

# Alirocumab in the Treatment of Hypercholesterolemia

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**ABSTRACT:** The role of low-density lipoprotein cholesterol (LDL-C) in the pathophysiology of atherosclerosis is well recognized, and statin therapy represents the standard of care for LDL-C lowering and reduction of cardiovascular risk. However, many patients fail to achieve LDL-C goals, whereas others are intolerant to statins due to side effects. Unfortunately, until recently, the efficacy of other nonstatin LDL-C-lowering agents was limited, achieving an LDL-C reduction of no more than 20%. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors represent a new class of LDL-lowering agents, producing large reductions in LDL-C. Alirocumab is a PCSK9 inhibitor, which was recently approved by the Food and Drug Administration as an adjunct to diet and maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-C levels. This review aims to provide the current clinical and scientific data pertaining to the treatment of hypercholesterolemia with alirocumab.

**KEYWORDS:** Hypercholesterolemia, LDL receptors, statins, PCSK9 inhibitors, alirocumab

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## Introduction

The role of low-density lipoprotein cholesterol (LDL-C) in the pathophysiology of atherosclerosis is well recognized, and statin therapy represents the standard of care for LDL-C lowering and reduction of cardiovascular risk. However, in many cases, patients fail to achieve LDL-C goals. Until recently, only 20% to 26% of high-risk patients treated with statin monotherapy for >90 days had LDL-C <70 mg/dL and 67% to 77% had LDL-C <100 mg/dL. The percentages of patients who attained both LDL-C goals and non-high-density lipoprotein cholesterol (HDL-C) goals were quantitatively smaller (13.5% to 19.0% and 46% to 70%, respectively).<sup>1</sup> However, many patients are intolerant to statins due to side effects, mostly myalgia and weakness, especially at high statin doses. Other more recently identified side effects, such as an increased risk of diabetes mellitus, particularly at higher doses, as well as reports of potential statin-induced memory loss, have prompted the Food and Drug Administration (FDA) to mandate additional safety-labeling warnings. However, until recently, the efficacy of other nonstatin LDL-C-lowering drugs was limited, achieving an LDL-C reduction of no more than 20%. More specifically, extended-release niacin has been reported to lower LDL-C by up to 17%. Fenofibrate has been reported to lower LDL-C levels by approximately 20%, although it may actually increase LDL-C levels in patients with hypertriglyceridemia.

Furthermore, ezetimibe, an intestinal cholesterol absorption inhibitor, and colestevlam, a bile acid sequestrant, have been reported to lower LDL-C by up to 18%. Thus, extensive research is being conducted to identify new LDL-C-lowering agents with an acceptable side effect profile, which, used alone or in combination with statins, would improve our ability to achieve LDL-C goals and reduce cardiovascular risk.<sup>2</sup>

## Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitors

Proprotein convertase subtilisin/kexin type 9 is a serine protease, mainly expressed in the liver and also in the intestine and kidneys, located in the human chromosome 1p32.3 that encodes a 692-amino-acid inactive glycoprotein, which undergoes an intramolecular autocatalytic cleavage in the endoplasmic reticulum.<sup>3</sup> It promotes the degradation of LDL receptors (LDLR) by reducing their recycling and targeting the receptors for lysosomal destruction, thus decreasing the rate of removal of LDL-C from circulation.<sup>4–8</sup> More specifically, PCSK9 binds to the LDLR at the cell surface with the catalytic domain of PCSK9 binding to the epidermal growth factor repeat A of the LDLR. The LDLR:PCSK9 complex is then internalized through clathrin-mediated endocytosis. Owing to an additional electrostatic interaction at acidic pH between the

