement by the European Society of Atherosclerosis highlighted differences in lipoprotein concentrations through the life course in women versus men, as well as sex differences in the relationships of lipoprotein levels to cardiovascular risk. The statement also specifically emphasized the importance of further research to define the role of lipoprotein(a) in atherosclerotic risk and risk mitigation in women.[4]

Compared with men, women have higher levels of circulating proprotein convertase subtilisin/kexin type 9 (PCSK9),[5] but PCSK9 inhibitor therapy reduces low-density lipoprotein cholesterol (LDL-C) somewhat less in women than in men.[6,7] This may be due in part to the fact that measurements of LDL-C include cholesterol from lipoprotein(a) particles, that lipoprotein(a) levels are higher in women than men,[8] and that PCSK9 inhibitors reduce lipoprotein(a) to a lesser extent than LDL-C. A recent analysis from the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial reported comparable reductions in cardiovascular events with evolocumab therapy in women and men with established stable atherosclerotic cardiovascular disease,[7] but sex differences in the effect of PCSK9 inhibitors on levels of lipoprotein(a) have not been defined. Moreover, an analysis of the impact of PCSK9 inhibitor therapy on clinical outcomes by sex among patients after recent acute coronary syndrome (ACS) has not been reported.

The ODYSSEY OUTCOMES trial compared the PCSK9 inhibitor alirocumab with placebo in 18,924 patients with recent ACS and persistent elevation of atherogenic lipoproteins despite optimized statin treatment. Over a median follow-up of 2.8 years, alirocumab reduced the primary outcome of major adverse cardiovascular events (MACE) by 15 %, with comparable benefits for secondary outcomes including a 15 % reduction in all-cause death.[9,10] Here, we report the results of a prespecified subgroup analysis of ODYSSEY OUTCOMES according to sex and treatment and a post-hoc analysis that examined the relationship of lipoprotein(a) levels to outcomes in women and men in both treatment groups.

Methods

Details of the ODYSSEY OUTCOMES trial (NCT01663402) design and results have been published.[9,11] The trial included 4762 women and 14,162 men aged ≥40 years hospitalized with ACS 1–12 months before randomization who had LDL-C ≥ 70 mg/dL, non-high-density lipoprotein cholesterol (non-HDL-C) ≥100 mg/dL, or apolipoprotein B ≥ 80 mg/dL on high-intensity or maximum-tolerated statin therapy. The trial was approved by the institutional review board of each site. All patients provided informed consent.

Please cite this article as: Bittner et al, Alirocumab and cardiovascular outcomes according to sex and lipoprotein(a) after acute coronary syndrome: ODYSSEY OUTCOMES, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2024.04.122

Patients were randomly assigned to treatment with alirocumab 75 mg subcutaneously every 2 weeks or matching placebo. Among patients assigned to alirocumab, the dose was blindly increased to 150 mg to maximize the number of patients who achieved an LDL-C value between 25 and 50 mg/dL, or blindly substituted with placebo to minimize the number with sustained LDL-C levels below 15 mg/dL. LDL-C was measured by beta-quantification when triglycerides were >400 mg dL or when the calculated LDL-C was <15 mg/dL; all other LDL-C values were calculated by the Friedewald formula.[12] Lipoprotein(a) was measured at baseline and 4 months at COVANCE Central laboratories with a mass assay using an automated Siemens BNII (Siemens, Healthcare Diagnostics, Malvern, Pennsylvania) as previously described.[13] The primary MACE outcome was the first event in a composite of death from coronary heart disease (CHD), non-fatal myocardial infarction (MI), fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalization. To maximize the number of events available for analyses of subgroups defined by sex and lipoprotein(a), total cardiovascular events were also included as an outcome and encompassed first and subsequent components of MACE, cardiovascular deaths other than those due to CHD, hemorrhagic stroke, hospitalization for heart failure, ischemia-driven coronary revascularization, peripheral artery disease events (critical limb ischemia, lower extremity revascularization procedures, or amputation for ischemia), and venous thromboembolism (deep vein thrombosis or pulmonary embolism). Non-cardiovascular deaths were also recorded, and all-cause death analyzed as an outcome. All efficacy events except peripheral artery disease events and venous thromboembolism were adjudicated by a blinded endpoint committee.

Statistical analysis

Analyses of subgroups defined by sex reported at randomization were prespecified. These include descriptive statistics, assessment of lipid effects in women and men, assessment of events stratified by sex, and assessment of the impact of alirocumab in women and men. Categorical variables are reported as count (percentage), and continuous variables as median (quartile 1, quartile 3). Event rates are expressed as the number of events per 100 patient-years of follow-up. Comparisons of baseline characteristics with patients grouped by sex were by χ^2 or Fisher's exact tests (where possible) for categorical variables and Wilcoxon's rank-sum tests for continuous variables. All analyses were according to intention-to-treat except for adverse events, where patients were grouped according to actual treatment received and events through 70 days after last dose of randomized treatment were considered.

Time to permanent discontinuation of randomized treatment, defined as a last prescribed dose >3 weeks prior to death or date last known alive, was calculated for women and men within each treatment group among patients who received at least 1 dose and was summarized by cumulative incidence functions, with comparisons by Cox proportional hazards models.

We assessed the effects of alirocumab or placebo on LDL-C, apolipoprotein B, high-density lipoprotein cholesterol (HDL-C), and non-HDL-C separately for women and men by analysis of covariance. Because triglyceride and lipoprotein(a) had a skewed distribution, effects of treatment on these variables were determined by robust regression with treatment group as a fixed effect and baseline lipid value as a covariate. Imputation of missing values followed prespecified methods.[9]

Relationships between sex and outcomes in the placebo group were determined by Cox proportional hazards models for first MACE and individual MACE components, or a marginal proportional hazards model in the case of total (first and subsequent) cardiovascular events, using sex as the predictor variable. The marginal model treated non-cardiovascular death as a competing event and accounted for the possibility of a given patient having multiple events by applying a robust sandwich variance estimate for the estimated standard error of the log hazard ratio to account for the dependence of event times within individual patients.[14] We constructed unadjusted models and multivariable models adjusted for demographic variables (age, race, region), clinical variables (history of diabetes, smoking, hypertension, cerebrovascular disease, or heart failure; myocardial infarction prior to the index ACS; coronary artery bypass grafting prior to the index ACS; type of index ACS (non-ST-segment elevation myocardial infarction [NSTEMI] vs other), revascularization for index ACS, time from index ACS to randomization; and estimated glomerular filtration rate (<60 mL/min/1.73 m^2 vs other), and evidence-based medications (high-intensity statin, aspirin, $P2Y_{12}$ inhibitors, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers). Rates of ezetimibe and hormone replacement therapy use were low and not considered in the modeling. Relative risks for women versus men are summarized by hazard ratios (HR) with associated 95 % confidence intervals (CI) and p values.

The relative treatment effects of alirocumab versus placebo on time to first MACE and its components were assessed by Cox proportional hazards models. For analyses of total cardiovascular events, we applied a marginal proportional hazards model described above for relative treatment effects, whereas absolute treatment effects were estimated by a Poisson regression model with logarithm of follow-up time included in the model as an offset.[14] All models had terms for treatment, sex, and their interaction, with results summarized by treatment HR, event rates per 100 patient-years of follow-up in each treatment group, or treatment absolute rate reduction (ARR) with associated 95 % CI and p values for the interaction terms.

