REPLY: alirocumab in polyvascular atherosclerotic disease

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We appreciate the comments by Dr. Alkhalil on our paper (1). Measurement of plaque burden might provide information that would complement levels of circulating biomarkers, including low-density lipoprotein cholesterol (LDL-C), to identify subsets of patients who derive particular benefit from alirocumab treatment. Although LDL-C reduction and regression or slowed progression of coronary atheroma volume have been closely linked in prior investigations (e.g., REVERSAL [Reversal of Atherosclerosis with Aggressive Lipid Lowering], SATURN [Sequential Tarceva in Unresectable NSCLC], GLAGOV [GLobal Assessment of Plaque reGression With a PCSK9 antibOdy as Measured by intraVascular Ultrasound]) (2), it is not established whether vascular imaging should guide therapy with PCSK9 inhibitors.

Although most patients in ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) underwent coronary angiography and 72% underwent percutaneous coronary intervention or coronary bypass surgery for the qualifying acute coronary syndrome, systematic collection of angiographic data accumulated before randomization was not possible in this large, multicenter, multinational trial. Therefore, we cannot determine whether the burden of coronary artery disease predicted the therapeutic benefit of alirocumab. It is possible that other imaging techniques that assess volume, virtual histology, or inflammatory characteristics of atherosclerotic plaque (3) might contribute in that regard, but such hypotheses remain to be tested. Moreover, application of vascular imaging techniques may be limited by invasiveness, sensitivity, cost, availability, or ease of implementation in daily clinical practice.

Risk stratification to guide optimal application of therapies in atherosclerosis is most often based on levels of lipid and inflammatory biomarkers and readily identified clinical features. The latter include diabetes, a history of coronary bypass grafting, or in the case of our analysis, polyvascular disease. Subanalyses of ODYSSEY OUTCOMES show that the presence of such high-risk characteristics is associated with absolute benefit of PCSK9 inhibition with alirocumab, when added to high-intensity statin therapy (1,4,5).

An important future research objective would be to determine whether vascular imaging adds further prognostic information that helps to predict the clinical benefit of PCSK9 inhibitor treatment.

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