Therapeutic Class Overview
Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors

Therapeutic Class Overview/Summary:
Praluent® (alirocumab) and Repatha® (evolocumab) are Food and Drug Administration (FDA)-approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).[1,2] Evolocumab is also indicated as an adjunct to diet and other lipid lowering therapies (statins, ezetimibe, LDL-C apheresis) in patients with homozygous familial hypercholesterolemia (HoFH).[2] Proprotein convertase subtilisin kexin 9 (PCSK9) is a serine protease produced predominantly in the liver that leads to the degradation of hepatocyte LDL receptors and increased LDL-C levels. These agents work by inhibiting the action of this enzyme leading to a decrease in LDL-C levels.[1,2]

Although both agents have demonstrated a benefit in reducing various measures of cholesterol, the extent of benefit on cardiovascular morbidity and mortality has not been determined. In addition, both were only approved as adjunctive therapy to maximally-dosed statin therapy, not in statin intolerant patients.[1,2] Currently available consensus treatment guidelines do not address the place in therapy of PCSK9 inhibitors. The 2013 consensus guidelines from the American Heart Association (AHA)/American College of Cardiology (ACC) emphasize the use of statin therapy with intensity stratified by risk level.[3] This differed significantly from the previous gold standard guidelines from the 2004 National Cholesterol Education Program that emphasized the use LDL-C to monitor response to therapy.[4] Significant discussion exists in the provider community over the best approach to treatment.

Recently in November 2014, results of the IMPROVE-IT trial supported the use of LDL-C target goals. In this trial, patients who had been hospitalized for an acute coronary syndrome within the preceding ten days were randomized to simvastatin alone or in combination with ezetimibe (N=18,144). The combination treatment group achieved an average lower LDL-C (53.7 mg/dL vs 69.5 mg/dL; P<0.001) and had a significantly lower event rate at seven years (32.7% vs 34.7%; P=0.016). The investigators concluded that “lowering LDL-C to levels below previous targets provided additional benefit” reemphasizing the use of LDL-C target goals as a marker of cholesterol response.[5]

Table 1. Current Medications Available in the Therapeutic Class[1-2]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Alirocumab (Praluent®)	Clinical atherosclerotic cardiovascular disease, HeFH, or Primary Hyperlipidemia	Prefilled Pen: 75 mg 150 mg Prefilled Syringe: 75 mg 150 mg	-
Evolocumab (Repatha®)	Clinical atherosclerotic cardiovascular disease, HeFH, or Primary Hyperlipidemia (adults only) HoFH (13 years of age or older)	Prefilled Pen: 140 mg/mL Prefilled Syringe: 140 mg/mL	-

HeFH=heterozygous familial hypercholesterolemia, HoFH=homozygous familial hyperlipidemia

Evidence-based Medicine

- The FDA-approval of the PCSK9 inhibitors is based on the results of many clinical trials, some of which are not currently published or available to the public.[1,2,7-25]
- FDA-approval of alirocumab is based on data from twelve phase III ODYSSEY trials (>5,000 patients). These trials include patients with HeFH, those with coronary heart disease (CHD) and those at risk for cardiovascular events (CVE). Across the clinical trial program, the agent was associated with an approximate 40% to 60% decrease in LDL-C from baseline. In addition, other lipid measures generally decreased at higher levels than with placebo. Most studies evaluated a protocol in which patients started at 75 mg every two weeks and were increased to 150 mg if LDL was above 70 mg/dL at week 12. In several studies, the majority of patients were able to reach goal LDL-C levels by week 12 without requiring dose titration. For example, in ODYSSEY COMBO I, 83.2% of evaluable alirocumab-treated patients remained on the 75 mg dose throughout the study. ODYSSEY CHOICE I also evaluated alirocumab at a dose of 300 mg every four weeks and found a significant decrease in LDL-C compared to placebo (placebo-corrected decrease= 58.7%); however, the agent did not receive approval for use at this dose.[1,7-18]
- The FDA-approval of evolocumab is based on data from ten phase III PROFICO trials (approximately 6,800 patients). These trials include patients with elevated cholesterol on statins with or without other lipid-lowering therapies, patients who cannot tolerate statins, patients with HeFH and patients with HoFH. Across these clinical trials, evolocumab was evaluated at two dosing schedules, 120 mg every two weeks and 420 mg monthly. The agent was generally associated with a 40 to 60% reduction in LDL-C from baseline. There was also a significant decrease in other lipid parameters compared to placebo.[2,19-25]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - The use of PCSK9 inhibitors are not addressed.
  - AHA/ACC guidelines emphasize the use of statin therapy with intensity stratified by risk level.[2]
  - This differed significantly from the previous gold standard guidelines from the 2004 National Cholesterol Education Program that emphasized the use LDL-C to monitor response to therapy.[3]
- As noted above, the ACC/AHA guidelines do not address the place in therapy of the PCSK9 inhibitors. However, the ACC president addressed the issue in a press release upon the approval of Praluent® (alirocumab):
  - "The ACC eagerly awaits the results of the clinical trials that are in progress. In the meantime, we continue to recommend physicians limit prescribing to the very high risk, hard-to-treat groups approved by the FDA and otherwise follow the current guidelines, which recommend lifestyle change and, if needed, statins for most patients with or at risk of heart disease. Improving diet and optimizing exercise are the cornerstones of heart disease management and prevention. Statins are available as low-cost generics, are well tolerated in most patients, and their effectiveness is supported by strong evidence."[6]

