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

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. Lipoprotein(a), a low-density lipoprotein whose levels are primarily under genetic control, has atherogenic, proinflammatory, and thrombogenic properties. Most observational cohort studies indicate an association of elevated lipoprotein(a) with incident PAD. In addition, the progression of chronic obstructive PAD to critical limb ischemia is influenced by thrombophilic factors, possibly including levels of lipoprotein(a).

Venous thromboembolism (VTE) and PAD events may share common pathophysiology related to thrombophilia and inflammation. VTE does not appear to be associated with levels of LDL-C. However, there are conflicting data regarding an association of VTE with concentration or genetic variants of lipoprotein(a). Statins reduce levels of LDL-C and triglycerides but not lipoprotein(a). Statins also improve exercise capacity in patients with PAD. Although observational data suggest that statins may reduce major adverse limb events including critical limb ischemia, revascularization, and amputation, 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.

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. 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. 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), and with a particularly pronounced benefit for this outcome in patients with PAD. 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. 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 18924 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 immunoturbidimetric 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 Dahlen35 to calculate LDL-C\(_{\text{corrected}}\) as measured LDL-C – [0.3 x 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\(_{\text{corrected}}\) and lipoprotein(a). The risk of PAD events was significantly related to baseline quartile of lipoprotein(a) \((P_{\text{trend}}=0.0021)\). 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\(_{\text{corrected}}\) \((P_{\text{trend}}=0.06)\) 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 \((P_{\text{trend}}=0.22)\) and without association with baseline quartile of LDL-C\(_{\text{corrected}}\) \((P_{\text{trend}}=0.85)\). HRs in quartile 4/quartile 1 of lipoprotein(a) and LDL-C\(_{\text{corrected}}\) 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) \((P_{\text{trend}}=0.009)\) and tended to associate with baseline quartile of LDL-C\(_{\text{corrected}}\) \((P_{\text{trend}}=0.06)\).

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\(_{\text{corrected}}\) 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\(_{\text{corrected}}\) with risk of PAD events \((P_{\text{trend}}=0.21)\). However, among patients with baseline lipoprotein(a) at or above the median there was an association of baseline quartile of LDL-C\(_{\text{corrected}}\) with risk of PAD events \((P_{\text{trend}}=0.04)\).

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

### 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\(_{\text{corrected}}\) 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\(_{\text{corrected}}\) and lipoprotein(a). The risk of PAD events was significantly related to the baseline quartile of lipoprotein(a) \((P_{\text{trend}}=0.0021)\). 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\(_{\text{corrected}}\) \((P_{\text{trend}}=0.06)\) 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 \((P_{\text{trend}}=0.22)\) and without association with baseline quartile of LDL-C\(_{\text{corrected}}\) \((P_{\text{trend}}=0.85)\). HRs in quartile 4/quartile 1 of lipoprotein(a) and LDL-C\(_{\text{corrected}}\) 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) \((P_{\text{trend}}=0.009)\) and tended to associate with baseline quartile of LDL-C\(_{\text{corrected}}\) \((P_{\text{trend}}=0.06)\).
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, Pinteraction=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-Ccorrected 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-Ccorrected from baseline to Month 4 increased across baseline quartiles of LDL-Ccorrected 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-Ccorrected. 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-Ccorrected (Figure 3). There was no evidence for a gradient of the relative treatment effect of alirocumab on PAD events across baseline quartiles of LDL-Ccorrected (Pinteraction=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 Pinteraction=0.03. Correspondingly, the absolute reduction in the risk of PAD events was nil in quartile 1 of lipoprotein(a) to risk of PAD events in each stratum. There were 61 PAD events among patients with baseline LDL-Ccorrected below the median and 84 PAD events among patients with baseline LDL-Ccorrected 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 (Pinteraction=0.50). However, among patients with baseline LDL-Ccorrected at or above the median there was an association of baseline quartile of lipoprotein(a) with risk of PAD events (Pinteraction=0.0026).

**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-Ccorrected                       | 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-Ccorrected, 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.
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...
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$_{\text{corrected}}$, 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$_{\text{corrected}}$ 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$_{\text{corrected}}$. 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.\(^\text{30}\) 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...
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. 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, 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.

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. 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, 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
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.

