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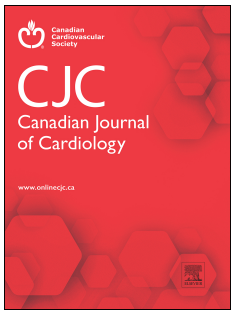

Lipoprotein(a) and the Effect of Alirocumab on Revascularization Following Acute Coronary Syndrome

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PII: S0828-282X(23)00366-5

DOI: https://doi.org/10.1016/j.cjca.2023.04.018

Reference: CJCA 4648

To appear in: *Canadian Journal of Cardiology*

Received Date: 24 January 2023

Revised Date: 14 April 2023

Accepted Date: 20 April 2023

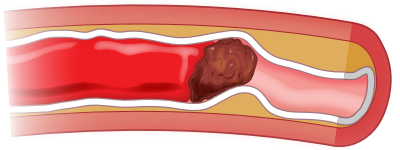
Please cite this article as: Steg PG, Szarek M, Valgimigli M, Islam S, Zeiher AM, Bhatt DL, Bittner VA, Chiang C-E, Diaz R, Goodman SG, Gotcheva N, Harrington RA, Jukema JW, Kim H-S, Kim S-H, Morais J, Pordy R, Scemama M, White HD, Schwartz GG, for the ODYSSEY OUTCOMES Investigators, Lipoprotein(a) and the Effect of Alirocumab on Revascularization Following Acute Coronary Syndrome, *Canadian Journal of Cardiology* (2023), doi: https://doi.org/10.1016/j.cjca.2023.04.018.

Lipoprotein(a) and the Effec[illegible]g Acute Coronary Syndrome

ODYSSEY OUTCOMES compared alirocumab with placebo in 18 924 patients with ACS and elevated atherogenic lipoproteins despite optimized statin treatment.
In this post hoc analysis, treatment effects are summarized by competing-risks proportional hazard models.

Post-hoc analysis of the ODYSSEY OUTCOMES trial

Patients with ACS



On steady-state treatment with high-intensity or maximum-tolerated dose of atorvastatin or rosuvastatin, at least one lipid criterion met:
LDL-C ≥1.8 mmol/L
Non-HDL-C ≥2.6 mmol/L
Apolipoprotein B ≥80 mg/dL

Randomization 1–12 months after ACS (n=18 924)

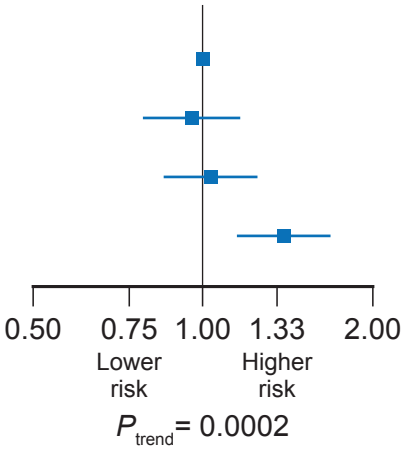
Placebo SC Q2W (n=9462)

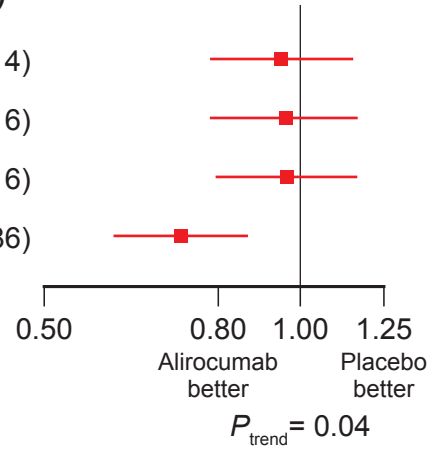
Alirocumab SC Q2W (n=9462)

Risk of total* coronary revascularization was increased in patients in the top baseline lipoprotein(a) quartile (as seen in placebo group) relative to patients in the bottom quartile

Benefit of alirocumab over placebo in reducing the risk of total* coronary revascularizations was present in patients with the highest baseline lipoprotein(a)

Baseline lipoprotein(a) Quartile	Events per 100 Patient-Years Alirocumab	Events per 100 Patient-Years Placebo	Placebo group HR (95% CI)	Treatment HR (95% CI)
Quartile 1 (<6.7 mg/dL)	3.2	3.5	Reference	0.95 (0.79, 1.14)
Quartile 2 (6.7 to <21.2 mg/dL)	3.1	3.2	0.96 (0.80, 1.15)	0.96 (0.79, 1.16)
Quartile 3 (21.2 to <59.6 mg/dL)	3.3	3.5	1.03 (0.86, 1.24)	0.96 (0.80, 1.16)
Quartile 4 (≥59.6 mg/dL)	3.4	4.7	1.40 (1.17, 1.67)	0.72 (0.61, 0.86)





*First and recurrent
ACS, acute coronary syndrome; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, high-density lipoprotein cholesterol

Lipoprotein(a) and the Effect of Alirocumab on Revascularization Following Acute Coronary Syndrome

Short title: Alirocumab, Lp(a) and revascularization after ACS

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Word count: 5450

Sources of Funding

The ODYSSEY OUTCOMES trial was supported by Sanofi and Regeneron Pharmaceuticals.