C-terminal domain of PCSK9 and the ligand-binding domain of the LDLR, PCSK9 remains bound to the LDLR in the sorting endosome. Consequently, the LDLR fails to adopt a closed conformation and is degraded instead of being recycled. The mechanism responsible for the failure of the LDLR to recycle appears to involve ectodomain cleavage of the extended LDLR by a cysteine cathepsin in the sorting endosome. The cleaved LDLR ectodomain remains confined in the vesicular part of the sorting endosome for eventual degradation via the endosomal/lysosomal system.<sup>4</sup> However, interacting partners of PCSK9 have also been found in plasma that may influence its versatility, concentration, and function and modulate its action. Plasma lipoproteins act as important extracellular partners for PCSK9, and PCSK9-LDL complexes have been found in both mouse and human plasma. Aside from LDL, PCSK9 may have other interacting partners in plasma that can modulate its activity. Resistin is a small protein, secreted by human macrophages and murine adipocytes, that increases PCSK9 expression in liver cells. Resistin levels are increased in obesity, may contribute to insulin resistance and inflammation in patients with metabolic syndrome, and are highly correlated with atherosclerotic cardiovascular diseases in humans.<sup>9</sup>

Genetic studies have shown that gain-of-function mutations of PCSK9 in humans result in hypercholesterolemia,<sup>10,11</sup> whereas loss-of-function mutations are associated with low LDL-C and diminished cardiovascular risk.<sup>12</sup> Ironically, statins upregulate PCSK9 with consequent attenuation of their LDL-C-lowering effect.<sup>13</sup> Thus, inhibition of PCSK9 represents an attractive target to enhance the lipid-lowering effect of statins.<sup>2</sup> Furthermore, PCSK9 inhibition may also have other beneficial effects beyond plain lipid lowering as there are also data to support the hypothesis that reduced PCSK9 function increases pathogen lipid clearance via the LDLR and thereby decreases the inflammatory response and improves outcomes in sepsis in both mice and humans.<sup>14</sup> So far, several therapeutic strategies have been developed to reduce circulating PCSK9; however, monoclonal antibodies have emerged as the new class of drugs that very effectively lower LDL-C levels, as well as levels of other apolipoprotein B (apoB)-containing lipoproteins, such as lipoprotein(a).<sup>15,16</sup> During the time of this writing, 2 PCSK9 inhibitors, alirocumab and evolocumab, have been approved by the US FDA as an adjunct to diet and maximally tolerated statin therapy for treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-C levels, as well as for treatment of adults with homozygous familial hypercholesterolemia, as an adjunct to diet and on top of other LDL-lowering therapies (eg, statins, ezetimibe, LDL apheresis) when additional LDL lowering is required.

### Alirocumab

As it is mentioned above, alirocumab is a human monoclonal antibody that binds to PCSK9 and effectively lowers LDL-C levels.

The Long-Term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled With Their Lipid Modifying Therapy (ODYSSEY LONG TERM) was a double-blind, randomized, controlled trial of alirocumab (150 mg subcutaneously every 2 weeks) versus placebo for 78 weeks in 2341 patients at high risk of cardiovascular events, who were already receiving the maximum tolerated doses of statins.<sup>17</sup>

In the ODYSSEY LONG TERM trial, the PCSK9 inhibitor alirocumab, administered on top of maximally tolerated statin therapy, with or without treatment with other lipid-lowering drugs, caused an additional 61.9% reduction in LDL-C levels, as compared with placebo. At week 24, 79.3% of the patients treated with alirocumab, but only 8.0% of the patients in the placebo group, achieved an LDL-C level <70 mg/dL ( $P < .001$ ). This effect of alirocumab on LDL-C reduction was consistent from week 4 to week 78 of the trial and was similar in patients with or without heterozygous familial hypercholesterolemia. Furthermore, alirocumab, as compared with placebo, reduced levels of non-HDL-C by 52.3%, apoB by 54%, total cholesterol by 37.5%, lipoprotein(a) by 25.6%, and fasting triglycerides by 17.3%. However, alirocumab, as compared with placebo, increased levels of HDL-C by 4.6% and apolipoprotein A1 by 2.9%.<sup>17</sup>

With respect to specific adverse events, the alirocumab group had higher rates than the placebo group of injection-site reactions (5.9% vs 4.2%), myalgia (5.4% vs 2.9%), neurocognitive events (1.2% vs 0.5%), and ophthalmologic events (2.9% vs 1.9%).<sup>17</sup> In general, however, the incidence of side effects of alirocumab seems to be low and mainly limited to nasopharyngitis, injection-site reactions, upper respiratory tract infections, and influenza and back pain.<sup>18</sup>