- Other Key Facts:
  - These agents are generally well tolerated, with few clinically significant adverse drug reactions.
  - Alirocumab has been studied in a wide population including patients with HeFH, in combination with a statin, in statin intolerant patients and in patients with a high risk of cardiovascular events or prior history of these events.[1,6-17]
  - Both agents are continuing to be evaluated in other populations.

References

1. Praluent® [package insert]. Bridgewater (NJ): Sanofi-Aventis U.S.; 2015 Jul.
2. Repatha® [package insert]. Thousand Oaks (CA): Amgen Inc.; 2015 Aug.
3. Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PWF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;00:000–000. DOI: 10.1161/01.cir.0000437738.63853.7a.
4. Grundy SM, Cleeman JI, Merz NB, Brewer Jr B, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation. 2004;110:227-39.
5. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015 Jun 18;372(25):2387-97. doi: 10.1056/NEJMoa1410489.
6. FDA Approves First of Novel Cholesterol-Lowering Drugs [press release on the Internet]. American College of Cardiology: 2015 July 24 [cited 2015 Jul 29]. Available from: http://www.acc.org/latest-in-cardiology/articles/2015/07/24/16/01/fda-approves-first-of-novel-cholesterol-lowering-drugs?w_nav=Tab
7. Moriarty PM, Jacobson TA, Bruckert E, Thompson PD, Guyton JR, Baccara-Dinet MT et al. Efficacy and safety of alirocumab, a monoclonal antibody to PCSK9, in statin-intolerant patients: design and rationale of ODYSSEY ALTERNATIVE, a randomized phase 3 trial. J Clin Lipidol. 2014 Nov-Dec;8(6):554-61. doi: 10.1016/j.jacl.2014.09.007.
8. Regeneron and Sanofi Announce New Results from Six Phase 3 Trials Showing that Alirocumab Significantly Reduced LDL Cholesterol [press release on the Internet]. Tarrytown (NY): Regeneron Pharmaceuticals: 2015 Nov 19 [cited 2015 Apr 15]. Available from: http://investor.regeneron.com/releaseDetail.cfm?ReleaseID=883807.
9. Stroes E, Guyton JR, Farnier M, Rader D, Moriarity PM, Bergeron J, et al. Efficacy and safety of alirocumab 150 mg and 300 mg every four weeks in patients with poorly controlled hypercholesterolemia: the ODYSSEY CHOICE I and CHOICE II studies. Presented at American College of Cardiology Annual Meeting. March 2015.
10. Kereiakes DJ, Robinson JG, Cannon CP, Lorenzato C, Pordy R, Chaudhari U et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: The ODYSSEY COMBO I study. Am Heart J. 2015 Jun;169(6):906-915.e13. doi: 10.1016/j.ahj.2015.03.004.
11. Colhoun HM, Robinson JG, Farnier M, Cariou B, Blom D, Kereiakes DJ et al. Efficacy and safety of alirocumab, a fully human PCSK9 monoclonal antibody, in high cardiovascular risk patients with poorly controlled hypercholesterolemia on maximally tolerated doses of statins: rationale and design of the ODYSSEY COMBO I and II trials. BMC Cardiovasc Disord. 2014 Sep 20;14:121. doi: 10.1186/1471-2261-14-121.
12. Cannon CP, Cariou B, Blom D, McKenney JM, Lorenzato C, Pordy R et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. Eur Heart J. 2015 Feb 16. pii: ehv028.
