Peripheral artery disease and venous thromboembolic events after acute coronary syndrome role of lipoprotein(a) and modification aby alirocumab: prespecified analysis of the ODYSSEY OUTCOMES randomized clinical trial

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ORIGINAL RESEARCH ARTICLE

Peripheral Artery Disease and Venous Thromboembolic Events After Acute Coronary Syndrome

Role of Lipoprotein(a) and Modification by Alirocumab: Prespecified Analysis of the ODYSSEY OUTCOMES Randomized Clinical Trial

BACKGROUND: Patients with acute coronary syndrome are at risk for peripheral artery disease (PAD) events and venous thromboembolism (VTE). PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors reduce lipoprotein(a) and low-density lipoprotein cholesterol (LDL-C) levels. Our objective was to ascertain whether PCSK9 inhibition reduces the risk of PAD events or VTE after acute coronary syndrome, and if such effects are related to levels of lipoprotein(a) or LDL-C.

METHODS: This was a prespecified analysis of the ODYSSEY OUTCOMES randomized clinical trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome), which was conducted in 18 924 patients with recent acute coronary syndrome on intensive or maximum-tolerated statin treatment who were randomized to the PCSK9 inhibitor alirocumab or placebo. In a prespecified analysis, PAD events (critical limb ischemia, limb revascularization, or amputation for ischemia) and VTE (deep vein thrombosis or pulmonary embolism) were assessed. LDL-C was corrected (LDL-C$_{corrected}$) for cholesterol content in lipoprotein(a).

RESULTS: At baseline, median lipoprotein(a) and LDL-C$_{corrected}$ were 21 and 75 mg/dL, respectively; with alirocumab, median relative reductions were 23.5% and 70.6%, respectively. PAD events and VTE occurred in 246 and 92 patients, respectively. In the placebo group, risk of PAD events was related to baseline quartile of lipoprotein(a) (P_{trend}=0.0021), and tended to associate with baseline quartile of LDL-C$_{corrected}$ (P_{trend}=0.06); VTE tended to associate with baseline quartile of lipoprotein(a) (P_{trend}=0.06), but not LDL-C$_{corrected}$ (P_{trend}=0.85). Alirocumab reduced risk of PAD events (hazard ratio [HR], 0.69 [95% CI, 0.54–0.89]; P=0.004), with nonsignificantly fewer VTE events (HR, 0.67 [95% CI, 0.44–1.01]; P=0.06). Reduction in PAD events with alirocumab was associated with baseline quartile of lipoprotein(a) (P_{trend}=0.03), but not LDL-C$_{corrected}$ (P_{trend}=0.50). With alirocumab, the change from baseline to Month 4 in lipoprotein(a), but not LDL-C$_{corrected}$, was associated with the risk of VTE and the composite of VTE and PAD events.

CONCLUSIONS: In statin-treated patients with recent acute coronary syndrome, risk of PAD events is related to lipoprotein(a) level and is reduced by alirocumab, particularly among those with high lipoprotein(a). Further study is required to confirm whether risk of VTE is related to lipoprotein(a) level and its reduction with alirocumab.

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Clinical Perspective

What Is New?

- In a trial that compared the PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitor alirocumab with placebo in 18 924 patients with recent acute coronary syndrome and dyslipidemia uncontrolled with statins, the risk of major peripheral artery disease (PAD) events was associated with baseline lipoprotein(a) concentration.
- Alirocumab lowered low-density lipoprotein cholesterol and lipoprotein(a) levels and reduced PAD events compared with placebo.
- The reduction of PAD events was associated with baseline lipoprotein(a) but not low-density lipoprotein cholesterol levels.
- Directionally similar but statistically nonsignificant relationships were found for association of venous thromboembolism with baseline lipoprotein(a) and the effect of alirocumab on risk of venous thromboembolism.

What Are the Clinical Implications?

- Lipoprotein(a) is associated with risk of major PAD events.
- In statin-treated patients, a PCSK9 inhibitor can reduce the risk of major PAD events, especially among those with high levels of lipoprotein(a).
- Further study is needed to confirm an association of venous thromboembolism with lipoprotein(a) levels and a reduction in risk of venous thromboembolism with PCSK9 inhibitors.

Peripheral artery disease (PAD) affects more than 200 million individuals worldwide,[1] has a prevalence exceeding 10% among adults in the United States,[2] is associated with a high risk of cardiovascular events,[3] and extracts a large toll from patients' quality of life and society's healthcare costs.[4,5]

Smoking, diabetes mellitus, and hypertension are the strongest risk factors for PAD, but dyslipidemia may be contributory. An association between elevated levels of triglyceride-rich lipoproteins or low-density lipoprotein cholesterol (LDL-C) and incident PAD has been found in some, but not all, analyses.[6–11] Lipoprotein(a), a low-density lipoprotein whose levels are primarily under genetic control, has atherogenic, proinflammatory, and thrombogenic properties.[12] Most observational cohort studies indicate an association of elevated lipoprotein(a) with incident PAD.[13–16] In addition, the progression of chronic obstructive PAD to critical limb ischemia is influenced by thrombophilic factors,[17] possibly including levels of lipoprotein(a).[18,19]

Venous thromboembolism (VTE) and PAD events may share common pathophysiology related to thrombophilia and inflammation.[20–22] VTE does not appear to be associated with levels of LDL-C.[23] However, there are conflicting data regarding an association of VTE with concentration or genetic variants of lipoprotein(a).[24–27]

Statins reduce levels of LDL-C and triglycerides but not lipoprotein(a). Statins also improve exercise capacity in patients with PAD.[28] Although observational data suggest that statins may reduce major adverse limb events including critical limb ischemia, revascularization, and amputation,[29] there is a dearth of corroborating evidence from randomized placebo-controlled trials. In one large, randomized placebo-controlled trial, rosuvastatin reduced VTE, but the effect was unrelated to levels of LDL-C.[23]

Inhibitors of PCSK9 (proprotein convertase subtilisin/kexin type 9) reduce LDL-C and lipoprotein(a) levels, with a modest effect on triglycerides. In the FOURIER trial (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk), the PCSK9 inhibitor evolocumab reduced major adverse limb events compared with placebo on a background of statin treatment.[30] However, the relationship of this effect to evolocumab-induced changes in individual lipoproteins was not assessed. It is important that the effects of PCSK9 inhibitors on VTE have not been evaluated.

The ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome) compared the PCSK9 inhibitor alirocumab with placebo in patients with recent acute coronary syndromes (ACS) on intensive statin treatment.[31] The primary outcome of major coronary heart disease events and ischemic stroke was reduced with the PCSK9 inhibitor alirocumab, with the benefit related to reductions in levels of both LDL-C and lipoprotein(a),[32] and with a particularly pronounced benefit for this outcome in patients with PAD.[33] In this prespecified analysis, we examined the relationship of PAD and VTE events to baseline lipoprotein levels, the effects of treatment with alirocumab or placebo on PAD or VTE events, and the relation of those treatment effects to lipoprotein levels.

METHODS

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

Patients and Outcomes

The design and principal results of the ODYSSEY OUTCOMES trial have been reported.[31,34] At each of 1315 sites in 57 countries, the trial was approved by the responsible institutional review committee and the subjects gave informed consent. The trial included 18 924 patients with recent ACS and elevated levels of atherogenic lipoproteins despite intensive or maximum-tolerated statin treatment. Between 1 and 12 (median 2.6) months after a qualifying ACS, patients were randomly assigned, in double-blind fashion and a 1:1 ratio (see Supplemental Methods in the Data Supplement), to

treatment with alirocumab 75 mg or placebo, administered subcutaneously every 2 weeks. The dose of alirocumab could be blindly increased to 150 mg or switched to placebo to target achieved LDL-C levels of 25 to 50 mg/dL (0.65–1.30 mmol/L) and avoid sustained levels below 15 mg/dL (0.39 mmol/L). History of PAD or VTE was determined from the medical history.

The primary outcome in the trial was the composite of death from coronary heart disease, nonfatal myocardial infarction, hospitalization for unstable angina, or ischemic stroke. PAD events and VTE were prespecified tertiary end points, considered separately and in aggregate. PAD events were defined as critical limb ischemia, limb revascularization, or amputation for ischemia not planned at time of randomization. VTE was defined as deep vein thrombosis or pulmonary embolism. PAD events and VTE were investigator-reported, nonadjudicated outcomes recorded on a case report form designed to define and document the occurrence of these events (see Supplemental Methods in the Data Supplement). A composite of the primary end point and PAD events and a composite of the primary end point, PAD events, and VTE were additional prespecified outcomes.

Lipid Measurements

Lipoprotein(a) mass concentration was measured with an immunoturbidometric assay (Siemens Healthcare Diagnostics, Malvern, Pennsylvania USA), with an interassay coefficient of variation of 3.1% to 4.8% depending on lipoprotein(a) concentration. LDL-C was calculated using the Friedewald formula unless the concomitant triglyceride level exceeded 400 mg/dL or the calculated LDL-C level was less than 15 mg/dL, in which case values were determined by β-quantification. Calculated or measured LDL-C includes cholesterol contained in lipoprotein(a). To account for this and to estimate the independent contributions of LDL-C and lipoprotein(a) lowering with alirocumab to the observed effects on PAD events or VTE, we used the relationship proposed by Dahlen[35] to calculate LDL-C$_{corrected}$ as measured LDL-C – [0.3 × lipoprotein(a)].

Statistical Analysis

In the placebo group, the risks of PAD events, VTE, and their combination were evaluated with proportional hazards models according to baseline quartiles of LDL-C$_{corrected}$ and lipoprotein(a). In each treatment group, the cumulative incidence of each category of event was displayed with Kaplan-Meier curves and the treatment effect of alirocumab versus placebo was determined by log-rank tests and proportional hazards models stratified for geographic region. Proportional hazards models were also constructed to determine relative treatment effects on events of interest by baseline lipoprotein(a) quartile, with stratification by geographic region. The independent contributions of reductions in LDL-C$_{corrected}$ and lipoprotein(a) with alirocumab treatment to a reduction in PAD events and VTE with alirocumab were determined in a multivariable Cox-regression model relating the change in these lipoproteins with alirocumab, from baseline to Month 4, to PAD events or VTE occurring in the alirocumab group after Month 4. The model was adjusted for baseline characteristics including age, sex, race, geographic region,

body mass index, smoking history, diabetes mellitus, time from index ACS to randomization, baseline triglyceride levels, LDL-C$_{corrected}$, and lipoprotein(a), as well as change in triglycerides from baseline to Month 4.

RESULTS

Patient flow is described in Figure I in the Data Supplement. Baseline characteristics of the trial cohort are shown in Table 1. Characteristics were well-balanced between the alirocumab and placebo groups. Of note, 4.0% of patients had a medical history of PAD and 1.1% had a previous VTE. Intensive statin therapy was used in 88.8%, aspirin in 95.6%, and dual antiplatelet therapy in 84.1%. Median baseline levels of LDL-C$_{corrected}$ and lipoprotein(a) were 75 mg/dL and 21 mg/dL, respectively.

Median (quartile 1, quartile 3) follow-up was 2.8 (2.3, 3.4) years. Over that time, PAD events occurred in 246 patients, VTE events in 92 patients, and either type of event in 325 patients.

Figure 1 shows the incidence of PAD and VTE events in the placebo group according to baseline quartile of LDL-C$_{corrected}$ and lipoprotein(a). The risk of PAD events was significantly related to the baseline quartile of lipoprotein(a) (P_{trend}=0.0021). The hazard ratio (HR) in quartile 4/quartile 1 was 2.22 (95% CI, 1.38–3.57). There was a trend toward greater risk of PAD events in progressively higher baseline quartiles of LDL-C$_{corrected}$ (P_{trend}=0.06) with an HR (quartile 4/quartile 1) of 1.46 (95% CI, 0.91–2.32). The risk of VTE was numerically higher in the highest baseline quartile of lipoprotein(a) without significant trend across quartiles (P_{trend}=0.22) and without association with baseline quartile of LDL-C$_{corrected}$ (P_{trend}=0.85). HRs in quartile 4/quartile 1 of lipoprotein(a) and LDL-C$_{corrected}$ were 1.64 (95% CI, 0.80–3.38) and 1.00 (95% CI, 0.49–2.05), respectively. For the combination of PAD events or VTE, risk was related to baseline quartile of lipoprotein(a) (P_{trend}=0.009) and tended to associate with baseline quartile of LDL-C$_{corrected}$ (P_{trend}=0.06).

