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Clinical Research

Alirocumab and Cardiovascular Outcomes in Patients With Previous Myocardial Infarction: Prespecified Subanalysis From ODYSSEY OUTCOMES*

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See editorial by Leung and Anderson, pages 1550-1552 of this issue.

ABSTRACT

Background: After acute coronary syndrome (ACS), patients with a previous myocardial infarction (MI) may be at particularly high risk for major adverse cardiovascular events (MACE) and death. We studied the effects of the PCSK9 inhibitor alirocumab in patients with recent

RÉSUMÉ

Contexte : Après un syndrome coronarien aigu (SCA), les patients ayant déjà subi un infarctus du myocarde (IM) peuvent présenter un risque particulièrement élevé d'événements cardiovasculaires indésirables majeurs (ECIM) et de décès. Nous avons évalué les effets

Among patients hospitalized with acute coronary syndrome (ACS), the event is not the first for 18% to 22%.[1-3] Patients with previous myocardial infarction (MI) have higher subsequent events than those with stable coronary disease or patients with multiple risk factors.[4] The risk of recurrent events in patients who have experienced previous MI continues for several years without evidence of decreasing risk.[5] The heightened risk of recurrent events is largely attributable to frequent coexistence of nonobstructive lesion with high-risk characteristics.[6] Therefore, management of patients with recurrent ACS after previous MI presents a particular challenge for clinicians: What additional medical therapies may help to prevent these recurrent events?

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ACS according to previous history of MI.

Methods: The ODYSSEY OUTCOMES trial compared alirocumab with placebo, beginning 1 to 12 months after ACS with median 2.8-year follow-up. The primary MACE outcome comprised death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, and hospitalization for unstable angina. Of 18,924 patients, 3633 (19.2%) had previous MI.

Results: Patients with previous MI were older, more likely male, with more cardiovascular risk factors and previous events. With placebo, 4-year risks of MACE and death were higher among those with vs without previous MI (20.5% vs 8.9%, $P < 0.001$; 7.4% vs 3.4%, $P < 0.001$, respectively). Alirocumab reduced the risk of events regardless of the presence or absence of a history of MI (MACE, adjusted hazard ratio [aHR] 0.90, 95% confidence interval [CI], 0.78-1.05 vs 0.82, 0.73-0.92; $P_{interaction} = 0.34$; death, aHR 0.84; 95% CI, 0.64-1.08 vs 0.87, 0.72-1.05; $P_{interaction} = 0.81$). Estimated absolute risk reductions with alirocumab were numerically greater with vs without previous MI (MACE, 1.91% vs 1.42%; death, 1.35% vs 0.41%).

Conclusions: A previous history of MI places patients with recent ACS at high risk for recurrent MACE and death. Alirocumab reduced the relative risks of these events consistently in patients with or without previous MI but with numerically greater absolute benefit in the former subgroup. (ODYSSEY OUTCOMES: NCT01663402)

de l'alirocumab, un inhibiteur de la proprotéine convertase subtilisine/kexine de type 9 (PCSK9), chez les patients ayant récemment subi un SCA et présentant des antécédents d'IM.

Méthodologie : Lors de l'essai ODYSSEY OUTCOMES, le traitement par l'alirocumab, comparé à un placebo, a été instauré de 1 à 12 mois après un SCA, avec un suivi médian de 2,8 ans. Le principal paramètre d'évaluation des ECIM comprenait le décès lié à la coronaropathie, l'IM non fatal, l'accident vasculaire cérébral ischémique fatal ou non fatal et l'hospitalisation pour angine instable. Sur les 18 924 patients de l'étude, 3 633 (19,2 %) avaient déjà eu un IM.