13. Kastelein JJ, Robinson JG, Farnier M, Krempf M, Langslet G, Lorenzato C et al. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia not adequately controlled with current lipid-lowering therapy: design and rationale of the ODYSSEY FH studies. Cardiovasc Drugs Ther. 2014 Jun;28(3):281-9. doi: 10.1007/s10557-014-6523-z.
14. Ginsberg HN, Rader DJ, Raal FJ, Guyton JR, Lorenzato C, Marzarin C, et al. ODYSSEY HIGH FH: Efficacy and Safety of alirocumab in patients with severe heterozygous familial hypercholesterolemia. Available from : http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_469616.pdf.
15. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M et al. Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events. N Engl J Med. 2015 Mar 15.
16. Roth EM, McKenney JM. ODYSSEY MONO: effect of alirocumab 75 mg subcutaneously every 2 weeks as monotherapy versus ezetimibe over 24 weeks. Future Cardiol. 2015;11(1):27-37. doi: 10.2217/fca.14.82.
17. Bays H, Gaudet D, Weiss R, Ruiz JL, Watts GF , Gouni-Berthold I et al. Alirocumab as Add-on To Atorvastatin Versus Other Lipid Treatment Strategies: ODYSSEY OPTIONS I Randomized Trial. J Clin Endocrinol Metab. 2015 Jun 1:jc20151520.
18. Robinson JG, Colhoun HM, Bays HE, Jones PH, Du Y, Hanotin C et al. Efficacy and safety of alirocumab as add-on therapy in high-cardiovascular-risk patients with hypercholesterolemia not adequately controlled with atorvastatin (20 or 40 mg) or rosuvastatin (10 or 20 mg): design and rationale of the ODYSSEY OPTIONS Studies. Clin Cardiol. 2014 Oct;37(10):597-604. doi: 10.1002/clc.22327.
19. Blom DJ, Hala T, Bolognese M, Lillestol MJ, Toth PD, Burgess L et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med. 2014 May 8;370(19):1809-19. doi: 10.1056/NEJMoa1316222.
20. Stroes E, Colquhoun D, Sullivan D, Civeira F, Rosenson RS, Watts GF et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. J Am Coll Cardiol. 2014 Jun 17;63(23):2541-8. doi: 10.1016/j.jacc.2014.03.019.
21. Robinson JG, Nedergaard BS, Rogers WJ, Fialkow J, Neutel JM, Ramstad D et al. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. JAMA. 2014 May 14;311(18):1870-82. doi: 10.1001/jama.2014.4030
22. Koren MJ, Lundqvist P, Bolognese M, Neutel JM, Monsalvo ML, Yang J et al. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol. 2014 Jun 17;63(23):2531-40. doi: 10.1016/j.jacc.2014.03.018.
23. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015 Apr 16;372(16):1500-9. doi: 10.1056/NEJMoa1500858.
24. Raal FJ, Stein EA, Dufour R, Turner T, Civeira F, Burgess L et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet. 2015 Jan 24;385(9965):331-40. doi: 10.1016/S0140-6736(14)61399-4.

25. Raal FJ, Honarpour N, Blom DJ, Hovingh GK, Xu F, Scott R et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet. 2015 Jan 24;385(9965):341-50. doi: 10.1016/S0140-6736(14)61374-X.
26. ClinicalTrials.gov. NCT01764633: Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) (http://ClinicalTrials.gov/show/NCT01764633).
27. FDA Approves Amgen's New Cholesterol-Lowering Medication Repatha™ (evolocumab) [press release on the Internet]. Amgen Inc: 2015 August 27 [cited 2015 August 29]. Available from: http://www.amgen.com/media/media_pr_detail.jsp?releaseID=2082837.