Nonstandard Abbreviations and Acronyms

ACS acute coronary syndromes

ARR absolute risk reduction

CABG coronary artery bypass graft surgery

CI confidence interval

eGFR estimated glomerular filtration rate

HDL-C high-density lipoprotein cholesterol

HR hazard ratio

IQR interquartile range

LDL-C low-density lipoprotein cholesterol

MACE major adverse ischemic cardiovascular event

PCI percutaneous coronary intervention

PCSK9 proprotein convertase subtilisin/kexin type 9

ABSTRACT

BACKGROUND: Many patients require revascularization after an index acute coronary syndrome (ACS). Lipoprotein(a) is thought to play a pathogenic role in atherothrombosis. In ODYSSEY OUTCOMES, alirocumab reduced major adverse cardiovascular events after ACS, with greater reduction among those with higher lipoprotein(a) levels. We explored whether risk of revascularization after ACS was modified by the level of lipoprotein(a) and treatment with alirocumab or placebo.

METHODS: ODYSSEY OUTCOMES compared alirocumab with placebo in 18 924 patients with ACS and elevated atherogenic lipoproteins despite optimized statin treatment. In this post hoc analysis, treatment effects are summarized by competing-risks proportional hazard models.

RESULTS: A total of 1559 (8.2%) patients had coronary, 204 (1.1%) had limb, and 40 (0.2%) had carotid revascularization. Alirocumab reduced coronary revascularization (2.8 versus 3.2 events per 100 patient-years; HR, 0.88 [95% CI, 0.80−0.97]; P=0.01) and any revascularization (3.2 versus 3.7 events per 100 patient-years; HR, 0.85 [95% CI, 0.78−0.94]; P=0.001). Baseline lipoprotein(a) quartile was directly associated with risk of coronary or any revascularization in the placebo arm and inversely related to treatment HRs (all P_{trend} <0.001). Alirocumab produced the greatest reduction of coronary revascularization in patients with baseline lipoprotein(a) in the top quartile (≥59.6 mg/dL) (HR, 0.69 [95% CI, 0.57−0.84]), but no apparent reduction in the bottom quartile (HR, 1.00 [95% CI, 0.82−1.22]). Findings were similar for the effect of alirocumab on any revascularization.

CONCLUSIONS Alirocumab reduced revascularization after ACS. The risk of revascularization and reduction in that risk with alirocumab were greatest in patients with elevated lipoprotein(a) at baseline. (ODYSSEY OUTCOMES NCT01663402)

Keywords: Acute coronary syndrome; alirocumab; revascularization; major adverse cardiovascular events

While low-density lipoprotein (LDL) is considered the principal atherogenic lipoprotein, lipoprotein(a) also influences the risk of major adverse cardiovascular events (MACE) after acute coronary syndrome (ACS). It is thought to play a physiologic role in wound healing and a pathogenic role in atherothrombosis.[1]

Both LDL cholesterol (LDL-C) and lipoprotein(a) are reduced by inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9). The ODYSSEY OUTCOMES trial (NCT01663402) compared the PCSK9 inhibitor alirocumab with placebo in patients with recent ACS and elevated atherogenic lipoproteins despite high-intensity or maximum-tolerated statin therapy. Alirocumab reduced the primary endpoint of MACE (death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, and hospitalization for unstable angina) as well as secondary endpoints including ischemia-driven coronary revascularization[1] and all-cause death.[2]

In this analysis of the trial, we described the effect of alirocumab on the risk of coronary, limb, or carotid revascularization procedures after ACS, the relation of that risk to the level of lipoprotein(a), and whether the latter modified the effect of alirocumab on the risk of revascularization.

METHODS

Study Design

The trial design[3] and primary results[4] have been published. All patients provided written informed consent. All sites obtained ethics committee approval as per local and national guidelines. Briefly, the trial included patients aged ≥40 years who had been hospitalized with ACS and had LDL-C levels ≥1.81 mmol/L (70 mg/dL), or non-high-density lipoprotein cholesterol (non−HDL-C) ≥2.59 mmol/L (100 mg/dL), or apolipoprotein B levels ≥80 mg/dL after at least 2 weeks of stable treatment with atorvastatin 40−80 mg daily, rosuvastatin

20−40 mg daily, or the maximum-tolerated dose of one of these statins. Randomization occurred 1−12 months after the index ACS. Patients were excluded if there had been a recurrent ACS or coronary revascularization procedure in the 2 weeks prior to intended randomization or if coronary revascularization was planned after randomization.