In a post-hoc analysis, we assessed the interaction of baseline lipoprotein(a), sex and treatment group on total cardiovascular events. Total cardiovascular events (a prespecified trial outcome, $N = 5769$) was chosen as the outcome measure in this analysis to afford greater power to detect this 3-way

Please cite this article as: Bittner et al, Alirocumab and cardiovascular outcomes according to sex and lipoprotein(a) after acute coronary syndrome: ODYSSEY OUTCOMES, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2024.04.122

interaction. Total cardiovascular events per 100 patients at 4 years as a function of baseline lipoprotein(a) were estimated by natural cubic splines from Poisson regression models with the logarithm of follow-up time as an offset variable by treatment group and sex with knots at sex-specific lipoprotein(a) quartiles. Estimated ARR with alirocumab was calculated by sex at several levels of lipoprotein(a).

Results

Baseline characteristics for women and men

Baseline characteristics are detailed in Table 1 and Suppl. Table 1. Overall, women comprised 25.2 % of the population, ranging from 18.6 % of participants from Western Europe to 30.2 % of participants from North America. Median age among women was 5 years greater than among men (62 vs 57 years) with 7.7 % of women versus 3.1 % of men above age 75. Over 75 % of both women and men were white. Within racial subgroups, the enrollment of women was highest among black patients (42.5 %) and lowest among Asian patients (20.8 %).

NSTEMI was the most common index ACS event in both sexes but was proportionately higher in women than in men. Men were proportionately more likely to be enrolled after STEMI and more likely to receive percutaneous coronary intervention for the index event (68.9 % vs 63.2 %, $p < 0.0001$). Time from index event to randomization was similar in women and men. Mean LDL-C, HDL-C, apolipoprotein B and particularly median lipoprotein(a) levels (28.0 vs 19.3 mg/dL) were higher in women than men (all $p < 0.0001$). Proportionately more women reported a history of diabetes, hypertension, prior cerebrovascular disease, and heart failure, but women were less likely to be current smokers or to have had a myocardial infarction or coronary artery bypass graft surgery prior to the index ACS (all $p < 0.0001$). Use of evidence-based therapy was high in both sexes, with small but statistically significant differences in use of high-intensity statins and antiplatelets favoring men.

Changes in alirocumab dose and permanent discontinuation of randomized treatment

In the alirocumab group, women were more likely than men to have blinded up-titration of the alirocumab dose from 75 to 150 mg (19.1 % vs 12.1 %; $p < 0.0001$) and were less likely to have blinded substitution of placebo for alirocumab (2.4 % vs 4.3 %; $p < 0.0003$), both expected because of higher baseline LDL-C levels. Women prematurely discontinued randomized treatment more often than men in the placebo group (20.2 % vs 15.6 %; HR 1.34, 95 % CI 1.21–1.50) but not in the alirocumab group (22.0 % vs 23.1 %; HR 0.96, 95 % CI 0.87–1.05; $p_{interaction} < 0.0001$; Suppl. Fig. 1). Consequently, any observed differences in achieved lipid levels over time between women and men in the alirocumab group would not appear to be due to differential discontinuation of active study treatment.

Changes in lipids and lipoproteins over time, stratified by treatment and sex

Effects of alirocumab on LDL-C, apolipoprotein B, and lipoprotein(a) over time are shown in Fig. 1; effects on HDL-C, non-HDL-C and triglycerides are shown in Suppl. Fig. 2. Achieved levels and changes between baseline and month 4 (i.e. generally prior to titration of alirocumab and/or blinded switching to placebo in the alirocumab group) are detailed in Suppl. Table 2. At month 4, men achieved lower levels of LDL-C, apolipoprotein B, non-HDL-C, and triglycerides with alirocumab than women, reflecting greater absolute decreases. In contrast, alirocumab lowered lipoprotein(a) to a greater degree in women than men (9.7 mg/dL vs 8.1 mg/dL, $p < 0.0001$), but men had lower achieved lipoprotein(a) levels due to lower baseline levels.

Outcomes by sex in the placebo arm

There were 1955 first MACE events over a median follow-up was 2.8 (2.3, 3.4) years. Event rates for women and men in the placebo arm are shown in Fig. 2. Outcomes by sex in the placebo group, expressed as women:men HR unadjusted and adjusted for demographics, clinical variables and evidence-based medications, are shown in Table 2. Although there were no statistically significant differences, women were at a numerically higher unadjusted relative risk than men, but after adjustment for baseline characteristics the opposite was the case, with women:men HR consistently <1.00.

Effect of alirocumab on time to MACE and all-cause death by sex

The cumulative incidence of the primary outcome (MACE) by sex and treatment group is shown in Fig. 2. Event rates for MACE, its principal component events, and all-cause death are shown in Fig. 3. The point estimates for effects of alirocumab on these outcomes were similar in both sexes, but with wider confidence intervals for women due to the smaller sample size. Sex-by-treatment interaction was non-significant for the HR for each outcome.

Relative and absolute effect of alirocumab on total cardiovascular events by sex

Fig. 4 shows that women and men in the placebo group had similar rates of a first cardiovascular event (6.9 vs 6.8 per 100 patient-years). However, among patients who had at least 1 event, the rate of subsequent events was higher for women (5.7 vs 4.4 per 100 patient-years). Thus, the rate of total cardiovascular events was numerically higher in women than men (12.7 vs 11.2 per 100 patient-years). The overall effects of alirocumab on the rates of first and total events (Fig. 5) indicate no formal evidence of heterogeneity.

Please cite this article as: Bittner et al, Alirocumab and cardiovascular outcomes according to sex and lipoprotein(a) after acute coronary syndrome: ODYSSEY OUTCOMES, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2024.04.122

Table 1 Baseline characteristics, treatments and medications by sex.

Variable	Women ($n = 4762$)	Men ($n = 14,162$)	p value*
Age, yrs	62 (55, 68)	57 (51, 64)	<0.0001
Age >75 yrs	365 (7.7)	437 (3.1)	<0.0001
Race			<0.0001
White	3744 (78.6)	11,280 (79.6)	
Asian	519 (10.9)	1979 (14.0)	
Black	201 (4.2)	272 (1.9)	
Other	298 (6.3)	628 (4.4)	
Region			<0.0001
Western Europe	777 (16.3)	3398 (24.0)	
Eastern Europe	1572 (33.0)	3865 (27.3)	
North America	868 (18.2)	2003 (14.1)	
South America	746 (15.7)	1842 (13.0)	
Asia	474 (10.0)	1819 (12.8)	
Rest of world	325 (6.8)	1235 (8.7)	
Index event			<0.0001
NSTEMI	2466 (51.8)	6709 (47.4)	
STEMI	1430 (30.0)	5106 (36.1)	
Unstable angina	863 (18.1)	2319 (16.4)	
Time from index event to randomization, months	2.6 (1.7, 4.4)	2.6 (1.7, 4.3)	0.83
PCI for index event	3009 (63.2)	9759 (68.9)	<0.0001
Laboratory measurements			
LDL-C, mg/dL	89.6 (75.3, 110.0)	85.3 (72.2, 102.0)	<0.0001
LDL-C $\geq$ 100 mg/dL	873 (36.5)	3922 (27.7)	<0.0001
HDL-C, mg/dL	47.5 (40.5, 56.0)	41.0 (35.1, 48.0)	<0.0001
Non-HDL-C, mg/dL	118.9 (101.9,143.0)	113.9 (98.5,135.0)	<0.0001
Apolipoprotein B, mg/dL	81 (70, 95)	79 (69, 92)	<0.0001
Lipoprotein(a), mg/dL	28.0 (9.1, 73.0)	19.3 (6.2, 55.3)	<0.0001
Estimated GFR <60 mL/min/1.73 m^2	1039 (21.8)	1500 (10.6)	<0.0001
Medical history prior to index event			
Current smoker	906 (19.0)	3654 (25.8)	<0.0001
Body mass index, kg/m^2	28.3 (25.1, 32.2)	27.8 (25.3, 30.8)	<0.0001
Diabetes	1736 (36.5)	3708 (26.2)	<0.0001
Hypertension	3599 (75.6)	8650 (61.1)	<0.0001
Myocardial infarction	756 (15.9)	2877 (20.3)	<0.0001
CABG	204 (4.3)	843 (6.0)	<0.0001
Heart failure	845 (17.7)	1969 (13.9)	<0.0001
Stroke	199 (4.2)	412 (2.9)	<0.0001
Cerebrovascular disease	301 (6.3)	643 (4.5)	<0.0001
Peripheral artery disease	200 (4.2)	559 (3.9)	0.44
Chronic obstructive pulmonary disease	222 (4.7)	502 (3.5)	0.0005
Medications			
High-intensity statin	4163 (87.4)	12,648 (89.3)	0.0004
Aspirin	4494 (94.4)	13,592 (96.0)	<0.0001
$P2Y_{12}$ antagonist	4059 (85.2)	12,482 (88.1)	<0.0001
ACE inhibitor/ARB	3746 (78.7)	10,970 (77.5)	0.09
Beta-blocker	4033 (84.7)	11,962 (84.5)	0.73
Ezetimibe	145 (3.0)	409 (2.9)	0.58