In a post hoc analysis, alirocumab, as compared with placebo, reduced the rate of major adverse cardiovascular events (MACE) (death from coronary heart disease [CHD], nonfatal myocardial infarction [MI], fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) by 48% (1.7% vs 3.3%; 95% confidence interval [CI], 0.31-0.90; nominal  $P = .02$ ).<sup>17</sup> In another very recent post hoc analysis from 10 ODYSSEY trials, greater percentage reductions in LDL-C and lower on-treatment LDL-C levels were associated with a lower incidence of MACE, including very low levels of LDL-C (<50 mg/dL). More specifically, for every 39 mg/dL lower achieved LDL-C, the risk of MACE appeared to be 24% lower (adjusted hazard ratio [HR]: 0.76; 95% CI: 0.63-0.91;  $P = .0025$ ). Percent reductions in LDL-C from baseline were inversely correlated with MACE rates (HR: 0.71 [0.57-0.89] per additional 50% reduction from baseline;  $P = .003$ ).<sup>19</sup> Again, it has to be noted that these reported beneficial results of alirocumab on cardiovascular outcomes should be interpreted with caution because these aforementioned studies are post hoc analyses and were not designed to look at outcomes.

Alirocumab was also proven to be effective in patients with statin intolerance, achieving greater LDL-C reductions, as

**Table 1.** List of trials included in this review and assessing the efficacy and safety of alirocumab therapy in patients with hypercholesterolemia.

STUDY	DESIGN	PARTICIPANTS	INTERVENTION	RESULTS
ODYSSEY LONG TERM trial <sup>17</sup>	Phase 3, randomized, double-blind, placebo-controlled parallel group	2341 patients at high risk of CVD with LDL >70 mg/dL on maximally tolerated dose of statin with or without other lipid-lowering therapy	Alirocumab 150 mg SC every 2 weeks for 78 weeks vs placebo	Alirocumab caused a decrease in the mean percentage change from baseline in calculated LDL by 62% vs placebo Side effects: (alirocumab vs placebo) Injection-site reactions: 5.9% vs 4.2% Myalgia: 5.4% vs 2.9% Neurocognitive events: 1.2% vs 0.5% Ophthalmologic events: 2.9% vs 1.9%
ODYSSEY LONG TERM trial <sup>17</sup>	Post hoc analysis	2341 patients at high risk of CVD with LDL >70 mg/dL on maximally tolerated dose of statin with or without other lipid-lowering therapy	Alirocumab 150 mg SC every 2 weeks for 78 weeks vs placebo	Major adverse CV events (alirocumab vs placebo): 1.7% vs 3.3% (HR: 0.52; <i>P</i> = .02)
Ray et al <sup>19</sup>	Post hoc analysis	4974 patients (3182 taking alirocumab, 1174 placebo, 618 ezetimibe) (Pooled data from 10 ODYSSEY double-blind trials—6699 patient-years of follow-up)	Alirocumab 75/150 mg every 2 weeks or control for 24 to 104 weeks, added to background statin therapy in 8 trials	For every 39-mg/dL lower achieved LDL-C, the risk of MACE appeared to be 24% lower (HR: 0.76; <i>P</i> = .0025) Percent reductions in LDL-C from baseline were inversely correlated with MACE rates (HR: 0.71 per additional 50% reduction from baseline; <i>P</i> = .003)
ODYSSEY ALTERNATIVE trial <sup>20</sup>	Randomized, double-blind, double-dummy, active-controlled parallel group	361 patients with primary hypercholesterolemia and well-documented statin intolerance 63 of those patients were rechallenged with atorvastatin	Alirocumab vs ezetimibe	Alirocumab reduced mean LDL-C by 45.0% vs 14.6% with ezetimibe (mean difference 30.4%; <i>P</i> < .0001) Skeletal muscle-related events were less frequent in the group of patients treated with alirocumab, as compared with the group of patients who were rechallenged with atorvastatin (HR: 0.61; <i>P</i> = .042)
ODYSSEY CHOICE I trial <sup>24</sup>	Phase 3, randomized, double-blind, placebo-controlled	803 patients with hypercholesterolemia at moderate to very high cardiovascular risk	Alirocumab (as monotherapy or add-on to statin therapy) 300 mg Q4W, 75 mg Q2W or placebo for 48 weeks, with dose adjustment for either alirocumab arm to 150 mg Q2W at week 12, depending on cardiovascular risk or LDL-C reduction at week 8	Treatment with alirocumab 300 mg every 4 weeks led to an LDL-C reduction in 52.7%, when alirocumab was given as monotherapy, and to an LDL-C reduction in 58.8%, when alirocumab was given as add-on to statin therapy
ODYSSEY CHOICE II trial <sup>25</sup>	Phase 3, randomized, double-blind, placebo-controlled	233 patients with hypercholesterolemia, not on statin therapy, receiving fenofibrate or ezetimibe or diet alone	Placebo, alirocumab 150 mg Q4W or 75 mg Q2W with dose adjustment to 150 mg Q2W at week 12 if predefined LDL-C target levels were not met at week 8	In the alirocumab 150 mg Q4W and 75 mg Q2W groups, least-squares mean LDL-C change from baseline to week 24 was -51.7% and -53.5%, respectively (placebo [+4.7%]); both groups <i>P</i> < .0001 vs placebo) Alirocumab 150 mg Q4W can be considered in patients not on statin with inadequately controlled hypercholesterolemia as a convenient option for lowering LDL-C
ODYSSEY Outcomes trial <sup>26</sup>	Randomized, double-blind, placebo-controlled parallel group	Estimated enrollment of 18 600 patients who have experienced an ACS event 4 to 52 weeks prior to randomization and are treated with evidence-based medical and dietary management of dyslipidemia	Alirocumab vs placebo	The study is ongoing and will compare the effect of alirocumab with placebo on the occurrence of cardiovascular events (composite endpoint of coronary heart disease death, nonfatal myocardial infarction, fatal and nonfatal ischemic stroke, unstable angina requiring hospitalization)