In an exploratory analysis, we stratified the study population by the median baseline lipoprotein(a) and evaluated the relationship of baseline quartile of LDL-C$_{corrected}$ to risk of PAD events in each stratum. There were 58 PAD events among patients with baseline lipoprotein(a) below the median and 87 PAD events among patients with baseline lipoprotein(a) at or above the median. In the former stratum, there was no association between baseline quartile of LDL-C$_{corrected}$ with risk of PAD events (P_{trend}=0.21). However, among patients with baseline lipoprotein(a) at or above the median there was an association of baseline quartile of LDL-C$_{corrected}$ with risk of PAD events (P_{trend}=0.04).

Similarly, we stratified the population by median baseline LDL-C$_{corrected}$ and evaluated the relationship of baseline

Table 1. Baseline Characteristics of the Patients

Characteristic	Alirocumab (N=9462)	Placebo (N=9462)
Demographics		
Age, y*	58.5 (9.3)	58.6 (9.4)
Women	2390 (25.3%)	2372 (25.1%)
Non-white race*†	1961 (20.7%)	1936 (20.5%)
Medical history		
Diabetes mellitus*†	2693 (28.5%)	2751 (29.1%)
Hypertension*	6205 (65.6%)	6044 (63.9%)
Current smoking*	2282 (24.1%)	2278 (24.1%)
MI, PCI, or CABG before qualifying ACS*†	2329 (24.6%)	2341 (24.7%)
Stroke*†	306 (3.2%)	305 (3.2%)
Congestive heart failure*	1365 (14.4%)	1449 (15.3%)
Peripheral artery disease*†	373 (3.9%)	386 (4.1%)
Venous thromboembolic event*†	100 (1.1%)	99 (1.0%)
Medications		
Any statin†	9229 (97.5%)	9235 (97.6%)
Intensive statin treatment	8380 (88.6%)	8431 (89.1%)
Aspirin	9050 (95.6%)	9036 (95.5%)
Dual antiplatelet therapy	7996 (84.5%)	7927 (83.8%)
Oral anticoagulant	378 (4.1%)	403 (4.3%)
Lipids, median (Q1, Q3), mg/dL		
LDL-C*	87 (73, 104)	87 (73, 104)
LDL-C$_{corrected}$	75 (61, 94)	75 (60, 93)
Lipoprotein(a)*	21 (7, 59)	22 (7, 60)
Triglycerides*†	129 (94, 181)	129 (95, 183)
High-density lipoprotein cholesterol	43 (37, 50)	42 (36, 50)

Data are mean (SD), number (%), or median, (Q1, Q3). To convert cholesterol to mmol/L, multiply by 0.02586; triglycerides to mmol/L, multiply by 0.01129. ACS indicates acute coronary syndrome; CABG, coronary artery bypass graft; LDL-C, low-density lipoprotein cholesterol; LDL-C$_{corrected}$, corrected low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; Q1, quartile 1; and Q3, quartile 3.

*Significantly associated (P<0.05) with risk of peripheral artery disease events during follow-up in total study population.

†Significantly associated (P<0.05) with risk of venous thromboembolic events during follow-up in total study population.

quartile of lipoprotein(a) to risk of PAD events in each stratum. There were 61 PAD events among patients with baseline LDL-C$_{corrected}$ below the median and 84 PAD events among patients with baseline LDL-C$_{corrected}$ at or above the median. In the former stratum, there was no significant association of baseline quartile of lipoprotein(a) with risk of PAD events (P_{trend}=0.0501). However, among patients with baseline LDL-C$_{corrected}$ at or above the median there was an association of baseline quartile of lipoprotein(a) with risk of PAD events (P_{trend}=0.0026).

Figure 2 shows the cumulative incidence of PAD events, VTE, and their combination in each treatment group. Alirocumab markedly decreased the risk of PAD events compared with placebo (HR, 0.69 [95% CI, 0.54–0.89]; P=0.004). The effect of treatment on the risk of PAD events was not influenced by time from index ACS to randomization (dichotomized at median 2.6 months, $P_{interaction}$=0.57). There was a trend toward reduced risk of VTE with alirocumab (HR, 0.67 [95% CI, 0.44–1.01]; P=0.06), and the combination of PAD events or VTE was reduced with alirocumab (HR, 0.69 [95% CI, 0.55–0.86]; P<0.001). Each type of PAD and VTE event was numerically less frequent in the alirocumab group than in the placebo group (Table I in the Data Supplement). The effects of randomized treatment on the combination of the primary trial end point and PAD events, and on the combination of the primary trial end point, PAD events, and VTE are shown in Figure II in the Data Supplement.

Although comprising only 4.0% of the study population, patients with a history of PAD contributed 46.7% of all PAD events. Among those patients, alirocumab reduced PAD events by 41.0% (HR, 0.59 [95% CI, 0.40–0.86]), corresponding to an 8.6% absolute reduction in risk of a PAD event at 3 years (Figure III in the Data Supplement). Among patients without a history of PAD, the absolute risk of PAD events was small and the absolute reduction in that risk with alirocumab was minimal. Similar analyses were not possible for VTE because of the smaller number of VTE than PAD events, and the small percentage of patients with a history of VTE.

Changes in lipoproteins from baseline to Month 4 are shown in Tables II and III in the Data Supplement. In the alirocumab group, median percent change in LDL-C$_{corrected}$ was −70.6% (quartile 1, quartile 3: −83.2%, −51.8%) and in lipoprotein(a) was −23.5% (quartile 1, quartile 3: −47.3%, 0%), with minimal variation of percent changes across baseline lipoprotein quartiles. The absolute decrease in LDL-C$_{corrected}$ from baseline to Month 4 increased across baseline quartiles of LDL-C$_{corrected}$ but was approximately constant across baseline quartiles of lipoprotein(a). Conversely, the absolute decrease in lipoprotein(a) increased across baseline quartiles of lipoprotein(a) but was approximately constant across baseline quartiles of LDL-C$_{corrected}$. In the placebo group, percent changes and absolute changes in lipoproteins from baseline to Month 4 were minimal.