Résultats : Les patients ayant des antécédents d'IM étaient plus âgés, étaient plus souvent de sexe masculin, et présentaient davantage de facteurs de risque cardiovasculaire et d'antécédents d'événements cardiovasculaires. Dans le groupe sous placebo, les risques d'ECIM et de décès à 4 ans étaient plus élevés chez les patients présentant des antécédents d'IM que chez ceux n'en présentant pas (20,5 % vs 8,9 %, $p < 0,001$; 7,4 % vs 3,4 %, $p < 0,001$, respectivement). L'alirocumab a réduit le risque de survenue d'événements, peu importe la présence ou l'absence d'antécédents d'IM (ECIM : rapport des risques instantanés corrigé [RRIc] de 0,90; intervalle de confiance [IC] à 95 % : de 0,78 à 1,05 vs RRIc de 0,82; IC à 95 % : de 0,73 à 0,92; $p_{interaction} = 0,34$; décès : RRIc de 0,84; IC à 95 % : de 0,64 à 1,08 vs RRIc de 0,87; IC à 95 % : de 0,72 à 1,05; $p_{interaction} = 0,81$). Les réductions estimées du risque absolu avec l'alirocumab étaient numériquement supérieures chez les patients ayant des antécédents d'IM que chez ceux sans antécédents d'IM (ECIM : 1,91 % vs 1,42 %; décès : 1,35 % vs 0,41 %).

Conclusions : Des antécédents d'IM exposent les patients ayant récemment subi un SCA à un risque plus élevé de récidive d'ECIM et de décès. L'alirocumab réduit le risque relatif de survenue de ces événements chez les patients avec ou sans antécédents d'IM, mais le bénéfice absolu est numériquement plus élevé chez les patients ayant des antécédents. (ODYSSEY OUTCOMES : NCT01663402)

Lipid lowering with high-intensity statin therapy is a cornerstone of management in ACS.[1,2] Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, added to statins, have the potential to lower atherogenic lipoproteins below levels achievable with statins and have been shown to improve clinical outcomes after ACS in patients with low-density lipoprotein cholesterol (LDL-C) above goal on optimized statin therapy.[7] In this prespecified analysis of the ODYSSEY OUTCOMES trial, we investigated the relative and absolute benefits of treatment with the PCSK9 inhibitor alirocumab in patients with ACS who had or did not have previous MI.

Material and Methods

Study population

ODYSSEY Outcomes (ClinicalTrials.gov: NCT01663402) was a randomized double-blind placebo-controlled trial that enrolled 18,924 patients $\geq$ 40 years of age who had been hospitalized with ACS (acute MI or unstable angina) 1 to 12 months before randomization.[7,8] The study conformed to the principles of the Declaration of Helsinki and was approved by the institutional review board at each site. All patients gave written informed consent to participate.

To be eligible, patients had to have LDL-C values $\geq$ 70 mg/dL (1.81 mmol/L) or non–high-density lipoprotein cholesterol (HDL-C) value $\geq$ 100 mg/dL (2.59 mmol/L), or apolipoprotein B value $\geq$ 80 mg/dL, measured after a minimum of 2 weeks on stable treatment with intensive LDL-C–lowering drugs (atorvastatin 40 to 80 mg daily, rosuvastatin 20 to 40 mg daily, or the maximum-tolerated dose of either statin, including no statin in the case of documented unacceptable side effects). Full inclusion and exclusion criteria have been published.[8]

Patients were randomly assigned (in a 1:1 ratio), stratified by country, to receive treatment with alirocumab 75 mg subcutaneously every 2 weeks or matching placebo. In the event of a persistent LDL-C value $\geq$ 50 mg/dL, the alirocumab dose was uptitrated to 150 mg. In patients who had 2 consecutive measurements of LDL-C $<$ 25 mg/dL, the alirocumab dose was reduced to 75 mg (for measurements made on the 150-mg dose), and safety was monitored by an independent physician blinded to treatment allocation. In the case of 2 consecutive measurements of LDL-C $<$ 15 mg/dL on alirocumab 75 mg, alirocumab was discontinued, with blinded substitution of placebo for the remainder of the trial. Occurrence of MI before the index ACS was a prespecified subgroup of interest, with the data collected at enrollment.[8]

Trial outcomes

The primary composite outcome was a composite of major adverse cardiovascular events (MACE: death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization). Secondary