Abbreviations: ACS, acute coronary syndrome; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; ODYSSEY LONG TERM, Long-Term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled With Their Lipid Modifying Therapy; Q2W, every 2 weeks; Q4W, every 4 weeks; SC, subcutaneous; ODYSSEY ALTERNATIVE, Study of Alirocumab in Patients With Primary Hypercholesterolemia and Moderate, High, or Very High Cardiovascular (CV) Risk, Who Are Intolerant to Statins; ODYSSEY CHOICE I, Study to Evaluate the Efficacy and Safety of an Every Four Weeks Treatment Regimen of Alirocumab in Patients With Primary Hypercholesterolemia; ODYSSEY CHOICE II, Phase III Study To Evaluate Alirocumab in Patients With Hypercholesterolemia Not Treated With a Statin.

compared with ezetimibe. More specifically, alirocumab reduced mean LDL-C by 45.0% vs 14.6% with ezetimibe (mean difference: 30.4%;  $P < .0001$ ). Skeletal muscle-related events were less frequent in the group of patients treated with alirocumab, as compared with a group of patients who were rechallenged with atorvastatin (HR: 0.61,  $P = .042$ ).<sup>20</sup>

The significant LDL-C reduction attained with alirocumab may reduce or even obviate the need for lipoprotein apheresis in certain patients with familial hypercholesterolemia. In one study, lipoprotein apheresis was discontinued in 63.4% of patients with heterozygous familial hypercholesterolemia on alirocumab who were previously undergoing regular apheresis, and the rate was at least halved in 92.7% of patients.<sup>21</sup> It has also been reported that the significant and persistent LDL-C reduction achieved during treatment with alirocumab may lead to regression and rapid resolution of xanthelasmas in patients with familial hypercholesterolemia.<sup>22</sup>