Legend: Values are median (quartile 1, quartile 3) or count (%). *Fisher's exact or Wilcoxon tests.

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CABG: coronary artery bypass graft; GFR: glomerular filtration rate; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction.

Post hoc analysis of total cardiovascular events by sex, treatment group, and baseline lipoprotein(a)

Fig. 6 shows spline plots of total cardiovascular events per 100 patients at 4 years as a function of continuous baseline lipoprotein(a) by sex and treatment group. In the placebo group, lipoprotein(a) was related to the rate of total cardiovascular events in both sexes (spline $p < 0.0001$) without interaction of sex and baseline lipoprotein(a) ($p = 0.95$). In both sexes, the absolute risk reduction (ARR) of total car-

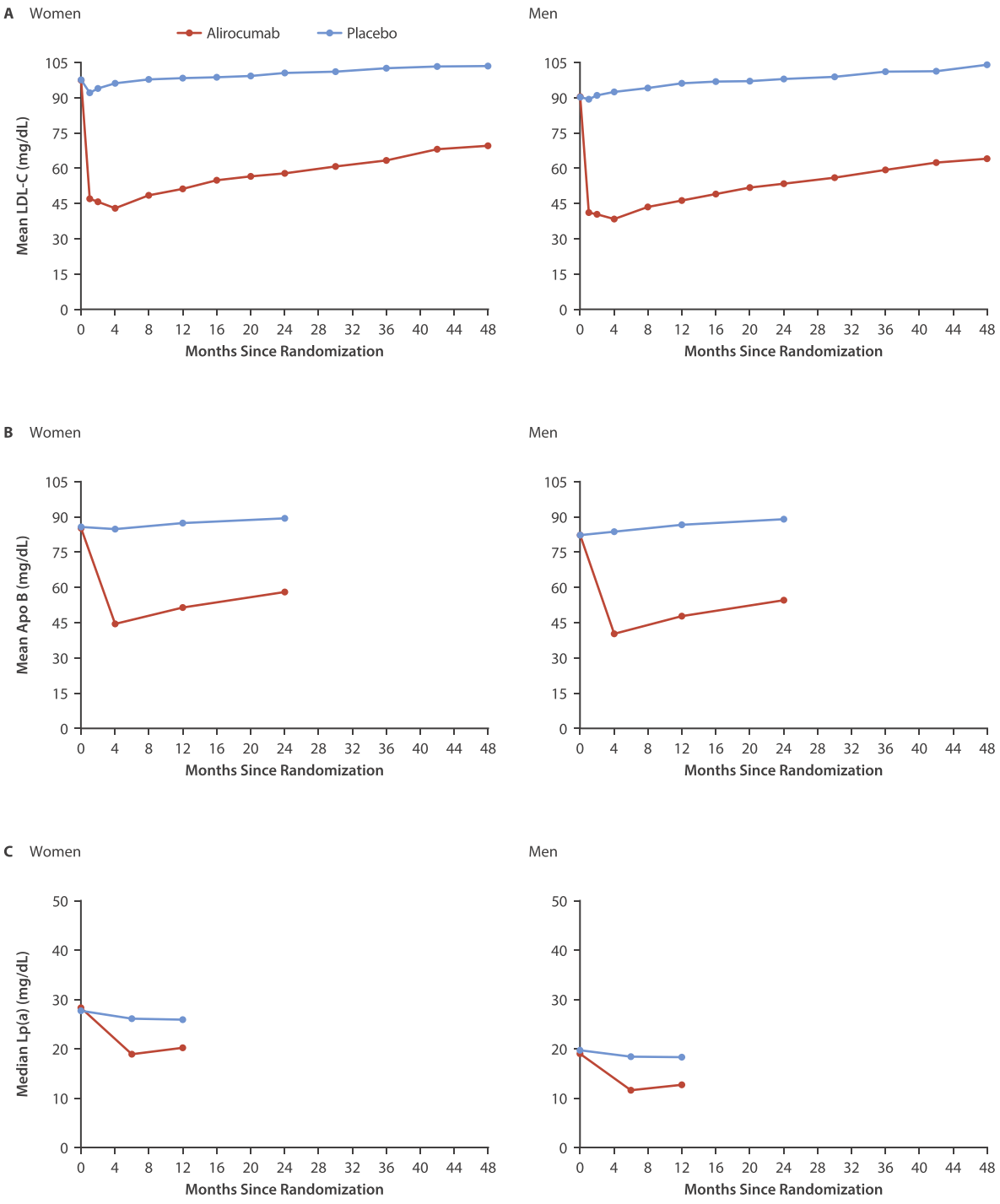

Fig. 1 Impact of alirocumab on low-density lipoprotein cholesterol (LDL-C), apolipoprotein B, and lipoprotein(a). Lipid values over time are shown for placebo and alirocumab for LDL-C (panel A), apolipoprotein B (panel B), and lipoprotein(a) (panel C). Men achieved lower levels of LDL-C and apolipoprotein B with alirocumab than women, reflecting greater absolute decreases. In contrast, women had larger decreases in lipoprotein(a) with alirocumab compared to men, but men had lower achieved levels due to lower baseline levels. When comparing lipid values between women and men at month 4, all p-values were <0.0001.

diovascular events with alirocumab tended to be more evident at higher baseline levels of lipoprotein(a). However, the dependence of treatment effect size on lipoprotein(a) was more pronounced in women than in men as reflected by a 3-way interaction of sex, lipoprotein(a) and treatment on total cardiovascular events with $p = 0.08$. Specifically, alirocumab reduced total cardiovascular event risk across the range of baseline lipoprotein(a) in men, with numerically greater reductions at higher lipoprotein(a) concentrations. In women, this risk was not reduced at very low baseline lipoprotein(a),

Please cite this article as: Bittner et al, Alirocumab and cardiovascular outcomes according to sex and lipoprotein(a) after acute coronary syndrome: ODYSSEY OUTCOMES, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2024.04.122