In the context of these lipoprotein changes, the treatment HR for PAD or VTE events was evaluated according to baseline quartile of lipoprotein(a) or LDL-C$_{corrected}$ (Figure 3). There was no evidence for a gradient of the relative treatment effect of alirocumab on PAD events across baseline quartiles of LDL-C$_{corrected}$ (P_{trend}=0.50). In contrast, the HR for PAD events decreased monotonically with increasing quartile of baseline lipoprotein(a), from 1.05 (95% CI, 0.61–1.83) in quartile 1 to 0.48 (95% CI, 0.30–0.77) in quartile 4, with P_{trend}=0.03. Correspondingly, the absolute reduction in the risk of PAD events was nil in quartile 1 of
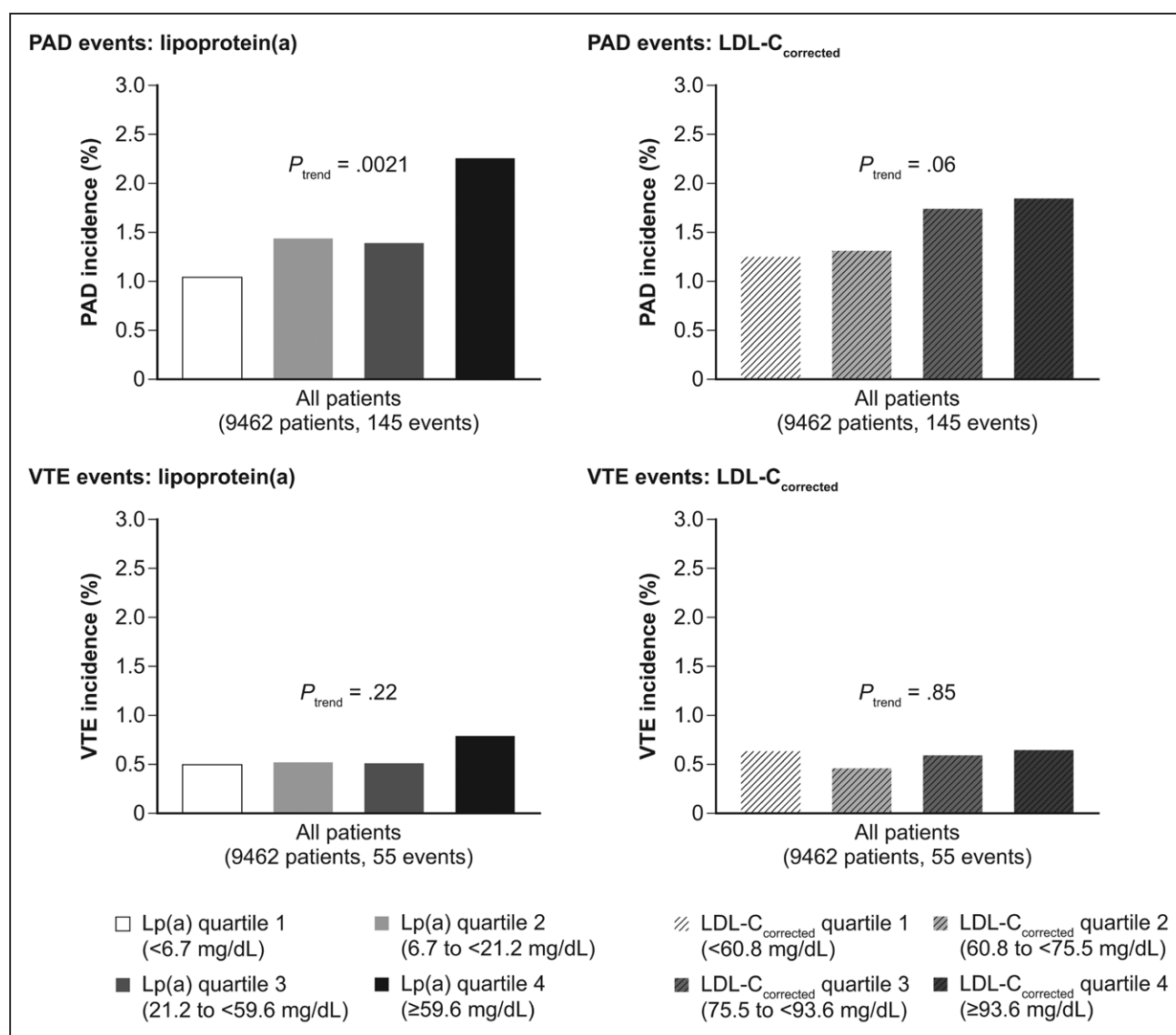
Figure 1. Risk of peripheral artery disease and venous thromboembolism events in the placebo group by baseline lipoprotein(a) or LDL-C$_{corrected}$ quartiles.

Peripheral artery disease (PAD) events (**top**) and venous thromboembolism (VTE) events (**bottom**) in the placebo group are shown according to baseline quartile of lipoprotein(a) (Lp(a); **left**) or baseline quartile of corrected low-density lipoprotein cholesterol (LDL-C$_{corrected}$; **right**). The hazard ratios (HRs [95% CIs]) for quartile 2, quartile 3, and quartile 4, relative to quartile 1, are 1.40 (0.83–2.35), 1.35 (0.81–2.28), and 2.22 (1.38–3.57) for lipoprotein(a) and PAD events; 1.06 (0.48–2.37), 1.03 (0.46–2.30), and 1.64 (0.80–3.38) for lipoprotein(a) and VTE events; 1.03 (0.62–1.70), 1.34 (0.84–2.15), and 1.46 (0.91–2.32) for LDL-C$_{corrected}$ and PAD events; and 0.72 (0.33–1.58), 0.90 (0.43–1.86), and 1.00 (0.49–2.05) for LDL-C$_{corrected}$ and VTE events. P values reflect linear trend across quartiles in an unadjusted Cox regression model.

baseline lipoprotein(a), but 1.2% in quartile 4. In sum, these data indicate greater relative and absolute reductions in risk of PAD events with alirocumab among patients with higher baseline levels of lipoprotein(a), in whom the reduction in lipoprotein(a) with treatment was larger. Findings were qualitatively similar for relationships of baseline lipoprotein quartiles to risk of VTE events, but with few events in each quartile statistical significance was not demonstrated.