The recommended starting dose of alirocumab is 75 mg administered subcutaneously once every 2 weeks. If the LDL-C response is inadequate, the dosage may be increased to the maximum dosage of 150 mg administered every 2 weeks.<sup>23</sup> However, monthly regimens of alirocumab administration have also been studied and proven effective. In the Study to Evaluate the Efficacy and Safety of an Every Four Weeks Treatment Regimen of Alirocumab in Patients With Primary Hypercholesterolemia (ODYSSEY CHOICE 1) trial,<sup>24</sup> treatment with alirocumab 300 mg every 4 weeks led to an LDL-C reduction of 52.7%, when alirocumab was given as monotherapy, and to an LDL-C reduction of 58.8%, when alirocumab was given as add-on to statin therapy. In the Phase III Study To Evaluate Alirocumab in Patients With Hypercholesterolemia Not Treated With a Statin (ODYSSEY CHOICE II) trial,<sup>25</sup> it was shown that alirocumab 150 mg every 4 weeks could also be considered in patients not on statin with inadequately controlled hypercholesterolemia as a convenient option for lowering LDL-C.

### Conclusions and Future Directions

From the above review of the clinical data, it becomes apparent that alirocumab, a PCSK9 inhibitor, used as monotherapy or on top of statins and other lipid-lowering agents, very effectively lowers LDL-C levels, as well as levels of all other apoB-containing lipoproteins, including lipoprotein(a), with an acceptable side effect profile. In addition, post hoc analyses appear promising regarding the effect of alirocumab on the reduction of cardiovascular risk. Nevertheless, the effect of alirocumab (and PCSK9 inhibitors in general) on cardiovascular morbidity and mortality has not been determined so far with large, prospective, randomized trials. However, the results of a large, ongoing outcome trial with alirocumab (ODYSSEY Outcomes: Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab)<sup>26</sup> are eagerly awaited and are expected to provide invaluable data regarding the true clinical benefits

of alirocumab in the reduction of cardiovascular risk. This trial is expected to enroll 18 600 patients and will compare the effect of alirocumab versus placebo on the rate of cardiovascular events (CHD death, nonfatal MI, fatal and nonfatal ischemic stroke, unstable angina requiring hospitalization) in patients who had suffered an acute coronary syndrome (ACS) event 4 to 52 weeks prior to randomization and are being treated with modern, standard of care, evidence-based medical therapy, as well as dietary management of dyslipidemia. The results of this trial will likely be available in late 2017 or in the first quarter of 2018.

A summary of the list of trials included in this review and assessing the efficacy and safety of alirocumab therapy in patients with hypercholesterolemia is shown on Table 1.

### Author Contributions

Conceived the concepts: CEK. Analyzed the data: CEK. Wrote the first draft of the manuscript: CA and CEK. Contributed to the writing of the manuscript: EDJ, DR, CT, TJV, EG. Agree with manuscript results and conclusions: CEK, CA, EDJ, DR, CT, TJV, EG. Jointly developed the structure and arguments for the paper: CEK. Made critical revisions and approved final version: CEK. All authors reviewed and approved the final manuscript.