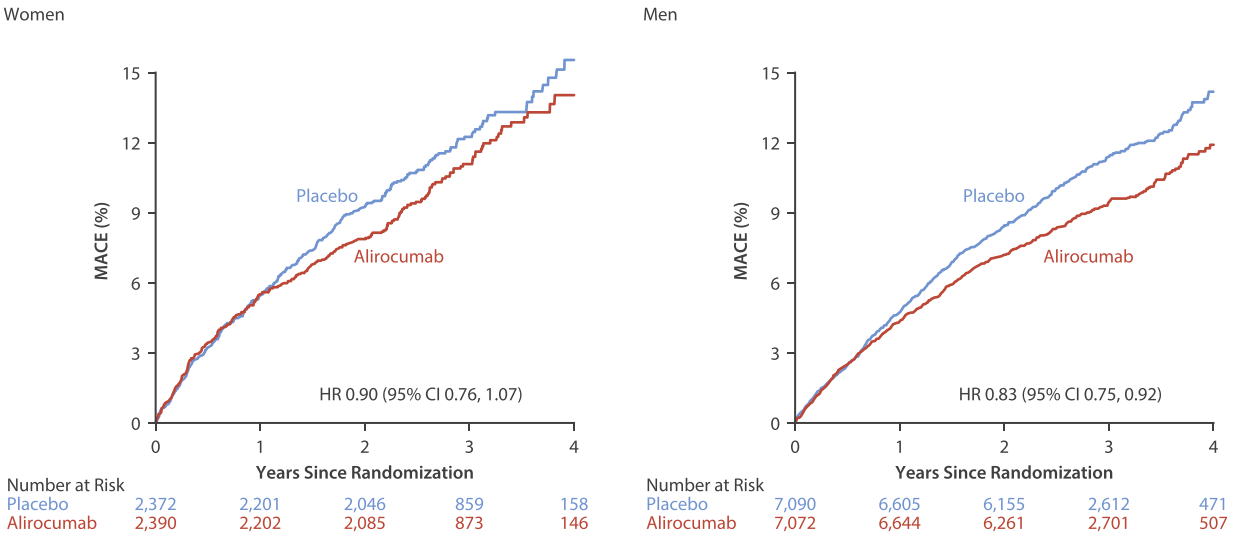

Fig. 2 Cumulative incidence of the primary outcome by sex and treatment group. The cumulative incidence curves of the primary outcome (major adverse cardiovascular events [MACE]) by sex and treatment group are shown. Point estimates for MACE reduction are similar for women and men, but with wider confidence intervals for women due to smaller sample size.
CI: confidence interval; HR: hazard ratio.

Table 2 Outcomes by sex in the placebo group.

Outcome	Event rates per 100 py: Women	Events Rates per 100 py: Men	Unadjusted model	Model fully adjusted for demographic and clinical variables and evidence-based medications
Primary composite (MACE)*	4.4	4.1	1.09 (0.95, 1.25) 0.22	0.93 (0.81, 1.07) 0.33
CHD death or non-fatal MI	3.8	3.4	1.12 (0.96, 1.29) 0.15	0.97 (0.83, 1.13) 0.66
Fatal or non-fatal ischemic stroke	0.6	0.5	1.18 (0.83, 1.68) 0.36	0.85 (0.59, 1.23) 0.40
All-cause death	1.6	1.4	1.16 (0.93, 1.45) 0.19	0.81 (0.65, 1.02) 0.08
First cardiovascular event	6.9	6.8	1.03 (0.92, 1.15) 0.60	0.91 (0.81, 1.02) 0.11
Total cardiovascular events	12.7	11.2	1.13 (0.99, 1.29) 0.08	0.96 (0.84, 1.09) 0.50

Legend: Values are women:men HR (95 % CI) and p value.
*Unstable angina not shown as separate component of MACE due to the low number of events in the subgroups.
CHD: coronary heart disease; MACE: major adverse cardiovascular event; MI, myocardial infarction; py, person-years.

with numerically greater ARR relative to men at higher lipoprotein(a) concentrations. This pattern of interaction is illustrated at several selected values of baseline lipoprotein(a) in Suppl. Table 3.

Adverse events stratified by sex

Adverse events by sex are shown in Suppl. Table 4. Among women, adverse events and serious adverse events did not differ between the placebo and alirocumab groups. Among men, adverse events and serious adverse events were less frequent in the alirocumab versus the placebo group ($p = 0.02$); however, there was no statistically significant interaction by sex ($p = 0.24$). Adverse events leading to discontinuation of study treatment were comparable in the alirocumab and placebo groups in both sexes.

Discussion

In this prespecified subgroup analysis of the ODYSSEY OUTCOMES trial, women and men with recent ACS on optimized statin therapy had similar risks of MACE in the placebo group and both sexes benefited similarly from alirocumab therapy without safety signals. However, there were several notable differences in risk and risk reduction with alirocumab according to sex. Women had a smaller absolute reduction than men in first cardiovascular events with alirocumab. Women had a significantly higher rate of total cardiovascular events than men in the placebo group, and consequently the absolute reduction in total cardiovascular events with alirocumab was nominally greater in women than men (Fig. 4). However, there was no significant heterogeneity by sex for the relative reduction in risk of total

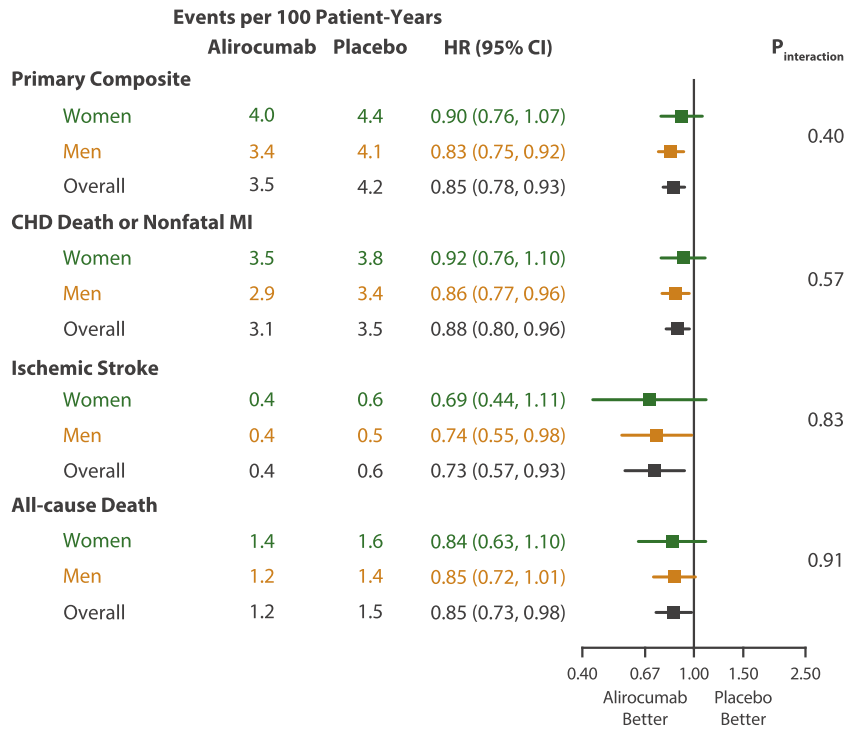

Fig. 3 Major adverse cardiovascular events (MACE) by sex and treatment. Event rates for MACE (coronary heart disease death or nonfatal myocardial infarction, and fatal or nonfatal stroke) are shown. The point estimates for effects of alirocumab on MACE were similar in both sexes, but with wider confidence intervals for women due to smaller sample size. Sex-by-treatment interaction was nonsignificant for the HR.
CHD: coronary heart disease; CI: confidence interval; HR: hazard ratio.