Therapeutic Class Review
Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors

Overview/Summary

Praluent® (alirocumab) and Repatha® (evolocumab) are Food and Drug Administration (FDA)-approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).[1,2] Evolocumab is also indicated as an adjunct to diet and other lipid lowering therapies (statins, ezetimibe, LDL-C apheresis) in patients with homozygous familial hypercholesterolemia (HoFH).[2] Proprotein convertase subtilisin kexin 9 (PCSK9) is a serine protease produced predominantly in the liver that leads to the degradation of hepatocyte LDL receptors and increased LDL-C levels. These agents work by inhibiting the action of this enzyme leading to a decrease in LDL-C levels.[1,2]

Although both agents have demonstrated a benefit in reducing various measures of cholesterol, the extent of benefit on cardiovascular morbidity and mortality has not been determined. In addition, both were only approved as adjunctive therapy to maximally-dosed statin therapy, not in statin intolerant patients.[1,2] Currently available consensus treatment guidelines do not address the place in therapy of PCSK9 inhibitors. The 2013 consensus guidelines from the American Heart Association (AHA)/American College of Cardiology (ACC) emphasize the use of statin therapy with intensity stratified by risk level.[3] This differed significantly from the previous gold standard guidelines from the 2004 National Cholesterol Education Program that emphasized the use LDL-C to monitor response to therapy.[4] Significant discussion exists in the provider community over the best approach to treatment. These guidelines are summarized in Table 10.

Recently in November 2014, results of the IMPROVE-IT trial supported the use of LDL-C target goals. In this trial, patients who had been hospitalized for an acute coronary syndrome within the preceding ten days were randomized to simvastatin alone or in combination with ezetimibe (N=18,144). The combination treatment group achieved an average lower LDL-C (53.7 mg/dL vs 69.5 mg/dL; P<0.001) and had a significantly lower event rate at seven years (32.7% vs 34.7%; P=0.016). The investigators concluded that “lowering LDL-C to levels below previous targets provided additional benefit” reemphasizing the use of LDL-C target goals as a marker of cholesterol response.[5]

As noted above, the ACC/AHA guidelines do not address the place in therapy of the PCSK9 inhibitors. However, the ACC president addressed the issue in a press release upon the approval of Praluent® (alirocumab):

> "The ACC eagerly awaits the results of the clinical trials that are in progress. In the meantime, we continue to recommend physicians limit prescribing to the very high risk, hard-to-treat groups approved by the FDA and otherwise follow the current guidelines, which recommend lifestyle change and, if needed, statins for most patients with or at risk of heart disease. Improving diet and optimizing exercise are the cornerstones of heart disease management and prevention. Statins are available as low-cost generics, are well tolerated in most patients, and their effectiveness is supported by strong evidence."[6]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Alirocumab (Praluent®)	PCSK9 Inhibitor	-
Evolocumab (Repatha®)	PCSK9 Inhibitor	-

Indications

Table 2. Food and Drug Administration Approved Indications[1-2]

Indication	Alirocumab	Evolocumab
Clinical Atherosclerotic Cardiovascular Disease*	a	a
Homozygous Familial Hypercholesterolemia*		a
Heterozygous Familial Hypercholesterolemia*	a	a
Primary Hyperlipidemia*	a	a

*As an adjunct to diet and maximally tolerated statin therapy**.**

Pharmacokinetics

Table 2. Pharmacokinetics[1-2]

Generic Name	Bioavailability (%)	Volume of Distribution (L)	Elimination	Serum Half-Life (days)
Alirocumab	85%	0.04 to 0.05	Protein degradation	17 to 20
Evolocumab	72%	3.3	Saturable target binding (low concentrations) Proteolysis (high concentrations)	11 to 17

Clinical Trials

The FDA-approval of the PCSK9 inhibitors is based on the results of many clinical trials, some of which are not currently published or available to the public.[1,2,7-25] Published studies are summarized in Table 4.