Table 1. Baseline characteristics stratified by MI status at baseline

Characteristics	Previous MI (n = 3633)	No previous MI (n = 15,291)	*P* value
Age, y	59.8 (9.3)	58.3 (9.3)	< 0.001
Female sex	756 (20.8)	4006 (26.2)	< 0.001
Medical history before index ACS			
Hypertension	2884 (79.4)	9365 (61.3)	< 0.001
Diabetes	1167 (32.1)	3478 (22.8)	< 0.001
Current tobacco smoker	849 (23.4)	3711 (24.3)	0.25
Family history of premature coronary artery disease	1543 (42.5)	5230 (34.2)	< 0.001
PCI	2,399 (66.0)	842 (5.5)	< 0.001
CABG	727 (20.0)	320 (2.1)	< 0.001
Stroke	180 (5.0)	431 (2.8)	< 0.001
Peripheral artery disease	265 (7.3)	494 (3.2)	< 0.001
Heart failure	970 (26.7)	1844 (12.1)	< 0.001
Body mass index, kg/m^2	29.2 (4.9)	28.3 (4.9)	< 0.001
Renal function			
EGFR, mL/min per 1.73 m^2	77.4 (19.7)	80.2 (19.1)	< 0.001
EGFR < 60 mL/min per 1.73 m^2	635 (17.5)	1905 (12.5)	< 0.001
Index ACS			
ST-segment elevation MI	866 (23.8)	5670 (37.1)	< 0.001
Non−ST-segment elevation MI	2064 (56.8)	7111 (46.5)	< 0.001
Unstable angina	695 (19.1)	2484 (16.2)	< 0.001
PCI or CABG for index ACS	2308 (63.5)	11,368 (74.3)	< 0.001
Median time from index ACS to randomization, months	2.6 (1.7-4.2)	2.6 (1.7-4.4)	0.27
LDL-C, mg/dL	90.0 (75.7-110.4)	85.7 (72.6-102.7)	< 0.001
LDL-C ≥ 100 mg/dL	1305 (35.9)	4324 (28.3)	< 0.001
HDL-C, mg/dL	42.0 (35.9−49.8)	42.9 (36.7−50.2)	0.004
Non−HDL-C, mg/dL	121.2 (103.9−145.0)	113.5 (98.5−135.0)	< 0.001
Triglycerides, mg/dL	137.0 (98.0−193.0)	127.4 (92.9−179.6)	< 0.001
Lipoprotein(a), mg/dL	41.8 (45.4)	38.3 (42.8)	< 0.001
Apolipoprotein B, mg/dL)	83.0 (72.0−98.0)	78.0 (68.0−92.0)	< 0.001
Apolipoprotein A, mg/dL	131.0 (118.0-147.0)	132.00 (118.0-147.0)	0.64
C-reactive protein, mg/dL	0.2 (0.1-0.4)	0.2 (0.1-0.4)	0.12
Hemoglobin A1c, %	5.9 (5.6-6.6)	5.8 (5.5-6.3)	< 0.001

Values are number (percentage), mean (standard deviation [SD]) or median (quartile 1 to quartile 3).

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; EGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein-cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation.

outcomes included all-cause death.[7] All primary and secondary outcomes were adjudicated by physicians who were unaware of the trial-group assignments.

Statistical analyses

Categorical variables were compared with χ^2 tests and continuous variables by Student's *t*-test. A Cox proportional hazards model was used to determine hazard ratios (HRs) and 95% confidence intervals (CIs) for MACE and death in patients with and without previous MI in the placebo group, adjusted for the following baseline variables: age (≥ 65 years vs < 65 years), sex, race, geographic region, diabetes mellitus, smoking; history of heart failure, ischemic stroke, and peripheral artery disease; intensive statin treatment; LDL-C and lipoprotein(a) concentrations; and systolic blood pressure. A Cox proportional hazards model was used to compare the treatment effect in the subgroups of patients with and without previous MI. Heterogeneity between patients with and without a previous MI was analyzed with a test for treatment-by-subgroup interaction. The Gail-Simon test was used to analyze the quantitative interaction for absolute risk reduction.[9] The cumulative incidence rates of MACE and death were estimated by the Kaplan-Meier method. *P* values were estimated by a log rank test over the previous MI status subgroups. The analysis was performed in SAS version 9.4 (IBM, Armonk, NY).