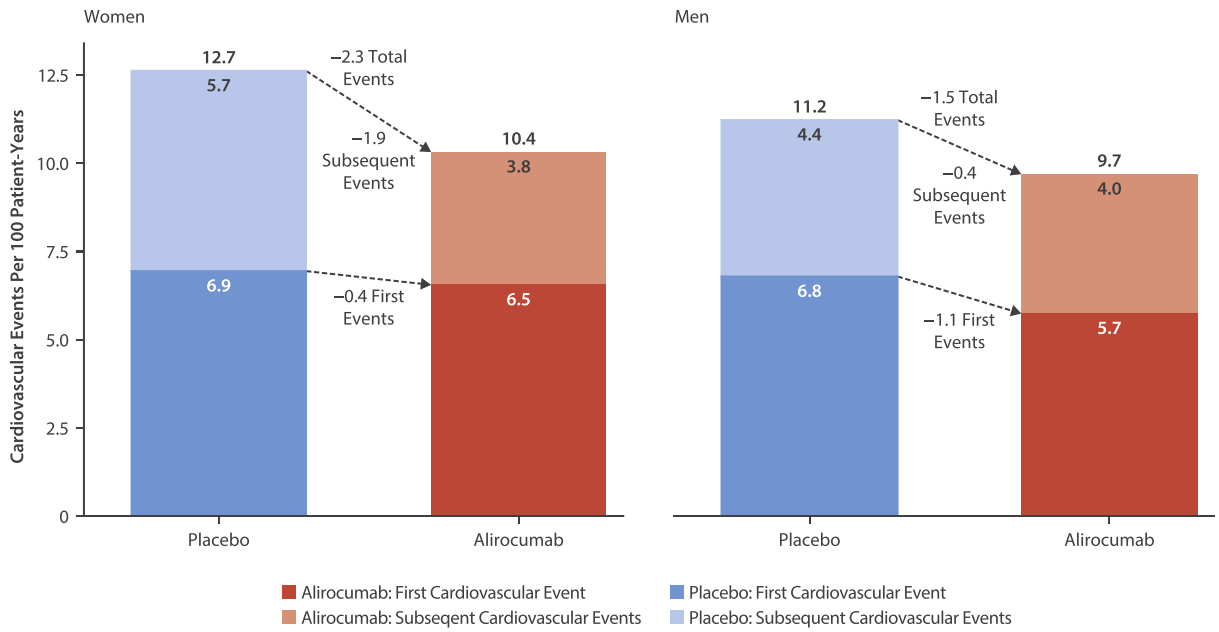

Fig. 4 First, subsequent, and total cardiovascular events. Blue bars show events in the placebo group, dark blue indicating first events and lighter blue subsequent events. Red bars show events in the alirocumab group, dark red indicating first events and lighter red subsequent events. Women and men in the placebo group had similar rates of first cardiovascular event (6.9 vs 6.8 per 100 patient-years; $p = 0.61$). However, among patients who had at least 1 event, the rate of subsequent events was higher for women than for men (5.7 vs 4.4 per 100 patient-years; $p = 0.0002$). Thus, the rate of total cardiovascular events was numerically higher in women than men in the placebo group (12.7 vs 11.2 per 100 patient-years; $p = 0.0028$) and in the alirocumab group (10.4 vs 9.7 per 100 patient-years; $p = 0.13$).

Please cite this article as: Bittner et al, Alirocumab and cardiovascular outcomes according to sex and lipoprotein(a) after acute coronary syndrome: ODYSSEY OUTCOMES, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2024.04.122

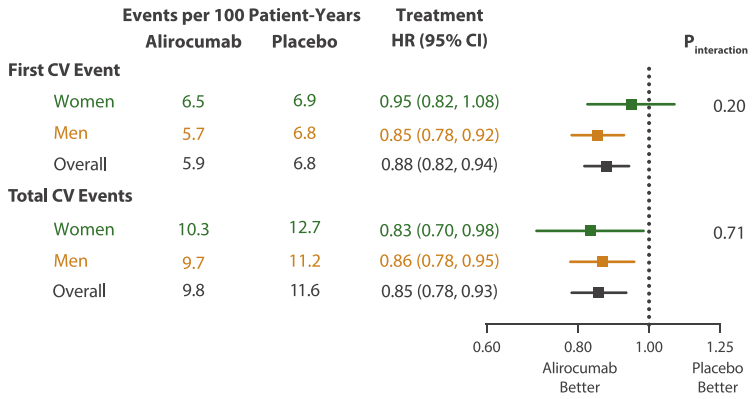

Fig. 5 Treatment effects on first and total cardiovascular events. Overall treatment effects of alirocumab on first and total cardiovascular events are shown for women and men. There was no evidence of interaction by sex for treatment effect of alirocumab on first or total cardiovascular events.
CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

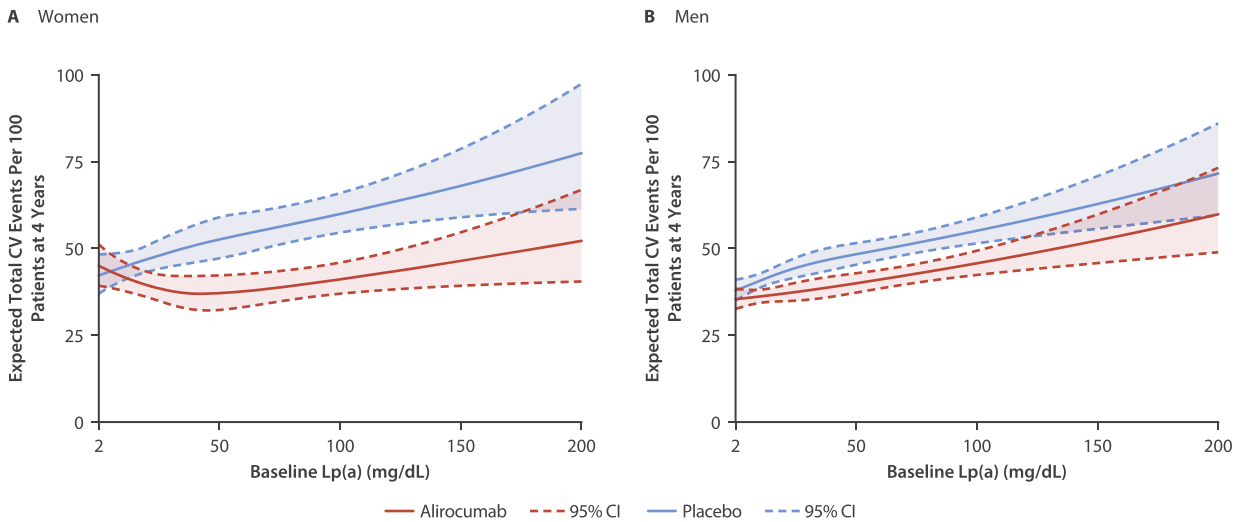

Fig. 6 Total cardiovascular events by lipoprotein(a) concentration, sex, and treatment group. Total cardiovascular events per 100 patients at 4 years as a function of baseline lipoprotein(a) were estimated by natural cubic splines from Poisson regression models with the logarithm of follow-up time as an offset variable by treatment group and sex with knots at sex-specific lipoprotein(a) quartiles. In the placebo group, lipoprotein(a) was related to the rate of total cardiovascular events in both sexes (splines $p < 0.0001$) without interaction of sex and baseline lipoprotein(a) ($p = 0.95$). In both sexes, the effect size of alirocumab for reduction of total cardiovascular events tended to be more evident at higher baseline levels of lipoprotein(a). However, the dependence of treatment effect size on lipoprotein(a) was more pronounced in women than in men, as reflected by a 3-way interaction of sex, lipoprotein(a), and treatment on total cardiovascular events with $p = 0.08$.
CI: confidence interval; CV: cardiovascular; Lp(a): lipoprotein(a).

cardiovascular events with alirocumab (Fig. 5). Overall, the effect of alirocumab on total cardiovascular events was similar across sexes.