Within the alirocumab group, multivariable Cox models were constructed to examine the HR for PAD, VTE, or their combination for a 1 mg/dL change in LDL-C$_{corrected}$ or lipoprotein(a). The models were adjusted

for baseline LDL-C$_{corrected}$, lipoprotein(a), and triglyceride levels, and the change in triglyceride levels from baseline to Month 4 (Table 2). For PAD events, VTE events, or their combination, there was no statistically significant association between the change in LDL-C$_{corrected}$ with alirocumab treatment and the risk of an event. In contrast, there was a significant association between the change in lipoprotein(a) with alirocumab and the risk of VTE events (HR for 1 mg/dL decrease in lipoprotein(a), 0.985 [95% CI, 0.972–0.999]; P=0.04) and risk of either PAD or VTE events (HR for 1 mg/dL decrease in lipoprotein(a), 0.991 [95% CI, 0.982–1.000]; P=0.04). These findings suggest that reduction in the risk of VTE
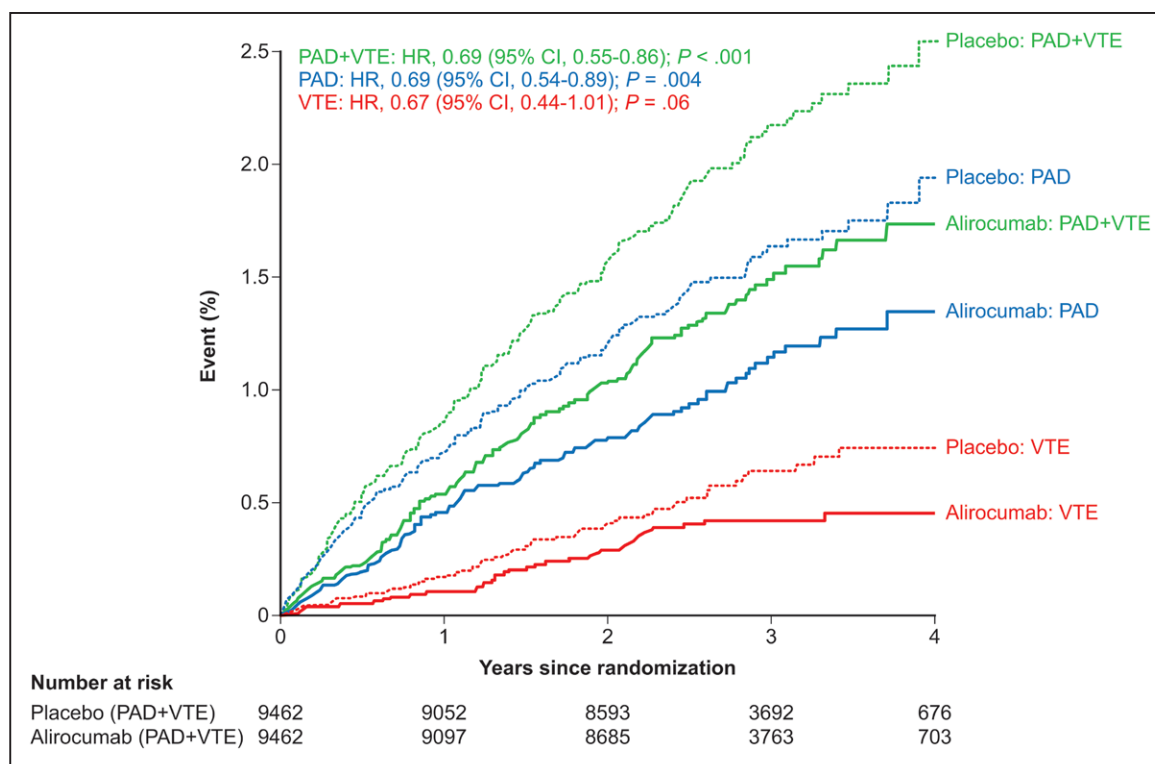
Figure 2. Effects of alirocumab or placebo on peripheral artery disease and venous thromboembolism events.
Kaplan-Meier curves depict the cumulative rate of peripheral artery disease (PAD) events (blue), venous thromboembolism (VTE) events (red), and the combination of PAD or VTE events (green). HR indicates hazard ratio.

or the combination of PAD and VTE events may be related to alirocumab-induced reduction of lipoprotein(a).

DISCUSSION

There are 4 key findings from this prespecified analysis of the ODYSSEY OUTCOMES trial. First, despite a history of PAD in only 4.0% of the trial cohort, there was a substantial risk of PAD events including critical limb ischemia, limb revascularization, and amputation for ischemia. The absolute risk of those events was approximately 2% in the placebo group at 4 years. Only 1.1% of the trial cohort had a previous history of VTE. Nonetheless, the risk of VTE during the trial was notable, occurring in approximately 0.7% of the placebo group at 4 years. These findings indicate that despite intensive statin and antiplatelet therapy, patients with a recent ACS remain at elevated risk for further events involving the peripheral arteries or the venous circulation.

Second, the risk of PAD events was strongly associated with the baseline level of lipoprotein(a), a lipoprotein believed to have thrombogenic, atherogenic, and inflammatory properties. There was a nonsignificant trend toward an association of PAD events with the baseline level of LDL-C$_{corrected}$, a parameter that estimates the cholesterol contained in low-density lipoprotein particles by algebraic correction for the cholesterol contained in lipoprotein(a), but ordinarily measured as LDL-C. Had

there been a larger number of PAD events, it is possible that a significant association of PAD events with baseline LDL-C$_{corrected}$ might have been identified. The relatively small number of VTE events limited power to determine whether VTE risk was associated with baseline levels of either lipoprotein(a) or LDL-C$_{corrected}$; nonetheless, the reduction in lipoprotein(a) under treatment with alirocumab was significantly associated with reduced risk of VTE.

Third, in patients with recent ACS, alirocumab resulted in a relative risk reduction for major PAD events of more than 30%, with the absolute risk reduction most pronounced in those with a previous history of PAD. This finding is consistent with the effect of evolocumab on PAD events in patients with chronic atherosclerotic cardiovascular disease.[30] The point estimates for relative effects of alirocumab on VTE and PAD events were similar, but as a result of the smaller number of VTE events the effect on that end point was not significant. Nonetheless, the likelihood of a true biological effect of alirocumab on both PAD and VTE events is strengthened by the fact that each type of component event (critical limb ischemia, limb revascularization or amputation, deep vein thrombosis, and pulmonary embolism) was numerically less frequent in the alirocumab group than in the placebo group.