### REFERENCES

- Jones PH, Nair R, Thakker KM. Prevalence of dyslipidemia and lipid goal attainment in statin-treated subjects from 3 data sources: a retrospective analysis. *J Am Heart Assoc.* 2012;1:e001800.
- Kosmas CE, Frishman WH. New and emerging LDL cholesterol-lowering drugs. *Am J Ther.* 2015;22:234–241.
- Seidah NG, Prat A. The biology and therapeutic targeting of the proprotein convertases. *Nat Rev Drug Discov.* 2012;11:367–383.
- Leren TP. Sorting an LDL receptor with bound PCSK9 to intracellular degradation. *Atherosclerosis.* 2014;237:76–81.
- Lambert G, Charlton F, Rye KA, Piper DE. Molecular basis of PCSK9 function. *Atherosclerosis.* 2009;203:1–7.
- Qian YW, Schmidt RJ, Zhang Y, et al. Secreted PCSK9 downregulates low density lipoprotein receptor through receptor-mediated endocytosis. *J Lipid Res.* 2007;48:1488–1498.
- Weinreich M, Frishman WH. Antihyperlipidemic therapies targeting PCSK9. *Cardiol Rev.* 2014;22:140–146.
- Kosmas CE, DeJesus E. Proprotein convertase subtilisin/kexin type 9 inhibitors: an emerging chapter in the field of clinical lipidology. *Enliven: Clin Cardiol Res.* 2015;2:e1.
- Tavori H, Rashid S, Fazio S. On the function and homeostasis of PCSK9: reciprocal interaction with LDLR and additional lipid effects. *Atherosclerosis.* 2015;238:264–270.
- Abifadel M, Varret M, Rabès JP, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet.* 2003;34:154–156.
- Leren TP. Mutations in the PCSK9 gene in Norwegian subjects with autosomal dominant hypercholesterolemia. *Clin Genet.* 2004;65:419–422.
- Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. *N Engl J Med.* 2006;354:1264–1272.
- Dubuc G, Chamberland A, Wassef H, et al. Statins upregulate PCSK9, the gene encoding the proprotein convertase neural apoptosis-regulated convertase-1 implicated in familial hypercholesterolemia. *Arterioscler Thromb Vasc Biol.* 2004;24:1454–1459.
- Walley KR, Thain KR, Russell JA, et al. PCSK9 is a critical regulator of the innate immune response and septic shock outcome. *Sci Transl Med.* 2014;6:258ra143.
- Norata GD, Ballantyne CM, Catapano AL. New therapeutic principles in dyslipidaemia: focus on LDL and Lp(a) lowering drugs. *Eur Heart J.* 2013;34:1783–1789.

16. Stein EA, Raal FJ. New therapies for reducing low-density lipoprotein cholesterol. *Endocrinol Metab Clin North Am.* 2014;43:1007–1033.
17. Robinson JG, Farnier M, Krempf M, et al; ODYSSEY LONG TERM Investigators. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med.* 2015;372:1489–1499.
18. Farnier M, Gaudet D, Valcheva V, et al. Efficacy of alirocumab in high cardiovascular risk populations with or without heterozygous familial hypercholesterolemia: pooled analysis of eight ODYSSEY Phase 3 clinical program trials. *Int J Cardiol.* 2016;223:750–757.
19. Ray KK, Ginsberg HN, Davidson MH, et al. Reductions in atherogenic lipids and major cardiovascular events: a pooled analysis of 10 ODYSSEY Trials Comparing Alirocumab to Control. *Circulation.* 2016;134:1931–1943.
20. Moriarty PM, Thompson PD, Cannon CP, et al; ODYSSEY ALTERNATIVE Investigators. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: the ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol.* 2015;9:758–769.
21. Moriarty PM, Parhofer KG, Babirak SP, et al. Alirocumab in patients with heterozygous familial hypercholesterolaemia undergoing lipoprotein apheresis: the ODYSSEY ESCAPE trial [published online ahead of print August 29, 2016]. *Eur Heart J.* doi:10.1093/eurheartj/ehw388
22. Civeira F, Perez-Calahorra S, Mateo-Gallego R. Rapid resolution of xanthelasma after treatment with alirocumab. *J Clin Lipidol.* 2016;10:1259–1261.
23. *Praluent (Alirocumab Injection) Prescribing Information.* Bridgewater, NJ: Sanofi-Aventis U.S., <http://products.sanofi.us/praluent/praluent.pdf>. Published July, 2015.
24. Roth EM, Moriarty PM, Bergeron J, et al; ODYSSEY CHOICE I investigators. A phase III randomized trial evaluating alirocumab 300 mg every 4 weeks as monotherapy or add-on to statin: ODYSSEY CHOICE I. *Atherosclerosis.* 2016;254:254–262.
25. Stroes E, Guyton JR, Lepor N, et al; ODYSSEY CHOICE II Investigators. Efficacy and safety of alirocumab 150 mg every 4 weeks in patients with hypercholesterolemia not on statin therapy: the ODYSSEY CHOICE II Study. *J Am Heart Assoc.* 2016;5:e.003421.
26. ODYSSEY Outcomes. Evaluation of cardiovascular outcomes after an acute coronary syndrome during treatment with alirocumab. ClinicalTrials.gov Identifier: NCT01663402. <https://clinicaltrials.gov/ct2/show/NCT01663402>.