For both women and men assigned to placebo, the risk of cardiovascular events increased with increasing levels of lipoprotein(a). In both sexes, the absolute reduction in total cardiovascular events with alirocumab tended to be more evident at higher baseline lipoprotein(a). However, the dependence of the alirocumab treatment effect size on lipoprotein(a) was more pronounced in women with a 3-way interaction of sex, lipoprotein(a), and treatment with $P = 0.08$. The data suggest that women with elevated levels of lipoprotein(a) and recent ACS may receive more substantial benefit from PCSK9 inhibitor treatment than men with similarly elevated levels of lipoprotein(a) and recent ACS. This hypothesis-generating observation may be supported by the fact that baseline lipoprotein(a) levels were approximately 50 % higher in women than men in this trial. This compares with findings in contemporary observational cohorts such as UK Biobank, Copenhagen General Study and the Multiethnic Study of Atherosclerosis where lipoprotein(a) concentrations in women were approximately 30 % higher than in men.[15-17] Thus, an index ACS event may select for women in whom lipoprotein(a) is a more important driver of risk and potentially more important for risk modification. Our finding warrants prospective confirmation.

Please cite this article as: Bittner et al, Alirocumab and cardiovascular outcomes according to sex and lipoprotein(a) after acute coronary syndrome: ODYSSEY OUTCOMES, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2024.04.122

The proportion of women (25.2 %) enrolled in ODYSSEY OUTCOMES is similar to that in other ACS and chronic CHD trials and well below the estimated percentage of women among post ACS and chronic CHD populations (40–50 %).[18,19] Non-white women and men were underrepresented. We observed regional and racial variation in proportional enrollment of women, with higher enrollment in Eastern Europe and the Americas compared with other geographical regions, and higher enrollment of women among black patients compared with other racial groups. These data suggest that under-representation of women is at least partly mediated by factors other than women's older age and greater co-morbidity and may be modifiable by intentional strategies of trial design and implementation. A recent Call to Action from the American Heart Association emphasizes the importance of developing approaches to increase participation of diverse populations of women in clinical trials.[1]

As noted, women in ODYSSEY OUTCOMES were older than men and had a greater burden of cardiovascular risk factors and comorbidities. In addition, women had higher levels of atherogenic lipoproteins, were more likely to present with NSTEMI versus STEMI and were less likely to undergo acute coronary revascularization than men. These findings align with those in prior observational analyses and other randomized clinical trials in ACS[20,21] and may reflect sex differences in pathophysiology as well as processes of care. Consistent with our enrollment criteria, use of high-intensity statin therapy was greater in both sexes in this study than in routine clinical practice and in other contemporary secondary prevention trials, with a small but statistically significant difference favoring men.[7,22] Consistent with women's higher baseline LDL-C levels, women were more likely to have their alirocumab dose up-titrated and less likely to have blinded substitution of placebo for alirocumab; adherence to alirocumab was comparable in the two groups. Thus, our observation of smaller reductions among women in LDL-C, apolipoprotein B, and non-HDL-C cannot be explained by differential background statin therapy or differential adherence to alirocumab therapy. These findings are consistent with the FOURIER trial and the LIPID REAL Registry, which also found smaller reductions in LDL-C in women treated with PCSK9 inhibition compared with men (52 % vs 58 % and 47 % vs 57 %, respectively) despite circulating levels of PCSK9 that are generally higher in women.[6,7] This may reflect higher lipoprotein(a) concentrations in women and lesser reduction in cholesterol contained in lipoprotein(a) particles than cholesterol in LDL particles by PCSK9 inhibition. It is unknown whether other biological mechanisms beyond differences in lipoprotein(a) and LDL distribution in women and men also contribute to this observation.

Epidemiologic analyses have shown a "female advantage" for incident CHD (i.e. lower rates of incident CHD among women than men), but significant attenuation of this "female advantage" in secondary prevention.[23,24] Rates of first MACE in the placebo group of ODYSSEY OUTCOMES were numerically higher in women than men in unadjusted analysis but were lower in women after adjustment for demographic and clinical covariates and use of evidence-based therapies. The interaction was not significant, and thus there was no apparent "female advantage" in risk of MACE after ACS in this cohort with high rates of use of evidence-based therapies. This extends the observations from the FOURIER investigators who found comparable benefits of evolocumab in women and men with chronic CHD.[7] Importantly, among those with a first cardiovascular event in ODYSSEY OUTCOMES, women experienced more subsequent events than men and thus had a greater burden of total cardiovascular events. Both first and subsequent events were reduced by alirocumab in both sexes. While the absolute reduction in first cardiovascular events was numerically less in women, the absolute reduction in total cardiovascular events was numerically greater.

Alirocumab was well tolerated in both women and men. Only local injection site reactions were more common in alirocumab-treated patients than among those in the placebo group without differences by sex.

Strengths of the present analyses include a high-risk secondary prevention population with many cardiovascular events (>2000), nearly 5000 female participants, high rates of evidence-based therapies, and the availability of lipoprotein(a) data at multiple time points. To our knowledge, this is the only report of sex-specific effects of PCSK9 inhibition after ACS and according to lipoprotein(a) concentration. Limitations include a small number of women who were black, Asian, or of other ethnicities, and only 7.7 % of women and 3.1 % of men above age 75, thus limiting our ability to extrapolate results to older women and men. Menopausal status and sex hormones were not assessed precluding an analysis of alirocumab efficacy stratified by menopausal status. Lipoprotein(a) was measured with a mass assay, which did not allow us to explore the impact of molar concentrations on outcomes by sex. However, a substudy of ODYSSEY OUTCOMES recently reported similar prognostic value of lipoprotein(a) whether lipoprotein(a) was measured by mass assay, molar assay or mass spectrometry.[25]

Conclusions and clinical implications

Women with recent ACS and elevated atherogenic lipoproteins despite maximum-tolerated statin therapy have a higher risk of multiple cardiovascular events following an index ACS compared with their male counterparts. Overall, women and men with recent ACS benefit similarly from the addition of alirocumab to their treatment regimen, but women with high lipoprotein(a) may be particularly suitable for alirocumab therapy.

Funding

Sanofi and Regeneron Pharmaceuticals, Inc.

Role of the funding source

Vera A. Bittner, Ph. Gabriel Steg, Gregory G. Schwartz and Michael Szarek developed the trial protocol and statistical analysis plan in conjunction with the other members of the executive steering committee, which includes representatives of the funders (appendix). The funders selected the study sites and monitored and supervised data collection, conducted the statistical analysis, contributed to data interpretation, and provided input on the report. Vera A. Bittner, Ph. Gabriel Steg, Gregory G. Schwartz and Michael Szarek had full access to all the data in the study. The executive steering committee decided to publish the paper and takes responsibility for the completeness and accuracy of the data and the fidelity of the trial to the protocol.

Ethical approval

The trial was approved by the institutional review board or ethics committee at each site. All participants provided written informed consent.

Use of AI and AI-assisted technologies statement

During the preparation of this work the authors did not use AI or AI-assisted technologies.

Declaration of competing interest

Vera A. Bittner reports grant support from Sanofi, Regeneron Pharmaceuticals, Amgen, Astra Zeneca, DalCor, Esperion, and Novartis; consulting fees from Pfizer; honoraria from Medscape; and fees for participating on Data Safety Monitoring Boards for the National Institutes of Health and for Verve Therapeutics.