Fourth, multivariable analysis indicates that on assigned treatment with alirocumab the risk of VTE or the combination of PAD and VTE events was inversely
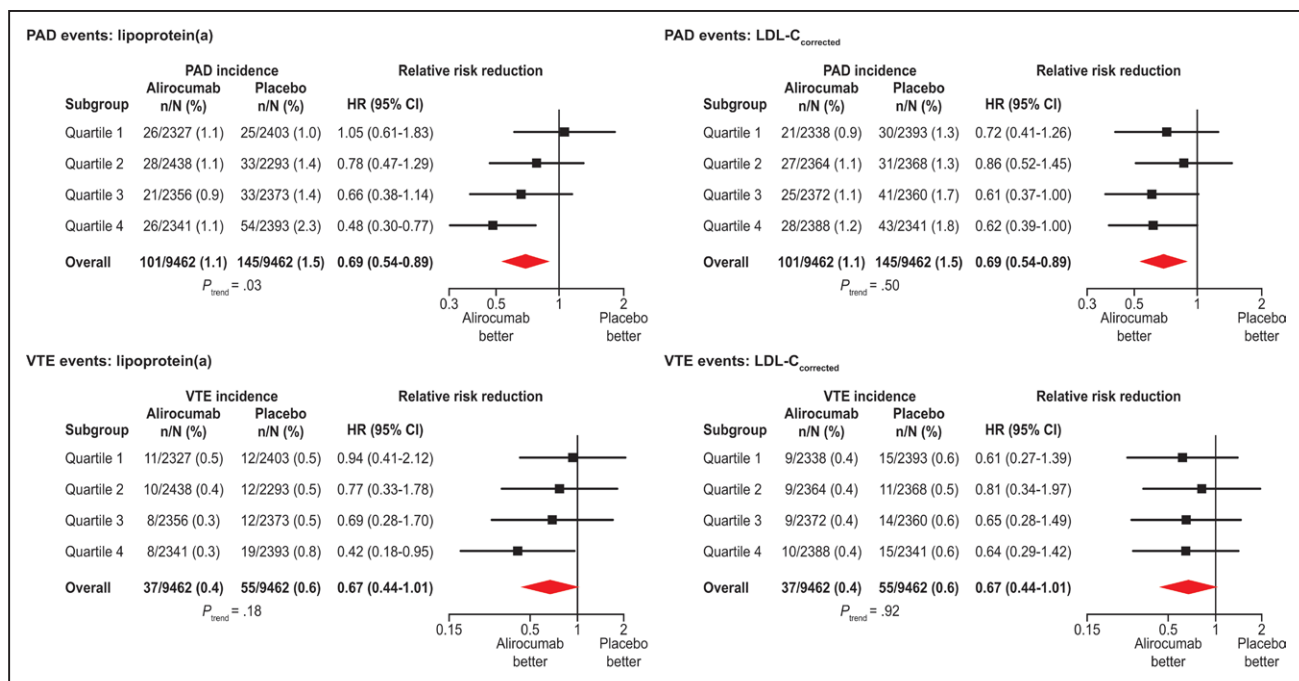
Figure 3. Treatment effect of alirocumab on peripheral artery disease and venous thromboembolism events according to baseline quartile of LDL-C$_{corrected}$ or lipoprotein(a).
Hazard ratios (HRs; alirocumab:placebo) for peripheral artery disease (PAD) events (**top**) and venous thromboembolism (VTE) events (**bottom**) according to baseline quartile of lipoprotein(a) (**left**) or baseline quartile of corrected low-density lipoprotein cholesterol (LDL-C$_{corrected}$; **right**). Overall treatment effect is shown in red. *P* values indicate test of linear trend across baseline quartiles.

related to the magnitude of lipoprotein(a) reduction, but not to the magnitude of reduction of LDL-C$_{corrected}$ (Table 2). The latter observation does not necessarily indicate that levels of LDL-C$_{corrected}$ have no impact on the risk of PAD or VTE events, because baseline LDL-C$_{corrected}$ levels were already reduced by statin therapy in 96% of patients and intensive statin therapy in 87% of patients, and nearly all patients achieved a further, substantial reduction in LDL-C$_{corrected}$ with alirocumab. Nonetheless, the findings suggest centrality of lipoprotein(a) reduction in the efficacy of alirocumab to reduce the risk of PAD or VTE events. Patients with high versus low baseline levels of lipoprotein(a) had substantial versus minimal absolute reductions in lipoprotein(a) with alirocumab, while similar absolute reductions in LDL-C$_{corrected}$ were observed in both categories. Alirocumab reduced the risk of PAD or VTE events in the former category, but not the latter (Figure 3 and Table III in the Data Supplement). Conversely, patients with higher versus lower baseline levels of LDL-C$_{corrected}$ had larger versus smaller absolute reductions in LDL-C$_{corrected}$ with alirocumab, without an apparent gradient of relative or absolute reduction in the risk of PAD or VTE events.

The current data point to a role of lipoprotein(a) in the pathogenesis of PAD events and possibly VTE, and suggest that lipoprotein(a) reduction may be a potential approach to reduce the risk of those events, particularly in patients with a previous history of PAD. The findings are consistent with data from the FOURIER trial, which showed that the PCSK9 inhibitor evolocumab reduced the risk of major PAD events.[30] This present report complements evolving data indicating that lipoprotein(a) levels are important determinants of the risk of coronary events, even on a background of statin treatment,[36] and previous data from ODYSSEY OUTCOMES that the reduction in risk of a composite of coronary and cerebrovascular events was related to baseline lipoprotein(a) levels and their reduction with alirocumab.[32]

Our findings suggest that PCSK9 inhibitors might mitigate the risk of VTE when added to intensive statin treatment in selected patients. However, the analysis is limited by a relatively small number of patients with VTE. The JUPITER trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) provides a precedent for modification of VTE risk with a lipid-lowering intervention.[23] However, in that trial, an effect of rosuvastatin to reduce VTE did not appear to depend on LDL-C levels, rosuvastatin did not affect lipoprotein(a) levels,[37] all patients had elevated C-reactive protein at entry, and the possibility of an anti-inflammatory effect was raised. To date, a direct anti-inflammatory effect of PCSK9 inhibitors has not been identified. Defining the role of lipoprotein(a) in the pathogenesis of VTE and the potential for PCSK9 inhibitors to modify VTE risk will require further prospective investigation.