At randomization, patients were assigned to receive blinded treatment with alirocumab 75 mg or matching placebo given by subcutaneous injection every 2 weeks. For patients assigned to receive alirocumab, blinded protocol-specified dose-adjustment algorithms were used to target achieved LDL-C levels between 0.65 and 1.29 mmol/L (25−50 mg/dL) and to avoid sustained levels below 0.39 mmol/L (15 mg/dL).[3, 4]

Lipoproteins were measured at baseline (randomization visit) and at defined subsequent time points. LDL-C was calculated with the Friedewald formula unless triglycerides exceeded 400 mg/dL (4.52 mmol/L) or calculated LDL-C was <15 mg/dL (0.39 mmol/L, in which case values were determined by ultracentrifugation/beta-quantification. Lipoprotein(a) mass was measured at randomization, 4 months, and 12 months at COVANCE Central Laboratories using an automated immunoturbidimetric assay[5] on a Siemens BNII (Siemens, Healthcare Diagnostics) validated against the International Federation of Clinical Chemistry and World Health Organization standards.

Outcome Definitions

The primary MACE outcome was adjudicated by a blinded clinical events committee. In addition, the committee reviewed all coronary revascularization procedures to adjudicate ischemia-driven coronary revascularization. This prespecified endpoint, considered outside the pre-specified hierarchy of key secondary endpoints, comprised revascularization procedures performed for new or progressive anginal symptoms, new or progressive abnormalities on stress testing, or recurrent acute ischemia (i.e., ACS), but excluded

revascularization performed solely for restenosis at a prior percutaneous coronary intervention (PCI) site or revascularization done during other cardiac surgery. In the present analysis, all post-randomization coronary revascularizations (including restenosis and regardless of the presence of angina or ischemia) were also examined as an exploratory endpoint that was prespecified in the statistical analysis plan. An additional post hoc analysis considered "any" arterial revascularization, which includes, in addition to surgical or nonsurgical coronary revascularization, limb and carotid procedures. Noncoronary (limb or carotid) revascularizations were reported by investigators but not adjudicated. "Total" revascularization refers to first and subsequent repeat revascularizations.

Statistical Analysis

Patients were categorized based on revascularization status at randomization: no prior coronary revascularization; revascularization before but not for the qualifying ACS; or revascularization for the qualifying ACS with or without prior revascularization.

Treatment effects on first and total (i.e., first and potentially subsequent) coronary and any revascularization procedures were summarized by competing-risks proportional hazard models (stratified according to geographic region of enrollment) with deaths treated as competing terminal events to generate hazard ratios (HR) with Wald 95% confidence intervals (CI) and *P*-values. For total revascularization procedures, marginal models were applied with the robust sandwich estimate for the estimated standard error of the log HR to account for the dependence of event times within individual patients. Accrual of events over time was estimated using cumulative incidence functions, with event rates calculated as the number of events per 100 patients-years of follow-up. Heterogeneity of alirocumab treatment effects by baseline revascularization category was assessed by competing-risks models with

interaction terms for relative risk reduction and tests for quantitative interaction for absolute risk reduction (ARR).

Measured or calculated LDL-C includes a contribution from cholesterol contained in lipoprotein(a). To examine the independent relationships of these two lipoproteins to revascularization events we calculated corrected LDL-C (LDL-C_{corr}) using the formula LDL-C_{corr} = LDL-C – 0.3 × lipoprotein(a) mass.[6] Relationships between baseline lipoprotein(a) or LDL-C_{corr} and first and total revascularizations in the placebo group were determined by competing-risks models stratified by geographic region using baseline lipoprotein(a) or LDL-C_{corr} quartile as the predictor variable; *P*-values were computed for linear trend in the estimated log HRs across baseline lipoprotein(a) or LDL-C_{corr} quartiles. The tests of linear trend represent interaction tests that account for the ordinal nature of the quartiles. These models were adjusted for the following demographic and clinical variables: coronary revascularization status at randomization, age, sex, race, body mass index, current smoking, history of diabetes, and baseline LDL-C_{corr} (in the lipoprotein(a) model) or baseline lipoprotein(a) (in the LDL-C_{corr} model).

Heterogeneity in the relative effects of alirocumab treatment on first and total revascularizations was assessed according to baseline lipoprotein(a) quartile. Competing-risks models stratified by geographic region were constructed with baseline lipoprotein(a) quartile, treatment, and their interaction as predictors, along with the demographic and clinical variables listed above. *P*-values for linear trend across baseline lipoprotein(a) quartiles were calculated for the estimated log treatment HRs. Similar models were constructed with baseline LDL-C_{corr} quartile.