Gregory G. Schwartz reports research support (all paid to institution) from Sanofi; grants or contracts from AstraZeneca, Resverlogix, Silence Therapeutics, and The Medicines Company/Novartis (all paid to institution); support for attending meetings from University of Oxford, American Society of Preventive Cardiology, and Cardiovascular Clinical Trialists; and receipt of medical writing support from Novartis.

Deepak L. Bhatt discloses the following relationships - Advisory Board: 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, Stasys; Board of Directors: AngioWave (stock options), Boston VA Research Institute, Bristol Myers Squibb (stock), DRS.LINQ (stock options), High Enroll (stock), Society of Cardiovascular Patient Care, TobeSoft; Chair: Inaugural Chair, American Heart Association Quality Oversight Committee; Consultant: Broadview Ventures; Data Monitoring Committees: Acesion Pharma, Assistance Publique-Hôpitaux de Paris, 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), 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, Population Health Research Institute; Rutgers University (for the NIH-funded MINT Trial); Honoraria: 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, 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 USA 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); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Patent: Sotagliflozin (named on a patent for sotagliflozin assigned to Brigham and Women's Hospital who assigned to Lexicon; neither I nor Brigham and Women's Hospital receive any income from this patent); Research Funding: Abbott, Acesion Pharma, Afimmune, Aker Biomarine, Amarin, Amgen, AstraZeneca, Bayer, Beren, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CinCor, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Javelin, Lexicon, Lilly, Medtronic, Merck, Moderna, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Owkin, Pfizer, PhaseBio, PLx Pharma, Recardio,

Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, Youngene, 89Bio; Royalties: Elsevier (Editor, Braunwald's Heart Disease); Site Co-Investigator: Abbott, Biotronik, Boston Scientific, CSI, Endotronix, St. Jude Medical (now Abbott), Philips, SpectraWAVE, Svelte, Vascular Solutions; Trustee: American College of Cardiology; Unfunded Research: FlowCo, Takeda.

Terrance Chua reports research grants from Sanofi.

Asita De Silva reports no disclosures.

Rafael Diaz reports research grants from Sanofi, DalCor Pharmaceuticals, Population Health Research Institute, Duke Clinical Research Institute, the TIMI group, Amgen, Cirius, Montreal Health Innovations Coordinating Center, and Lepetit; and personal fees, as a member of the Executive Steering Committee, from Amgen and Cirius.

Genevieve Garon is an employee of Sanofi and may hold shares and/or stock options in the company.

Shaun G. Goodman reports research grant support (e.g., steering committee or data and safety monitoring committee) and/or speaker/consulting honoraria (e.g., advisory boards) from: Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CSL Behring, Daiichi-Sankyo/American Regent, Eli Lilly, Esperion, Ferring Pharmaceuticals, GlaxoSmithKline, HLS Therapeutics, JAMP Pharma, Janssen/Johnson & Johnson, Merck, Novartis, Novo Nordisk A/C, Pendopharm, Pfizer, Regeneron, Sanofi, Servier, Valeo Pharma; and salary support/honoraria from the Heart and Stroke Foundation of Ontario/University of Toronto (Polo) Chair, Canadian Heart Research center and MD Primer, Canadian VIGOUR Centre, Cleveland Clinic Coordinating center for Clinical Research, Duke Clinical Research Institute, New York University Clinical Coordinating center, and PERFUSE Research Institute.

Robert A. Harrington reports research grants from the Patient-Centered Outcomes Research Institute, National Institutes of Health, CSL and Janssen; consulting for Atropos Health, Bitterroot Bio, Bridge Bio, Bristol Myers Squibb, Foresight, Element science; and serving on the boards of directors for the American Heart Association (unpaid) and Cytokinetics.

J. Wouter Jukema reports research grants from the Netherlands Heart Foundation, the Interuniversity Cardiology Institute of the Netherlands, and the European Commission Seventh Framework Programme; and research support from Amgen, Astellas, AstraZeneca, Daiichi- Sankyo, Lilly, Merck-Schering-Plough, Pfizer, Roche, and Sanofi.

Jennifer McGinniss is an employee of Regeneron Pharmaceuticals, Inc. and holds share options in the company.

Robert Pordy is an employee of Regeneron Pharmaceuticals, Inc., and may hold shares and/or stock options in the company.

Michel Scemama is an employee of Sanofi may hold shares and/or stock options in the company.

Harvey D. White reports grant support paid to the institution for serving on a Steering Committee for the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) from Sanofi-Aventis and Regeneron Pharmaceuticals, for the ACCELERATE study (A Study of Evacetrapib in High-Risk Vascular Disease) from Eli Lilly and Company, for the STRENGTH trial (Outcomes Study to Assess Statin Residual Risk Reduction With EpaNova in High CV Risk Patients With Hypertriglyceridemia) from Omthera Pharmaceuticals, for the CAMELLIA-TIMI study (A Study to Evaluate the Effect of Long-term Treatment With BELVIQ [Lorcaserin HC] on the Incidence of Major Adverse Cardiovascular Events and Conversion to Type 2 Diabetes Mellitus in Obese and Overweight Subjects With Cardiovascular Disease or Multiple Cardiovascular Risk Factors) from Eisai Inc, for the HEART-FID study (Randomized Placebo-Controlled Trial of FCM as Treatment for Heart Failure With Iron Deficiency) from American Regent, and for the ISCHEMIA Trial (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches) and the MINT Trial (Myocardial Ischemia and Transfusion) from the National Institutes of Health USA. He also received grants to the institution and personal fees as Steering Committee member for the dal-GenE study (Effect of Dalcetrapib vs Placebo on CV Risk in a Genetically Defined Population With a Recent ACS) from DalCor Pharma UK Inc, for the AEGIS-II study (The Safety and Tolerability of CSL112, a Reconstituted, Infusible, Plasma-Derived Human ApoA-I, After Acute Myocardial Infarction: The ApoA-I Event reducinG in Ischemic Syndromes I) from CSL Behring, for the SCORED trial (Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk) and the SOLOIST-WHF trial (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type2 Diabetes Post Worsening Heart Failure) from Sanofi-Aventis Australia Pty Ltd, and for the CLEAR Outcomes Study (Evaluation of Major Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant Treated With Bempedoic Acid [ETC-1002] or Placebo) from Esperion Therapeutics Inc. Dr White was on the Advisory Boards for CSL Behring and Genentech, Inc. (an affiliate of F. Hoffmann-La Roche Ltd, "Roche"; Lytics Post-PCI Advisory Board at European Society of Cardiology.

Ph. Gabriel Steg reports grants, personal fees, and nonfinancial support from Sanofi; grants and personal fees from Amarin, Servier and Bayer; personal fees from Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Idorsia, Pfizer, and Novartis. In addition, Dr Steg has a patent use of alirocumab to reduce risk after ACS (royalties to Sanofi) pending.

Michael Szarek reports serving as a consultant or on advisory boards (or both) for CiVi, Resverlogix, Baxter, Esperion, Sanofi, and Regeneron Pharmaceuticals, Inc.