ARTICLE INFORMATION

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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<sub>corrected</sub> | 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<sub>corrected</sub>, 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<sub>corrected</sub> indicates low-density lipoprotein cholesterol; PAD, peripheral artery disease; and VTE, venous thromboembolic event.

*P=0.04.

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Disclosures

Dr Schwartz reports research grants to the University of Colorado from Resverlogix, Roche, Sanofi, and The Medicines Company. In addition, Dr Schwartz is co-inventor of pending US patent 62/860313 “Methods for Reducing Cardiovascular Risk,” assigned in full to University of Colorado. Dr Steg reports grants and nonfinancial support (cochair of the ODYSSEY OUTCOMES trial (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab)); as such he received no personal fees, but his institution has received funding for the time he has devoted to trial coordination, and he has received support for some travel related to trial management (not funded from Sanofi-Aventis, Astellas, or Astra Zeneca). Dr Pordy reports research grants to his institution from AstraZeneca, Myokardia, Familial Hypercholesterolemia Foundation, and Bayer; and consulting honoraria (eg, advisory boards) from: Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Pfizer, Novartis, Regeneron Pharmaceuticals, Lilly, and AstraZeneca. Dr Steg also has a European application number/patent number, issued on October 26, 2016 (No. 15712241.7), for a method for reducing cardiovascular risk. Dr Szarek reports serving as a consultant or on ad visory boards (or both) for: Civi, Reversologix, Baxter, Esperion, and Regeneron Pharmaceuticals. Dr Bittner reports research grant support from Sanofi, Astra Zeneca, Daiichi-Sankyo, Bayer, and Agenon; paid direct to her institution; and speaker fees from Agenon; and a research grant from The Medicines Company. Dr Díaz reports research grants from Sanofi, DaiCor Pharmaceuticals, Population Health Research Institute, Duke Clinical Research Institute, the TIMI group, Amgen, Cirus, Montreal Health Innovations Coordinating Center and Lepetit and personal fees, as a member of the Executive Steering Committee, from Amgen and Cirus; and speaker fees from Eli Lilly. Dr Goodman reports research grant support (eg, steering committee or data monitoring committee) and speaker fees from Agenon, Bristol Myers Squibb, Boehringer Ingelheim, Pfizer, Novartis, Regeneron Pharmaceuticals, Lilly, and AstraZeneca. Dr Pordy is an employee of Regeneron Pharmaceuticals, and has personal fees from Amgen, Bristol Myers Squibb, CSL Behring, Daichi-Sankyo/American Regent, Eli Lilly, Esperion, Ferring Pharmaceuticals, GlaxoSmithKline, HLS Therapeutics, JanssenJohnson & Johnson, Merck, Novartis, Novo Nordisk A/C, Pfizer, Regeneron, Sanofi, Servier, and salary support from the Heart and Stroke Foundation of Ontario.University of Toronto (Polo) Chair, Canadian Heart Research Center and MD Primer, Canadian VIGOUR Center, Duke Clinical Research Institute, New York University Clinical Coordinating Center, and PERFUSE. Dr Kim is an employee of Sanofi. Dr Jukema reports research grants from the Netherlands Heart Foundation, the Interuniversity Cardiology Institute of the Netherlands, and the European Commission Seventh Framework Program; and research support from Amgen, Astellas, AstraZeneca, Daichi-Sankyo, Lilly, Merck-Schering-Plow, Pfizer, Roche, and Sanofi. Dr Poty is an employee of Regeneron Pharmaceuticals, Inc. Dr Roe reports research grant funding from Sanofi-Aventis, AstraZeneca, Patient Centered Outcomes Research Institute, Ferring Pharmaceuticals, Myokardia, Familial Hypercholesterolemia Foundation, and Bayer; and consultant or honoraria from AstraZeneca, Amgen, Cytokinetics, Eli Lilly, Roche-Genentech, Janssen Pharmaceuticals, Regeneron, Novo Nordisk, Pfizer, Sanofi-Aventis, Signal Path, and Elsevier Publishers. All conflicts of interest are listed at https://www.dcn.org/about-us/conflict-of-interest. Dr White reports receiving grant support paid to the institution and fees for serving on a steering committee for the ODYSSEY OUTCOMES trial from Sanofi-Aventis and Regeneron Pharmaceuticals, for the ACCELERATE study (A Study of Evacetrapib in High-Risk Vascular

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Role of Lipoprotein(a) in PAD and VTE After ACS

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