RESULTS

The trial comprised 18 924 patients randomized at 1315 sites in 57 countries a median of 2.6 (interquartile range [IQR], 1.7−4.3) months after the qualifying ACS. Baseline characteristics of trial participants according to lipoprotein(a) quartile[7] are shown in **Supplemental Table S1**. Baseline lipoprotein(a) values were 2.0 (2.0−4.8), 12.2 (9.3−15.9), 37.6 (28.3−47.7), and 92.2 (73.2−119.0) mg/dL in the 4 quartiles respectively, while baseline LDL-C levels were 2.15 (1.79−2.62) mmol/L (83 [69−101] mg/dL), 2.20 (1.86−2.64) mmol/L (85 [72−102] mg/dL),
2.23 (1.89−2.69) mmol/L (86 [73−104] mg/dL), and 2.38 (2.02−2.82) mmol/L (92 [78−109] mg/dL), respectively. Baseline characteristics overall were well-balanced between alirocumab and placebo groups (**Supplemental Table S2**). Patients were followed for a median of 2.8 (IQR, 2.3−3.4) years. As previously described,[4] median (quartile Q1−Q3) lipoprotein(a) was 21.2 (6.7−59.6), median LDL-C was 2.24 (1.89−2.69) mmol/L (86.5 [73.0−104.0] mg/dL), and median baseline LDL-C_{corr} was 1.95 (1.57−2.42) mmol/L (75.4 [60.6−93.6] mg/dL). During follow-up, 1559 (8.2%) patients had coronary, 204 (1.1%) had limb, and 40 (0.2%) had carotid revascularizations.

Effect of Alirocumab on First and Total Coronary Revascularizations

Alirocumab treatment reduced first ischemia-driven coronary revascularizations (2.8 versus 3.2 events per 100 patient-years; HR, 0.88 [95% CI, 0.80−0.97]; *P*=0.01) (**Figure 1**). Alirocumab also reduced total (including recurrent) ischemia-driven coronary revascularizations, with 3.2 versus 3.7 events per 100 patient-years with alirocumab and placebo, respectively (HR, 0.87 [95% CI, 0.78−0.97]; *P*=0.008).

The numbers of patients who underwent first or total coronary revascularizations including those that were not ischemia-driven by PCI or coronary artery bypass graft

(CABG) as well as ischemia-driven subcategories (ACS-driven or elective) are described in **Table 1**. There were numerically fewer coronary revascularizations with alirocumab compared to placebo for both PCI and CABG, and for both urgent (ACS) and elective indications. The largest numerical difference was for urgent PCI. The number of CABG procedures appeared similar between groups, with the caveat of far fewer procedures than for PCI. Angiographic findings are described in **Supplemental Table S3**. Compared with placebo, there were fewer de novo lesions with alirocumab, with small differences in the number of events related to restenosis or stent thrombosis. Among patients who underwent PCI or CABG, the rates of periprocedural complications were low and did not differ by treatment group (**Supplemental Table S4**).

Effect of Alirocumab on Any (Coronary and Noncoronary) Revascularization

The incidence of first and total coronary, limb, and carotid revascularizations by treatment group is summarized in **Table 2**. Alirocumab treatment resulted in fewer first revascularizations (3.2 versus 3.7 events per 100 patient-years; HR, 0.85 [95% CI, 0.78−0.94]; *P*=0.001) and total revascularizations (3.7 versus 4.5 events per 100 patient-years; HR, 0.83 [95% CI, 0.75-0.91]; *P*=0.0002) (**Supplemental Figure S1**). The reduction in revascularizations with alirocumab appeared consistent across coronary, limb, and carotid revascularizations.

Impact of Lipoprotein(a) and Corrected LDL-C on Risk of Coronary or Other Arterial Revascularization and Alirocumab Treatment Effect

At Month 4 of treatment, alirocumab reduced lipoprotein(a) by a median (Q1−Q3) of 5.0 (13.5−0) mg/dL overall, with median reductions of 0 (1.4−0), 5.1 (7.9−2.3), 9.8 (16.2−3.1), and 20.2 (34.1−8.0) mg/dL across increasing baseline lipoprotein(a) quartiles. Importantly,

median (Q1, Q3) changes in LDL-C (−1.39 [−1.79, −0.92] mmol/L [−53.7 (−69.1, −35.5) mg/dL], −1.40 [−1.84, −0.96] mmol/L [−54.1 (−71.0, −37.1) mg/dL], −1.38 [−1.82, −0.93] mmol/L [−53.3 (−70.3, −36.0) mg/dL], and −1.40 [−1.84, −0.95] mmol/L [−54.1 (−71.0, −36.7) mg/dL] mg/dL) and LDL-C_{corr} (−1.39 [−1.79, −0.93] mmol/L [−53.7 (−69.1, −35.9) mg/dL], −1.37 [−1.79, −0.94] mmol/L [−52.8 (−69.2, −36.4) mg/dL], −1.33 [−1.72, −0.88] mmol/L [−51.2 (−66.4, −34.0) mg/dL], and −1.23 [−1.65, −0.82] mmol/L [−47.3 (−63.6, −31.5) mg/dL] mg/dL) were similar across baseline lipoprotein(a) quartiles. In the placebo group, changes from baseline to Month 4 were minimal.[4]