Limitations of the present analysis include the fact that PAD events and VTE were investigator-reported. Adjudication of events might have enhanced contrast between

Table 2. Hazard Ratios for PAD or VTE Events for a 1-mg/dL Reduction in Corrected LDL-C or a 1-mg/dL Reduction in Lipoprotein(a) With Alirocumab

Change Parameter	PAD Events (N=87)	VTE Events (N=33)	PAD or VTE Events (N=116)
LDL-C$_{corrected}$	1.001 (0.993–1.009)	1.001 (0.989–1.014)	1.002 (0.995–1.009)
Lipoprotein(a)	0.993 (0.982–1.003)	0.985 (0.972–0.999)*	0.991 (0.982–1.000)*

Data are hazard ratio (95% CI). Hazard ratios for major adverse cardiovascular events after Month 4 in the alirocumab group for a 1-mg/dL reduction in lipoprotein concentration between baseline and Month 4, derived from proportional hazards models adjusted for the baseline concentrations of LDL-C$_{corrected}$, lipoprotein(a), triglycerides, change in triglycerides from baseline to Month 4, age, sex, race, geographic region, body mass index, smoking history, diabetes mellitus, and time from index acute coronary syndrome to randomization. LDL-C indicates low-density lipoprotein cholesterol; LDL-C$_{corrected}$, corrected low-density lipoprotein cholesterol; PAD, peripheral artery disease; and VTE, venous thromboembolic event.

*P=0.04.

randomized treatment groups. The ODYSSEY OUTCOMES trial was not powered to detect effects of randomized treatment on PAD events or VTE; future studies could be designed specifically for this purpose. Lipoprotein(a) was measured with a mass concentration assay. Use of a molar concentration assay might have refined our findings.[38]

Conclusions

In patients with recent ACS on intensive statin treatment, the risk of PAD events is substantial, related to levels of lipoprotein(a), and is reduced with PCSK9 inhibition with alirocumab. A mechanism of this effect may be alirocumab-induced reduction of lipoprotein(a) levels. Further study is required to confirm whether the risk of VTE is related to lipoprotein(a) concentration and modified by PCSK9 inhibition.

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Supplemental Materials

Expanded Methods and Materials
Data Supplement Tables I–III
Data Supplement Figures I–III
List of ODYSSEY OUTCOMES Committee members, investigators, and contributors

REFERENCES

1. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UK, Williams LJ, Mensah GA, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet*. 2013;382:1329-1340. doi: 10.1016/S0140-6736(13)61249-0

2. Nehler MR, Duval S, Diao L, Annex BH, Hiatt WR, Rogers K, Zakharyan A, Hirsch AT. Epidemiology of peripheral arterial disease and critical limb ischemia in an insured national population. *J Vasc Surg*. 2014;60:686–95.e2. doi: 10.1016/j.jvs.2014.03.290

3. Steg PG, Bhatt DL, Wilson PW, D'Agostino R Sr, Ohman EM, Röther J, Liau CS, Hirsch AT, Mas JL, Ikeda Y, et al; REACH Registry Investigators. One-year cardiovascular event rates in outpatients with atherothrombosis. *JAMA*. 2007;297:1197–1206. doi: 10.1001/jama.297.11.1197

4. Hirsch AT, Hartman L, Town RJ, Virnig BA. National health care costs of peripheral arterial disease in the Medicare population. *Vasc Med*. 2008;13:209–215. doi: 10.1177/1358863X08089277

5. Wu A, Coresh J, Selvin E, Tanaka H, Heiss G, Hirsch AT, Jaar BG, Matsushita K. Lower extremity peripheral artery disease and quality of life among older individuals in the community. *J Am Heart Assoc*. 2017;6. pii: e004519. doi: 10.1161/JAHA.116.004519

6. Aday AW, Lawler PR, Cook NR, Ridker PM, Mora S, Pradhan AD. Lipoprotein particle profiles, standard lipids, and peripheral artery disease incidence. *Circulation*. 2018;138:2330–2341. doi: 10.1161/CIRCULATIONAHA.118.035432

7. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: a comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. *JAMA*. 2001;285:2481–2485. doi: 10.1001/jama.285.19.2481

8. Vidula H, Liu K, Criqui MH, Szklo M, Allison M, Sibley C, Ouyang P, Tracy RP, Chan C, McDermott MM. Metabolic syndrome and incident peripheral artery disease - the Multi-Ethnic Study of Atherosclerosis. *Atherosclerosis*. 2015;243:198–203. doi: 10.1016/j.atherosclerosis.2015.08.044

9. Wattanakit K, Folsom AR, Selvin E, Weatherley BD, Pankow JS, Brancati FL, Hirsch AT. Risk factors for peripheral arterial disease incidence in persons with diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. *Atherosclerosis*. 2005;180:389–397. doi: 10.1016/j.atherosclerosis.2004.11.024

10. Emanuelsson F, Nordestgaard BG, Tybjærg-Hansen A, Benn M. Impact of LDL cholesterol on microvascular versus macrovascular disease: a mendelian randomization study. *J Am Coll Cardiol*. 2019;74:1465–1476. doi: 10.1016/j.jacc.2019.07.037

11. Kennedy M, Solomon C, Manolio TA, Criqui MH, Newman AB, Polak JF, Burke GL, Enright P, Cushman M. Risk factors for declining ankle-brachial index in men and women 65 years or older: the Cardiovascular Health Study. *Arch Intern Med*. 2005;165:1896–1902. doi: 10.1001/archinte.165.16.1896

12. Tsimikas S. A test in context: lipoprotein(a): diagnosis, prognosis, controversies, and emerging therapies. *J Am Coll Cardiol*. 2017;69:692-711. doi: 10.1016/j.jacc.2016.11.042

13. Gurdasani D, Sjouke B, Tsimikas S, Hovingh GK, Luben RN, Wainwright NW, Pomilla C, Wareham NJ, Khaw KT, Boekholdt SM, et al. Lipoprotein(a) and risk of coronary, cerebrovascular, and peripheral artery disease: the EPIC-Norfolk prospective population study. *Arterioscler Thromb Vasc Biol*. 2012;32:3058–3065. doi: 10.1161/ATVBAHA.112.255521

14. Kosmas CE, Silverio D, Sourlas A, Peralta R, Montan PD, Guzman E, Garcia MJ. Role of lipoprotein (a) in peripheral arterial disease. *Ann Transl Med*. 2019;7(Suppl 6):S242. doi: 10.21037/atm.2019.08.77

15. Laschkolnig A, Kollerits B, Lamina C, Meisinger C, Rantner B, Stadler M, Peters A, Koenig W, Stöckl A, Dähnhardt D, et al. Lipoprotein (a) concentrations, apolipoprotein (a) phenotypes, and peripheral arterial disease in three independent cohorts. *Cardiovasc Res*. 2014;103:28–36. doi: 10.1093/cvr/cvu107

16. Pradhan AD, Shrivastava S, Cook NR, Rifai N, Creager MA, Ridker PM. Symptomatic peripheral arterial disease in women: nontraditional biomarkers of elevated risk. *Circulation*. 2008;117:823–831. doi: 10.1161/CIRCULATIONAHA.107.719369