Results

Patient characteristics

Among 18,924 patients in the trial, 3633 (19.2%) had histories of MI before the qualifying ACS. The baseline characteristics of the patients are shown in Table 1. Compared with patients without previous MI, those with a previous MI were older; more likely to be male, white; and to have more underlying cardiovascular conditions, previous cardiovascular events and procedures including stroke, peripheral artery disease, heart failure, impaired renal function, percutaneous coronary intervention, and coronary artery bypass graft surgery. In patients with previous MI, the qualifying ACS was more often non-ST elevation MI, and they had higher baseline levels of LDL-C, non−HDL-C, triglycerides, apolipoprotein B, lipoprotein(a), and hemoglobin A1c, but lower HDL-C. Other baseline characteristics are shown in Supplemental Table S1. Findings were similar when patients with and without previous MI were compared in each randomization arm (alirocumab or placebo) (Supplemental Table S2).

Risks of mace and death in the placebo group stratified by previous MI status at baseline

In the placebo group, the incidence of MACE (20.5% vs 8.9%; adjusted HR [aHR], 1.85; 95% CI, 1.62-2.11; *P* <

0.001), all-cause death (7.4% vs 3.4%; aHR, 1.56, 95% CI, 1.25-1.95; $P < 0.001$), and other outcomes were higher among those with previous MI (Table 2). Exceptions were ischemic stroke and hospitalization for unstable angina, which were directionally congruent.

Effect of alirocumab on MACE and death stratified by previous MI status at baseline

Figure 1 shows adjusted risk of outcomes for alirocumab vs placebo stratified according to previous MI status at baseline. In the overall study population, alirocumab reduced MACE by 15.0% (HR, 0.85; 95% CI, 0.78-0.93; $P < 0.001$).[7] Among patients with previous MI, MACE occurred in 20.5% of patients in the placebo group vs 18.6% in the alirocumab group (aHR, 0.90; 95% CI, 0.78-1.05). Among patients without previous MI, MACE occurred in 8.8% of patients in the placebo group vs 7.4% in the alirocumab group (aHR, 0.82, 95% CI, 0.73-0.92; $P_{\text{interaction}} = 0.34$). The estimated 4-year absolute risk reduction in MACE was numerically greater in patients with previous MI (1.91%; 95% CI, −0.67 to 4.49 vs 1.42%; 95% CI, 0.55-2.28; quantitative $P_{\text{heterogeneity}} = 0.72$). Among patients with previous MI, 7.4% of patients in the placebo group died vs 6.0% in the alirocumab group (aHR 0.84; 95% CI, 0.64-1.08). Among patients without previous MI, 3.4% of patients in the placebo group died vs 2.9% in the alirocumab group (aHR 0.87; 95% CI, 0.72-1.05; $P_{\text{interaction}} = 0.81$). Likewise, estimated absolute risk reduction for death was numerically greater in patients with vs without previous MI (1.35%; 95% CI, −0.28 to 2.97% vs 0.41%,; 95% CI, −0.14 to 0.97; quantitative $P_{\text{heterogeneity}} = 0.29$). The unadjusted risks of outcomes are shown in Supplemental Fig. S1. Cumulative incidence curves are shown in Figure 2.

Effect of alirocumab on outcomes stratified by timing of previous MI

In patients with previous MI, the median time from the last MI to the index ACS was 4.5 years. The effect of alirocumab vs placebo on MACE in patients with MI that occurred ≤ 2 years before the qualifying ACS (20.5% vs 19.9%; HR, 1.02; 95% CI, 0.78-1.34) did not differ from that in patients with MI that occurred > 2 years before the qualifying ACS (17.8% vs 20.9%; HR, 0.85; 95% CI, 0.71-1.03; $P_{\text{interaction}} = 0.16$) (Fig. 3).

Safety outcomes

Adverse events and laboratory abnormalities were, in general, similar for alirocumab vs placebo when stratified by previous MI status at baseline (Supplemental Table S3).

Discussion

Among patients with recent ACS who did not receive alirocumab, those with vs without previous MI had higher risks of MACE and all-cause death. Alirocumab was associated with consistent relative risk reductions in both patients with and without previous MI, with numerically greater absolute benefit in patients with previous MI.