In the placebo arm, using the lowest quartile as a reference, there was a uniform risk of first ischemia-driven coronary revascularization in quartiles 1−3 of baseline lipoprotein(a), with markedly greater risk in the top quartile compared with the bottom quartile (HR 1.45 [95% CI, 1.20−1.76]; P_{trend}=0.0001 for trend; **Figure 2**). Notably, the reduction of first coronary revascularization produced by alirocumab was most pronounced in the top quartile of lipoprotein(a) (P_{trend}=0.001; **Figure 2** and **Figure 3D**). In that quartile, relative risk reduction was substantial (HR, 0.69 [95% CI, 0.57−0.84], paralleled by an ARR of 1.3 events per 100 patient-years. Moreover, the reduction in first coronary revascularization in the top quartile of lipoprotein(a) became apparent within the first year after randomization (**Figure 3D**). Similar observations were made when total coronary revascularizations were considered, with an ARR of 1.3 procedures per 100 patient-years of observation in the highest baseline quartile of lipoprotein(a) and with significant interactions between baseline lipoprotein(a) and the risk of total coronary revascularizations in the placebo group and between baseline lipoprotein(a) and the benefit of alirocumab (P_{trend}=0.0002 and P_{trend}=0.04 respectively, **Graphical Illustration**). Similar relationships between baseline LDL-C_{corr} quartile and first and total revascularizations were evident in the placebo arm; however, unlike lipoprotein(a), there was no evidence of heterogeneity in the treatment effects across

quartiles (first revascularization P_{trend}=0.55, **Supplemental Figure S2;** total revascularizations P_{trend}=0.83, **Supplemental Figure S3**).

Regarding all (coronary, limb, and carotid) revascularizations, there was also a relationship within the placebo group between baseline lipoprotein(a) quartile and risk of first (P_{trend}<0.0001) and total (P_{trend}=0.0002) events, and between baseline lipoprotein(a) quartile and benefit of alirocumab for first (P_{trend}=0.003) and total (P_{trend}=0.03) events (**Figure 4** and **Table 3**). Similar to the findings for coronary revascularization, in the lower 3 quartiles of baseline lipoprotein(a), there was minimal effect of alirocumab on all revascularizations; however, in the top quartile of baseline lipoprotein(a) alirocumab reduced that risk substantially (HR, 0.67 [95% CI, 0.56−0.80] for first; HR, 0.69 [95% CI, 0.59−0.82] for total; ARR per 100 patient-years 1.6 for first, 1.7 for total).

DISCUSSION

In this large trial of patients with recent ACS and elevated atherogenic lipoproteins despite intensive or maximum-tolerated statin therapy, alirocumab reduced the risk of coronary or any (coronary, limb, or carotid) arterial revascularization. Both first and total (first and recurrent) revascularization events were reduced.

Baseline lipoprotein(a) was associated with the risk of arterial revascularization after ACS, but also significantly modified the effect of alirocumab on revascularization: the greatest and earliest benefit of alirocumab on revascularization was seen in patients with baseline lipoprotein(a) in the top quartile (≥59.6 mg/dL). In contrast, there was little or no apparent benefit of alirocumab on revascularization in the lowest quartile of lipoprotein(a) (<6.7 mg/dL). These findings are particularly notable in light of similar and substantial reductions in LDL-C_{corr} across baseline lipoprotein(a) quartiles. The benefit of alirocumab on revascularization was not associated with baseline LDL-C_{corr} quartiles. This is important

because LDL-C incorporates both LDL-C_{corr} and lipoprotein(a) cholesterol, but in our observations it suggests that the apparent relationship between reductions in LDL-C and reduction in revascularization with alirocumab may actually be driven by the reduction in lipoprotein(a) cholesterol particles rather than by any change in "true" LDL-C (which is approximated by LDL-C_{corr}).