CRediT authorship contribution statement

Vera A. Bittner: Writing – original draft, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Gregory G. Schwartz:** Writing – review & editing, Su-

Please cite this article as: Bittner et al, Alirocumab and cardiovascular outcomes according to sex and lipoprotein(a) after acute coronary syndrome: ODYSSEY OUTCOMES, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2024.04.122

pervision, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Deepak L. Bhatt:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization. **Terrance Chua:** Writing – review & editing, Investigation, Data curation. **H. Asita De Silva:** Writing – review & editing, Investigation, Data curation. **Rafael Diaz:** Writing – review & editing, Supervision, Investigation, Data curation, Conceptualization. **Robert A. Harrington:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Jennifer McGinniss:** Writing – review & editing, Formal analysis. **Robert Pordy:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Genevieve Garon:** Writing – review & editing, Project administration, Methodology. **Michel Scemama:** Writing – review & editing, Project administration, Methodology. **Harvey D. White:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Ph. Gabriel Steg:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Michael Szarek:** Writing – review & editing, Methodology, Investigation, Formal analysis, Conceptualization.

Acknowledgements

We thank the patients, study coordinators, and investigators who participated in this trial. Sophie Rushton-Smith, PhD (MedLink Healthcare Communications, London) provided editorial assistance in the preparation of the manuscript (limited to editing for style and referencing, and figure editing) and was funded by Sanofi, Paris, France.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jacl.2024.04.122.

References

1. Wenger NK, Lloyd-Jones DM, Elkind MSV, et al. Call to action for cardiovascular disease in women: epidemiology, awareness, access, and delivery of equitable health care: a presidential advisory from the american heart association. *Circulation*. 2022;145(23):e1059–e1071. doi:10.1161/CIR.0000000000001071.
2. Carland C, Hansra B, Parsons C, Lyubarova R, Khandelwal A. Adequate enrollment of women in cardiovascular drug trials and the need for sex-specific assessment and reporting. *American Heart Journal Plus: Cardiology Research and Practice*. 2022:17. doi:10.1016/j.ahjo.2022.100155.
3. Cholesterol Treatment Trialists C, Fulcher J, O'Connell R, et al. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet*. 2015;385(9976):1397–1405. doi:10.1016/S0140-6736(14)61368-4.
4. Roeters van Lennep JE, Tokgozoglu LS, Badimon L, et al. Women, lipids, and atherosclerotic cardiovascular disease: a call to action from the European Atherosclerosis Society. *Eur Heart J*. 2023. doi:10.1093/eurheartj/ehad472.
5. Ferri N, Ruscica M, Coggi D, et al. Sex-specific predictors of PCSK9 levels in a European population: the IMPROVE study. *Atherosclerosis*. 2020:30939–30946. doi:10.1016/j.atherosclerosis.2020.07.014.
6. Cordero A, Fernandez Del Olmo MR, Cortez Quiroga GA, et al. Sex differences in low-density lipoprotein cholesterol reduction with PCSK9 inhibitors in real-world patients: the LIPID-REAL registry. *J Cardiovasc Pharmacol*. 2022;79(4):523–529. doi:10.1097/FJC.0000000000001205.
7. Sever P, Gouni-Berthold I, Keech A, et al. LDL-cholesterol lowering with evolocumab, and outcomes according to age and sex in patients in the FOURIER Trial. *Eur J Prev Cardiol*. 2021;28(8):805–812. doi:10.1177/2047487320902750.
8. Kronenberg F, Mora S, Stroes ESG, et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a european atherosclerosis society consensus statement. *Eur Heart J*. 2022;43(39):3925–3946. doi:10.1093/eurheartj/ehac361.
9. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379(22):2097–2107. doi:10.1056/NEJMoa1801174.
10. Steg PG, Szarek M, Bhatt DL, et al. Effect of alirocumab on mortality after acute coronary syndromes. *Circulation*. 2019;140(2):103–112. doi:10.1161/CIRCULATIONAHA.118.038840.
11. Schwartz GG, Bessac L, Berdan LG, et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY outcomes trial. *Am Heart J*. 2014;168(5):682–689. doi:10.1016/j.ahj.2014.07.028.
12. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972:18499–18502.
13. Bittner VA, Szarek M, Aylward PE, et al. Effect of alirocumab on lipoprotein(a) and cardiovascular risk after acute coronary syndrome. *J Am Coll Cardiol*. 2020;75(2):133–144. doi:10.1016/j.jacc.2019.10.057.
14. Andersen PK, Angst J, Ravn H. Modeling marginal features in studies of recurrent events in the presence of a terminal event. *Lifetime Data Anal*. 2019;25(4):681–695. doi:10.1007/s10985-019-09462-4.
15. Patel AP, Wang M, Pirruccello JP, et al. Lp(a) (Lipoprotein[a]) concentrations and incident atherosclerotic cardiovascular disease: new insights from a large national biobank. *Arterioscler Thromb Vasc Biol*. 2021;41(1):465–474. doi:10.1161/ATVBAHA.120.315291.
16. Simony SB, Mortensen MB, Langsted A, Afzal S, Kamstrup PR, Nordestgaard BG. Sex differences of lipoprotein(a) levels and associated risk of morbidity and mortality by age: the Copenhagen General Population Study. *Atherosclerosis*. 2022:35576–35582. doi:10.1016/j.atherosclerosis.2022.06.1023.
17. Forbang NI, Criqui MH, Allison MA, et al. Sex and ethnic differences in the associations between lipoprotein(a) and peripheral arterial disease in the Multi-Ethnic Study of Atherosclerosis. *J Vasc Surg*. 2016;63(2):453–458. doi:10.1016/j.jvs.2015.08.114.
18. Scott PE, Unger EF, Jenkins MR, et al. Participation of women in clinical trials supporting FDA approval of cardiovascular drugs. *J Am Coll Cardiol*. 2018;71(18):1960–1969. doi:10.1016/j.jacc.2018.02.070.
19. Jin X, Chandramouli C, Allocco B, Gong E, Lam CSP, Yan LL. Women's participation in cardiovascular clinical trials from 2010 to 2017. *Circulation*. 2020;141(7):540–548. doi:10.1161/CIRCULATIONAHA.119.043594.
20. Worrall-Carter L, McEvedy S, Wilson A, Rahman MA. Gender differences in presentation, coronary intervention, and outcomes of 28,985 acute coronary syndrome patients in victoria, Australia. *Womens Health Issues*. 2016;26(1):14–20. doi:10.1016/j.whi.2015.09.002.
21. Matetic A, Shamkhani W, Rashid M, et al. Trends of sex differences in clinical outcomes after myocardial infarction in the united states. *CJC Open*. 2021;3(12):S19–S27 Suppl. doi:10.1016/j.cjco.2021.06.012.
22. Peters SAE, Colantonio LD, Zhao H, et al. Sex differences in high-intensity statin use following myocardial infarction in the United States. *J Am Coll Cardiol*. 2018;71(16):1729–1737. doi:10.1016/j.jacc.2018.02.032.

23. Peters SAE, Colantonio LD, Chen L, et al. Sex differences in incident and recurrent coronary events and all-cause mortality. *J Am Coll Cardiol*. 2020;76(15):1751–1760. doi:10.1016/j.jacc.2020.08.027.
24. Sarma AA, Braunwald E, Cannon CP, et al. Outcomes of women compared with men after non-st-segment elevation acute coronary syndromes. *J Am Coll Cardiol*. 2019;74(24):3013–3022. doi:10.1016/j.jacc.2019.09.065.
25. Szarek M, Reijnders E, Wouter Jukema J, et al. Relating Lipoprotein(a) concentrations to cardiovascular event risk after acute coronary syndrome: a comparison of three tests. *Circulation*. 2023 Publication ahead of print.

Please cite this article as: Bittner et al, Alirocumab and cardiovascular outcomes according to sex and lipoprotein(a) after acute coronary syndrome: ODYSSEY OUTCOMES, Journal of Clinical Lipidology, https://doi.org/10.1016/j.jacl.2024.04.122