On the basis of multiple major atherosclerotic cardiovascular disease events, the subgroup with previous MI would be classified as very high risk according to the US guidelines.[10] Approximately 18% to 22% of patients with ACS have histories of previous MI.[1-3,7] Indeed, the adjusted risks for MACE and all-cause death were higher for patients with vs without previous MI. The management of patients with recurrent ACS presents a particular challenge for clinicians. Alirocumab reduced risk of MACE and all-cause death in

Table 2. Event rates and HR of outcomes stratified by MI status at baseline: placebo arm

	Previous MI n (%)	No previous MI n (%)	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Primary composite outcome*	378 (20.5)	674 (8.9)	2.41 (2.12-2.73)	< 0.001	1.85 (1.62-2.11)	< 0.001
Any coronary heart disease event†	440 (23.9)	909 (11.9)	2.08 (1.86-2.34)	< 0.001	1.67 (1.48-1.88)	< 0.001
Major coronary heart disease event‡	336 (18.2)	563 (7.4)	2.56 (2.23-2.93)	< 0.001	1.97 (1.71-2.28)	< 0.001
Any cardiovascular event§	477 (25.9)	997 (13.1)	2.07 (1.85-2.30)	< 0.001	1.63 (1.45-1.83)	< 0.001
Composite of death from any cause, nonfatal MI, or nonfatal ischemic stroke	398 (21.6)	728 (9.6)	2.35 (2.08-2.66)	< 0.001	1.81 (1.59-2.06)	< 0.001
Death from coronary heart disease	87 (4.7)	135 (1.8)	2.62 (2.00-3.43)	< 0.001	1.87 (1.40-2.50)	< 0.001
Death from cardiovascular causes	102 (5.5)	169 (2.2)	2.45 (1.92-3.13)	< 0.001	1.70 (1.31-2.21)	< 0.001
Death from any cause	136 (7.4)	256 (3.4)	2.15 (1.75-2.65)	< 0.001	1.56 (1.25-1.95)	< 0.001
Nonfatal MI	273 (14.8)	449 (5.9)	2.61 (2.24-3.03)	< 0.001	2.03 (1.73-2.38)	< 0.001
Fatal or nonfatal ischemic stroke	50 (2.7)	102 (1.3)	2.01 (1.44-2.83)	< 0.001	1.33 (0.92-1.92)	0.13
Unstable angina requiring hospitalization	20 (1.1)	40 (0.5)	2.05 (1.20-3.51)	0.009	1.73 (0.99-3.04)	0.06
Ischemia-driven coronary revascularization procedure	260 (14.1)	568 (7.5)	1.93 (1.67-2.24)	< 0.001	1.62 (1.38-1.90)	< 0.001
Hospitalization for congestive heart failure	73 (4.9)	106 (1.4)	2.85 (2.11-3.83)	< 0.001	1.66 (1.21-2.28)	0.002

CI, confidence interval; HR, hazard ratio; MI, myocardial infarction.

*Death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring revascularization.

†Death from coronary heart disease, nonfatal MI, unstable angina requiring hospitalization, or ischemia-driven coronary revascularization.

‡Death from coronary heart disease or nonfatal MI.

§Death from cardiovascular cause, nonfatal MI, unstable angina requiring hospitalization, ischemia-driven coronary revascularization procedure, or nonfatal ischemic stroke.