The relation between elevated lipoprotein(a) and risk of atherosclerotic events has been well documented[8-10] and appears to be monotonic over a broad range of lipoprotein(a) concentrations. Others have previously observed that the association of LDL-C with incident cardiovascular events, including coronary revascularization, is due in part to the contribution of lipoprotein(a) to measured or calculated LDL-C.[11] Likewise, elevated lipoprotein(a) has been previously associated with an increased risk of coronary revascularization.[12] Prior studies relating elevated lipoprotein(a) and an increased attributable risk for MACE events have categorized elevated lipoprotein(a) at values >50 mg/dL − consistent with the values from the highest quartile in the present analysis.[9]

Prior analyses of ODYSSEY OUTCOMES have shown that baseline lipoprotein(a) predicted first and total MACE,[7, 13] and that alirocumab-induced reductions in lipoprotein(a) contributed, independently of LDL-C reduction, to the reduced risk of MACE. In the present analysis, the benefit of alirocumab on revascularization was nearly confined to patients with baseline lipoprotein(a) in the top quartile. However, with rather broad confidence intervals in each quartile, our observations cannot rule out a continuous relationship between baseline lipoprotein(a) and the benefit of alirocumab on revascularization, akin to that demonstrated for primary MACE events[7] and peripheral artery disease events.[14]

Statin treatment is associated with a reduced need for coronary revascularization,[15] and greater statin-induced LDL-C reduction is associated with a greater benefit on coronary revascularization.[16, 17] There is also evidence that LDL lowering with statins reduces the risk

of peripheral revascularizations.[18, 19] In contrast, there is uncertainty regarding the relationship of lipoprotein(a) levels and risk of peripheral revascularization. Some,[20] but not all,[21] studies have suggested that elevated lipoprotein(a) levels are predictive of a higher risk of peripheral revascularization in patients with peripheral artery disease.

PCSK9 inhibitors such as alirocumab provide substantial reduction of LDL-C[22, 23] and modest reduction of lipoprotein(a). In patients with stable atherosclerotic cardiovascular disease, evolocumab reduced coronary revascularization by 22%, with a consistent reduction in urgent and elective procedures, a reduction in the need for complex PCI,[24] and a 24% reduction in the need for CABG[25]. The benefit of evolocumab on revascularization was not associated with baseline LDL-C (dichotomized at 1.81 mmol/L [70 mg/dL]) but associations with lipoprotein(a) levels were not reported.

The effect of alirocumab on revascularization was manifested predominantly by fewer PCIs. The number of CABG procedures may have been too small to detect an effect of treatment. In fact, in the FOURIER trial, with more patients undergoing CABG than in ODYSSEY OUTCOMES, there was a reduction in CABG with the PCSK9 inhibitor evolocumab[26] and in the CTT meta-analysis of LDL-lowering trials, there was a reduction in revascularization and specifically both in PCI and CABG with statins.[27] Given these prior observations, the lack of clear reduction in CABG with alirocumab in ODYSSEY OUTCOMES might reflect type II error.

Revascularization was the most frequent event at follow-up in ODYSSEY OUTCOMES,[4] is an important cause of hospital readmission and a major driver of healthcare costs.[28, 29] As such, reductions in the need for revascularization likely contribute to the cost-effectiveness of lipid-lowering therapies.

Strengths and Limitations

Strengths of this analysis include a large number of revascularizations in a diverse, international cohort, systematic measurement of lipoprotein(a) as well as the standard lipid profile, and rigorous adjudication of coronary revascularization with specific criteria for ischemia-driven revascularization, restenosis, and stent thrombosis. Total coronary revascularizations was a prespecified outcome in the statistical analysis plan, but should be interpreted conservatively as it was not included in the hierarchical analysis of secondary endpoints. Given the potent LDL-C lowering effect of alirocumab, and its moderate lipoprotein(a) lowering effect, it is difficult to definitely ascertain the contribution of lipoprotein(a) lowering and LDL-C_{corr} lowering to the improved outcomes with alirocumab. Mediation analyses and, more importantly, future studies using specific and potent therapies to lower lipoprotein(a)30 will help clarify the role of lipoprotein(a) lowering in the reduction of revascularization. Finally, the correction factor used to compute LDL-C_{corr} does not recognize interindividual variability, and the optimal correction factor remains debated.[31]Finally, we measured mass lipoprotein(a), which is influenced by apolipoprotein(a) isoform size. At high lipoprotein(a) mass, molar concentration is underestimated, and vice versa.[32] However, the magnitude of lipoprotein(a) lowering by alirocumab is not affected by apolipoprotein(a) size.[33, 34]

CONCLUSIONS

In patients with recent ACS alirocumab reduced the risk of coronary, limb, or carotid revascularizations. Patients with elevated levels of lipoprotein(a) were at high risk for revascularization after ACS, and derived a substantial reduction in that risk with alirocumab. Conversely, patients with low lipoprotein(a) appeared to derive minimal benefit of alirocumab on revascularization, despite substantial reductions in LDL-C. These observations have substantial implications for the cost-effectiveness of alirocumab, for our understanding

of the pathogenic role of lipoprotein(a) in atherosclerosis and, potentially for the selection of the best candidates for therapy.

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

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Figure Legends

Figure 1. Cumulative incidence of first and total ischemia-driven coronary revascularizations by treatment allocation. CI indicates confidence interval; HR, hazard ratio for alirocumab vs placebo.