17. Sartori M, Favaretto E, Legnani C, Cini M, Conti E, Amato A, Palareti G. Thrombophilic risk factors and peripheral arterial disease severity. *Thromb Haemost*. 2010;104:71–77. doi: 10.1160/TH09-11-0772

18. Cheng SW, Ting AC. Lipoprotein (a) level and mortality in patients with critical lower limb ischaemia. *Eur J Vasc Endovasc Surg*. 2001;22:124–129. doi: 10.1053/ejvs.2001.1431

19. Weiss N, Julius U. Lipoprotein(a) apheresis in patients with peripheral arterial disease: rationale and clinical results. *Clin Res Cardiol Suppl*. 2019;14(Suppl 1):39–44. doi: 10.1007/s11789-019-00097-1

20. Folsom AR, Lutsey PL, Astor BC, Cushman M. C-reactive protein and venous thromboembolism. A prospective investigation in the ARIC cohort. *Thromb Haemost*. 2009;102:615–619. doi: 10.1160/TH09-04-0274

21. Franchini M, Mannucci PM. Association between venous and arterial thrombosis: clinical implications. *Eur J Intern Med*. 2012;23:333-337. doi: 10.1016/j.ejim.2012.02.008

22. Prandoni P, Bilora F, Marchiori A, Bernardi E, Petrobelli F, Lensing AW, Prins MH, Girolami A. An association between atherosclerosis and venous thrombosis. *N Engl J Med*. 2003;348:1435–1441. doi: 10.1056/NEJMoa022157

23. Glynn RJ, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. *N Engl J Med*. 2009;360:1851–1861. doi: 10.1056/NEJMoa0900241

24. Danik JS, Buring JE, Chasman DI, Zee RY, Ridker PM, Glynn RJ. Lipoprotein(a), polymorphisms in the LPA gene, and incident venous thromboembolism among 21483 women. *J Thromb Haemost*. 2013;11:205–208. doi: 10.1111/jth.12056

25. Dentali F, Gessi V, Marcucci R, Gianni M, Grandi AM, Franchini M. Lipoprotein(a) as a risk factor for venous thromboembolism: a systematic review and meta-analysis of the literature. *Semin Thromb Hemost*. 2017;43:614–620. doi: 10.1055/s-0036-1598002

26. Sticchi E, Magi A, Kamstrup PR, Marcucci R, Prisco D, Martinelli I, Mannucci PM, Abbate R, Giusti B. Apolipoprotein(a) kringle-IV type 2 copy number variation is associated with venous thromboembolism. *PLoS One*. 2016;11:e0149427. doi: 10.1371/journal.pone.0149427

27. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. *Arch Intern Med*. 2002;162:1182–1189. doi: 10.1001/archinte.162.10.1182

28. Bonaca MP, Creager MA. Pharmacological treatment and current management of peripheral artery disease. *Circ Res*. 2015;116:1579–1598. doi: 10.1161/CIRCRESAHA.114.303505

29. Kumbhani DJ, Steg PG, Cannon CP, Eagle KA, Smith SC Jr, Goto S, Ohman EM, Elbez Y, Sritara P, Baumgartner I, et al; REACH Registry Investigators. Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: insights from the REACH registry. *Eur Heart J*. 2014;35:2864–2872. doi: 10.1093/eurheartj/ehu080

30. Bonaca MP, Nault P, Giugliano RP, Keech AC, Pineda AL, Kanevsky E, Kuder J, Murphy SA, Jukema JW, Lewis BS, et al. Low-density lipoprotein cholesterol lowering with evolocumab and outcomes in patients with peripheral artery disease: insights from the FOURIER trial (Further

Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). *Circulation*. 2018;137:338-350. doi: 10.1161/CIRCULATIONAHA.117.032235

31. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, Harrington RA, et al; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379:2097–2107. doi: 10.1056/NEJMoa1801174

32. Bittner VA, Szarek M, Aylward PE, Bhatt DL, Diaz R, Edelberg JM, Fras Z, Goodman SG, Halvorsen S, Hanotin C, et al; ODYSSEY OUTCOMES Committees and Investigators. Effect of alirocumab on lipoprotein(a) and cardiovascular risk after acute coronary syndrome. *J Am Coll Cardiol*. 2020;75:133–144. doi: 10.1016/j.jacc.2019.10.057

33. Jukema JW, Szarek M, Zijlstra LE, de Silva HA, Bhatt DL, Bittner VA, Diaz R, Edelberg JM, Goodman SG, Hanotin C, et al; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab in patients with polyvascular disease and recent acute coronary syndrome: ODYSSEY OUTCOMES trial. *J Am Coll Cardiol*. 2019;74:1167–1176. doi: 10.1016/j.jacc.2019.03.013

34. Schwartz GG, Bessac L, Berdan LG, Bhatt DL, Bittner V, Diaz R, Goodman SG, Hanotin C, Harrington RA, Jukema JW, 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;168:682–689. doi: 10.1016/j.ahj.2014.07.028

35. Dahlen GH. Incidence of Lp(a) Among Populations. In: Scanu AM, ed. *Lipoprotein(a)*. San Diego: Academic Press; 1990:151–173.

36. Willeit P, Ridker PM, Nestel PJ, Simes J, Tonkin AM, Pedersen TR, Schwartz GG, Olsson AG, Colhoun HM, Kronenberg F, et al. Baseline and on-statin treatment lipoprotein(a) levels for prediction of cardiovascular events: individual patient-data meta-analysis of statin outcome trials. *Lancet*. 2018;392:1311–1320. doi: 10.1016/S0140-6736(18)31652-0

37. Khera AV, Everett BM, Caulfield MP, Hantash FM, Wohlgemuth J, Ridker PM, Mora S. Lipoprotein(a) concentrations, rosuvastatin therapy, and residual vascular risk: an analysis from the JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). *Circulation*. 2014;129:635–642. doi: 10.1161/CIRCULATIONAHA.113.004406

38. Tsimikas S, Fazio S, Ferdinand KC, Ginsberg HN, Koschinsky ML, Marcovina SM, Moriarty PM, Rader DJ, Remaley AT, Reyes-Soffer G, et al. NHLBI working group recommendations to reduce lipoprotein(a)-mediated risk of cardiovascular disease and aortic stenosis. *J Am Coll Cardiol*. 2018;71:177–192. doi: 10.1016/j.jacc.2017.11.014

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