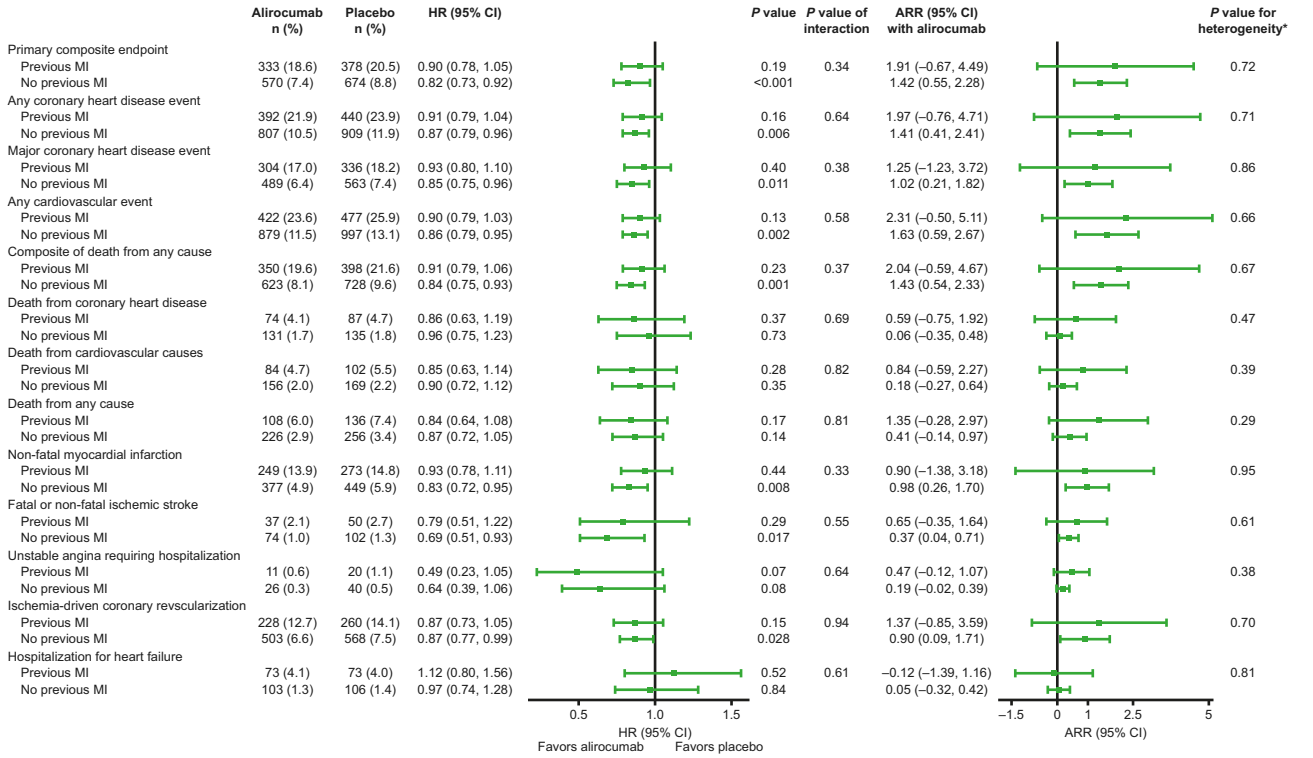

Figure 1. Outcomes for alirocumab vs placebo stratified by previous myocardial infarction (MI) status. *Adjusted for the following independent variables: age (≥ 65 vs < 65 years), sex, race, diabetes mellitus, geographic region, history of heart failure, baseline low-density lipoprotein-cholesterol (LDL-C), lipoprotein(a), intensive statin use, systolic blood pressure at baseline, smoking status, history of ischemic stroke, and history of peripheral artery disease. CI, confidence interval; HR, hazard ratio.

patients receiving maximum tolerated (including ∼90% high-intensity) statins with a numerally greater absolute effect in patients with previous MIs, supporting recent guideline recommendations.[10-12] The lack of statistical significance of alirocumab on MACE and all-cause death in the subgroup of patients with previous MI is most likely due to a relative small number of patients with previous MI.

A previous analysis of the **F**urther Cardiovascular **Ou**tcomes **R**esearch With PCSK9 **I**nhibition in Subjects With **E**levated **R**isk (FOURIER) trial in patients with stable atherosclerotic cardiovascular disease and previous MI found that treatment with the PCSK9 inhibitor evolocumab was effective in reducing MACE in those with recent MI (< 2 years) but not in those with only remote MI (≥ 2 years).[13] In the current analysis, the efficacy of alirocumab in patients with ACS was consistent with or without previous MI and in those with previous MI irrespective of whether it had occurred ≤ 2 or > 2 years before the qualifying ACS. Therefore, it may be reasonable to consider PCSK9 inhibitor treatment in all patients with ACS and dyslipidemia uncontrolled by statins.