Figure 2. Forest plot relating baseline lipoprotein(a) quartile to the risk of first ischemia-driven coronary revascularization in the placebo group (left side of the graph) and the effect of alirocumab on the risk of first ischemia-driven coronary revascularization (right side of the graph). Absolute risk reduction (events per 100 patient-years) with alirocumab: 0 for quartile 1, 0.1 for quartile 2, 0.3 for quartile 3, and 1.3 for quartile 4. CI indicates confidence interval; HR, hazard ratio.

Figure 3. Kaplan-Meier curve for time to first ischemia-driven coronary revascularization by baseline lipoprotein(a) quartile: (A) quartile 1 (<6.7 mg/dL); (B) quartile 2 (6.7 to <21.2 mg/dL); (C) quartile 3 (21.2 to <59.6 mg/dL); and (D) quartile 4 (≥59.6 mg/dL).

Figure 4. Relationship between baseline lipoprotein(a) quartile and first revascularization in the placebo group, and between baseline lipoprotein(a) quartile and benefit of alirocumab for first coronary, peripheral, and carotid revascularization. CI indicates confidence interval; HR, hazard ratio.

Table 1. Type of and Reason for Coronary Revascularization and First and Total Events

Event number	Type of Revascularization	Reason for Revascularization	Events per 100 patient-years [number of events]		HR (95% CI)	p- value
			Alirocumab	Placebo		
First	All (PCI + CABG)	Any	3.2 [811]	3.6 [903]	0.89 (0.81, 0.98)	0.0207
		Ischemia-driven	2.8 [727]	3.2 [823]		
		ACS	*1.7 [438]*	*2.1 [521]*		
		Elective	*1.1 [289]*	*1.2 [302]*		
		Nonischemia-driven	0.3 [84]	0.3 [80]		
	PCI	Any	2.7 [699]	3.1 [785]	0.89 (0.80, 0.98)	0.0205
		Ischemia-driven	2.5 [629]	2.8 [721]		
		ACS	*1.5 [393]*	*1.9 [474]*		
		Elective	*0.9 [236]*	*1.0 [247]*		
		Nonischemia-driven	0.3 [70]	0.3 [64]		
	CABG	Any	0.4 [112]	0.5 [118]	0.94 (0.73, 1.22)	0.67
		Ischemia-driven	0.4 [98]	0.4 [102]		

Event number	**Type of Revascularization**	**Reason for Revascularization**	**Events per 100 patient-years [number of events]**		**HR (95% CI)**	**p- value**
			Alirocumab	**Placebo**		
		ACS	*0.2 [45]*	*0.2 [47]*		
		Elective	*0.2 [53]*	*0.2 [55]*		
		Nonischemia-driven	0.1 [14]	0.1 [16]		
Total	All (PCI+CABG)	Any	3.7 [990]	4.1 [1115]	0.89 (0.81, 0.98)	0.0188
		Ischemia-driven	3.2 [875]	3.7 [1003]		
		ACS	*2.0 [535]*	*2.4 [650]*		
		Elective	*1.3 [340]*	*1.3 [353]*		
		Nonischemia-driven	0.4 [115]	0.4 [112]		
	PCI	Any	3.2 [860]	3.6 [977]	0.89 (0.80, 0.98)	0.0190
		Ischemia-driven	2.8 [764]	3.3 [884]		
		ACS	*1.8 [482]*	*2.2 [591]*		
		Elective	*1.0 [282]*	*1.1 [293]*		
		Nonischemia-driven	0.4 [96]	0.3 [93]		

Event number	**Type of Revascularization**	**Reason for Revascularization**	**Events per 100 patient-years [number of events]**		**HR (95% CI)**	**p- value**
			Alirocumab	**Placebo**		
	CABG	Any	0.5 [130]	0.5 [138]	0.95 (0.75, 1.20)	0.67
		Ischemia-driven	0.4 [111]	0.4 [119]		
		ACS	*0.2 [53]*	*0.2 [59]*		
		Elective	*0.2 [58]*	*0.2 [60]*		
		Nonischemia-driven	0.1 [19]	0.1 [19]		

ACS indicates acute coronary syndrome; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

Table 2. Treatment Effects on First and Total Ischemia-Driven Coronary, Peripheral Artery, and Carotid Revascularizations