This analysis from the ODYSSEY OUTCOMES trial indicates that previous MI is a marker of higher risk of MACE and death following ACS and, accordingly, that such patients might derive a larger absolute benefit from alirocumab treatment. Previously, effects of alirocumab in patients at very high-risk vs not, according to the US guidelines,[10] have been reported in the ODYSSEY OUTCOMES trial, showing similar findings that patients at very high risk derived a larger absolute benefit from treatment with alirocumab.[14] Similarly, analyses from this trial have identified several subgroups of post-ACS patients at high risk for recurrent cardiovascular events who derive a greater absolute benefit from alirocumab treatment, including those with type 2 diabetes,[15] polyvascular disease,[16] previous coronary artery bypass graft surgery,[17] higher lipoprotein(a) concentration,[18] and high genome-wide polygenic risk scores.[19] Although the primary analysis of the current study did not reach statistical significance, the numerically greater benefits in patients with previous MI might suggest a true effect if the sample size could be enlarged.

The effects of alirocumab on MACE in patients with previous MI seemed to occur earlier, with the MACE curves separated at approximately 1 year after randomization compared with approximately 2 years for patients without previous MI. Similar findings have also been observed in the FOURIER trial in which the MACE curves separated at approximately 180 days in patients with recent MI (≤ 12 months), compared with approximately 540 days in patients with remote MI (> 12 months).[20] Although we did not collect systematic angiographic information at baseline, it is likely that patients who have had > 1 ACS event have a greater burden of coronary atherosclerosis. More pronounced atherosclerotic lesions are susceptible to be modified by LDL-C lowering. Therefore, intensive LDL-C lowering with alirocumab has a favourable effect on plaque stabilization.[21] More recently, the addition of subcutaneous biweekly alirocumab, compared with placebo, to high-intensity statin therapy in patients with acute MI resulted in significantly