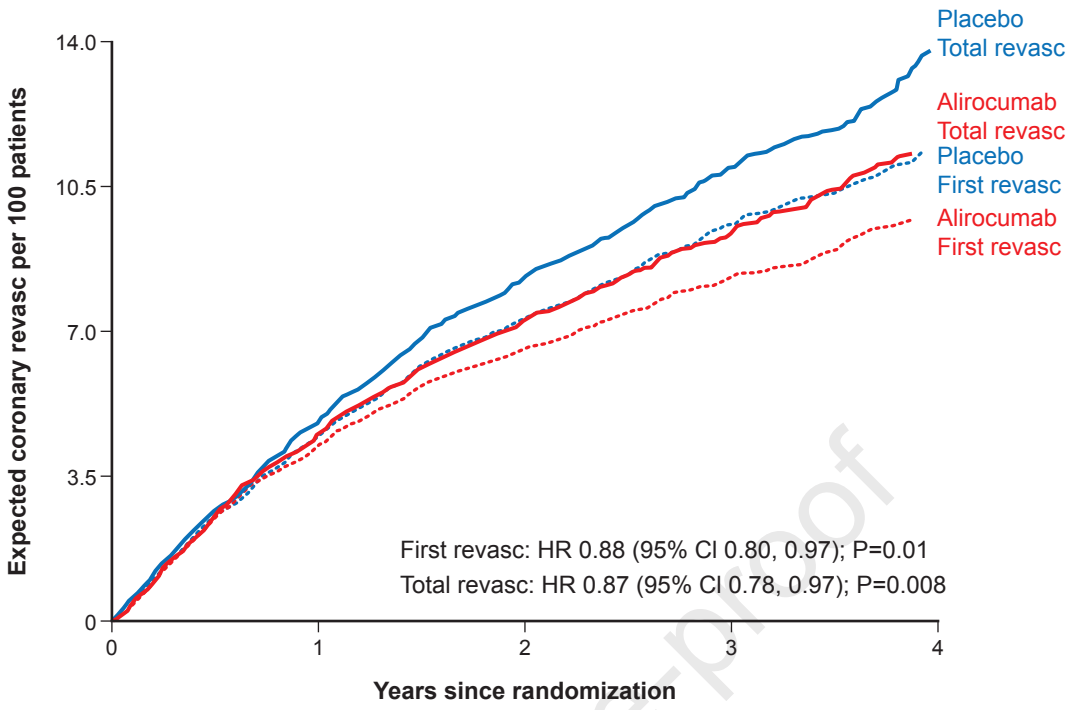
Event	Type of Revascularization	Events per 100 patient-years [number of events]		HR (95% CI)	p-value
		Alirocumab	Placebo		
First	Any	3.2 [814]	3.7 [945]	0.85 (0.78−0.94)	0.0010
	Ischemia-driven coronary	2.8 [725]	3.2 [816]	0.88 (0.80, 0.97)	0.0134
	Peripheral artery	0.3 [76]	0.4 [106]	0.71 (0.53, 0.95)	0.0226
	Carotid	0.1 [13]	0.1 [23]	0.56 (0.28, 1.10)	0.09
Total	Any	3.7 [1001]	4.5 [1202]	0.83 (0.75−0.91)	0.0002
	Ischemia-driven coronary	3.2 [875]	3.7 [1003]	0.88 (0.80, 0.97)	0.0126
	Peripheral artery	0.4 [110]	0.6 [169]	0.66 (0.49, 0.89)	0.0064
	Carotid	0.1 [16]	0.1 [30]	0.54 (0.28, 1.03)	0.06

CI indicates confidence interval; HR, hazard ratio.

Table 3. Relationship Between Baseline Lipoprotein(a) Quartile and Total Ischemia-driven Coronary, Limb, And Carotid Revascularizations in the Placebo Group, and Between Baseline Lipoprotein(a) Quartile and Benefit of Alirocumab for Total Coronary, Limb, and Carotid Revascularizations

Baseline lipoprotein(a) quartile	**Placebo group** **HR (95% CI)**	***P*trend**	**Treatment** **HR (95% CI)**	***P*trend**
Quartile 1 (<6.7 mg/dL)	Reference	0.0002	0.93 (0.77−1.12)	0.03
Quartile 2 (6.7 to <21.2 mg/dL)	0.99 (0.82−1.19)		0.91 (0.76−1.10)	
Quartile 3 (21.2 to <59.6 mg/dL)	1.04 (0.86−1.25)		0.92 (0.76−1.10)	
Quartile 4 (≥59.6 mg/dL)	1.40 (1.17−1.67)		0.69 (0.59−0.82)	

CI indicates confidence interval; HR, hazard ratio.



Baseline lipoprotein(a) Quartile	Events per 100 Patient-Years Alirocumab	Events per 100 Patient-Years Placebo	Placebo group HR (95% CI)	Treatment HR (95% CI)
Quartile 1 (<6.7 mg/dL)	3.0	3.0	Reference	1.00 (0.82, 1.22)
Quartile 2 (6.7 to <21.2 mg/dL)	2.7	2.8	0.93 (0.75, 1.13)	0.98 (0.80, 1.21)
Quartile 3 (21.2 to <59.6 mg/dL)	2.8	3.1	1.04 (0.85, 1.27)	0.93 (0.76, 1.14)
Quartile 4 (≥59.6 mg/dL)	2.9	4.2	1.45 (1.20, 1.76)	0.69 (0.57, 0.84)