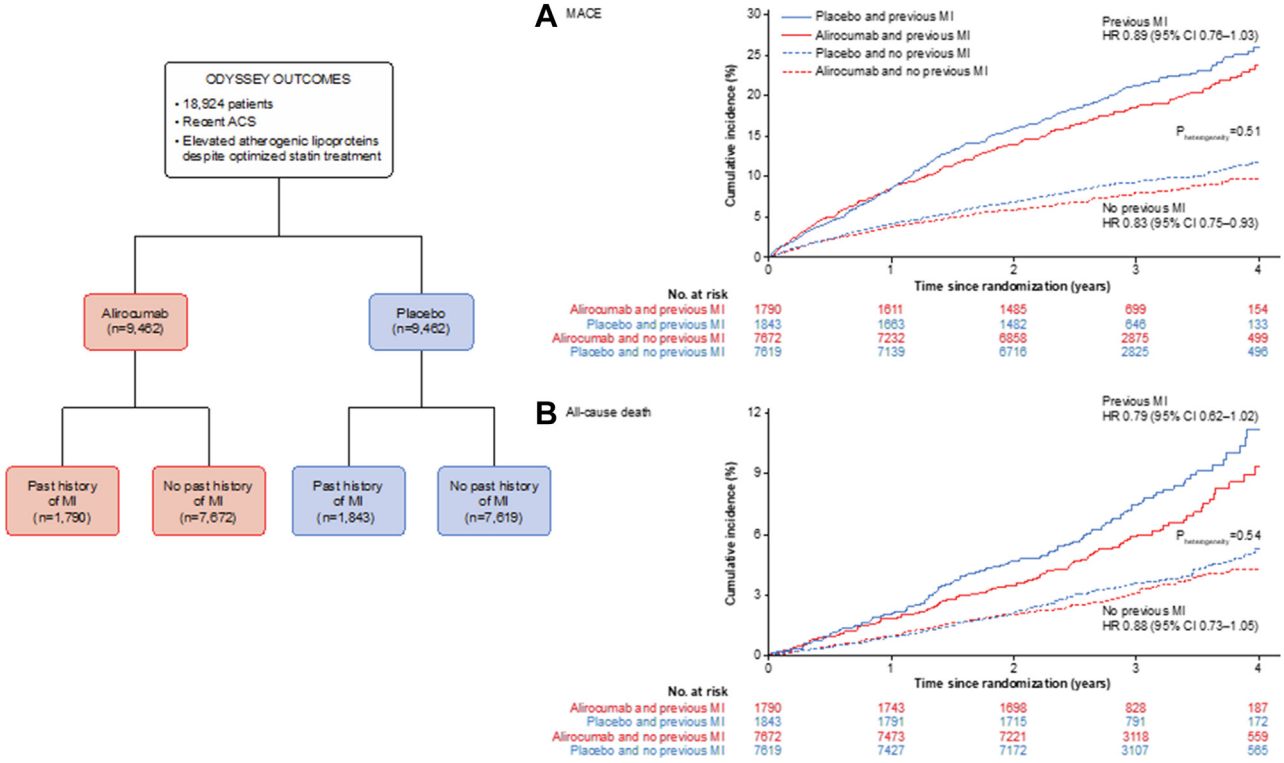

Figure 2. Cumulative incidence for alirocumab vs placebo stratified by previous myocardial infarction (MI). (**A**) Major adverse cardiovascular event (MACE) (composite of death from coronary heart disease, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization). (**B**) All-cause death. CI, confidence interval; HR, hazard ratio; LDL-C, low-density lipoprotein-cholesterol.

greater coronary plaque regression in noninfarct-related arteries after 52 weeks.[22] Whether earlier initiation of treatment (ie, before hospital discharge after ACS) would magnify an early treatment benefit is a hypothesis worthy of testing prospectively.

Limitations

First, analyses in subgroups are limited by sample size and power, and the confidence interval of the relative risk reduction in patients with previous MI crossed the line of unity. Second, number of MIs was not recorded, and details on previous MI were based on medical history rather than systematic review of laboratory data and electrocardiographic tracings. Third, we did not investigate the impact of previous atherosclerotic cardiovascular disease events other than MI, such as stroke or peripheral artery disease events, on the clinical efficacy of alirocumab.

Conclusions

Patients with recent ACS and previous MI were at higher risk for MACE and death than those without previous MI. Alirocumab reduced the relative risks of these events consistently in patients with or without previous MI but with numerically greater absolute benefit in the former subgroup.

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Disclosures

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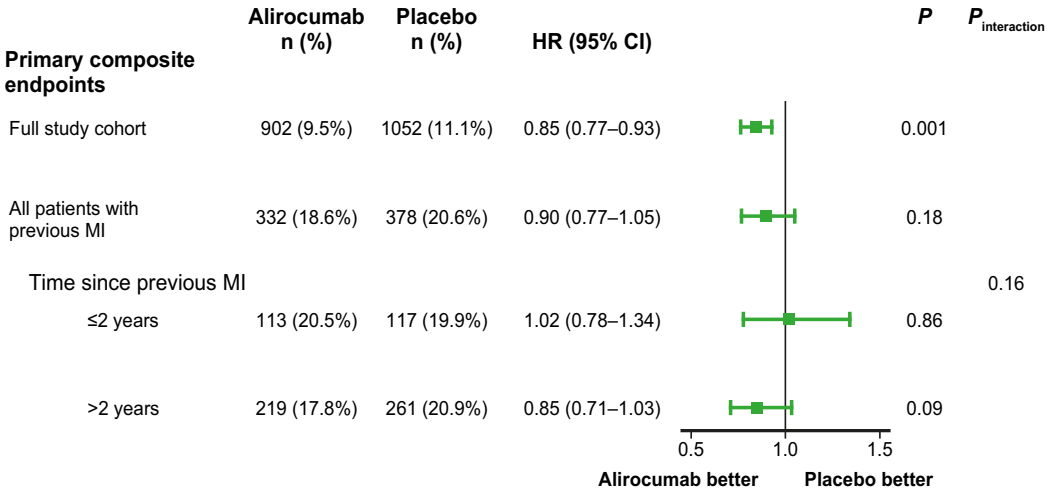

Figure 3. Adjusted risk of major adverse cardiovascular event (MACE) stratified by timing of previous myocardial infarction (MI). *Adjusted for the following independent variables: age ($\geq$ 65 vs $<$ 65 years), sex, race, diabetes mellitus, geographic region, history of heart failure, baseline LDL-C, lipoprotein(a), intensive statin use, systolic blood pressure at baseline, smoking, history of ischemic stroke, and history of peripheral artery disease. CI, confidence interval; HR, hazard ratio; LDL-C, low-density lipoprotein-cholesterol.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2022.05.021.