FDA-approval of alirocumab is based on data from twelve phase III ODYSSEY trials (>5,000 patients). These trials include patients with HeFH, those with coronary heart disease (CHD) and those at risk for cardiovascular events (CVE). Across the clinical trial program, the agent was associated with an approximate 40% to 60% decrease in LDL-C from baseline. In addition, other lipid measures generally decreased at higher levels than with placebo. Most studies evaluated a protocol in which patients started at 75 mg every two weeks and were increased to 150 mg if LDL was above 70 mg/dL at week 12. In several studies, the majority of patients were able to reach goal LDL-C levels by week 12 without requiring dose titration. For example, in ODYSSEY COMBO I, 83.2% of evaluable alirocumab-treated patients remained on the 75 mg dose throughout the study. ODYSSEY CHOICE I also evaluated alirocumab at a dose of 300 mg every four weeks and found a significant decrease in LDL-C compared to placebo (placebo-corrected decrease= 58.7%); however, the agent did not receive approval for use at this dose.[1,7-18]

In a post-hoc analysis of one key study, ODYSSEY LONG-TERM, investigators observed a decreased risk of cardiovascular events compared to placebo (1.7% vs 3.3%; hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.31 to 0.90; P=0.02).[15]

The FDA-approval of evolocumab is based on data from ten phase III PROFICO trials (approximately 6,800 patients). These trials include patients with elevated cholesterol on statins with or without other lipid-lowering therapies, patients who cannot tolerate statins, patients with HeFH and patients with HoFH. Across these clinical trials, evolocumab was evaluated at two dosing schedules, 120 mg every two weeks and 420 mg monthly. The agent was generally associated with a 40 to 60% reduction in LDL-C from baseline. There was also a significant decrease in other lipid parameters compared to placebo.[2, 19-25]

In addition, in an extension study of a phase II and III clinical trial (OSLER 1 and 2), the rate of cardiovascular events at one year was reduced from 2.18% in the standard-therapy group to 0.95% in the evolocumab group (HR in the evolocumab group, 0.47; 95% CI, 0.28 to 0.78; P=0.003).[23]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Kereiakes et al[10,11] ODYSSEY COMBO I Alirocumab 75 mg SQ every two weeks (dose increased to 150 mg at week 12 if LDL ≥70 mg/dL) vs placebo Patients continued to take statin therapy with or without other lipid lowering therapy.	DB, MC, PG, RCT Patients ≥18 years of age with established heart disease or CHD equivalent, with LDL-C ≥70 mg/dL and established heart disease or LDL-C ≥100 mg/dL and no established heart disease but at a high risk for CVE* and elevated LDL-C despite maximal doses of statins at maximum tolerated dosage for at least four weeks before screening	N=316 52 weeks	Primary: Percent change in calculated LDL-C from baseline to week 24 Secondary: Percentage of patients achieving LDL-C <70 mg/dL, other lipid parameters and safety evaluations	Primary: Alirocumab was associated with a significantly greater reduction in LDL-C from baseline to week 24 compared with placebo (48.2% vs 2.3%; P<0.0001). At week 12, 83.2% of evaluable alirocumab-treated patients remained on the 75 mg dose. In patients with a dose increase, LDL-C was reduced by an additional mean 22.8% at week 24 compared with week 12. These patients achieved similar reductions in LDL-C as those not requiring a dose increase (N=32). Secondary: LDL-C <70 mg/dL was achieved by 75% of the alirocumab group compared to 9% of the placebo group at week 24. Significant reductions from baseline to week 24 after therapy with alirocumab (P<0.0001 vs placebo) were observed in non–HDL-C (−39.1% vs −1.6%), apoB (−36.7% vs −0.9%), TC (−27.9% vs −2.9%), and lipoprotein(a) (−20.5% vs −5.9%). No significant change was observed in TG levels; whereas, a significant increase in HDL-C was observed in the alirocumab group (3.5% vs −3.8%; P<0.0001). The frequency of treatment-emergent adverse events and study medication discontinuations were generally comparable between treatment groups.
Cannon et al[11,12] ODYSSEY COMBO II Alirocumab 75 mg injected SQ every two weeks (dose increased to 150 mg at week 12 if LDL ≥1.8 mmol/L)	AC, DB, DD, MC, PG, RCT Patients ≥18 years of age with established heart disease or CHD equivalent, LDL-	N=720 104 weeks	Primary: Percent change in calculated LDL-C from baseline to week 24 Secondary:	Primary: Alirocumab was associated with a significantly greater reduction in mean LDL-C from baseline at week 24 compared to ezetimibe (50.6 ± 1.4% vs 20.7 ± 1.9%; 29.8% ± 2.3% difference; P<0.0001). Secondary: Seventy seven percent of alirocumab and 45.6% of ezetimibe patients achieved LDL-C <1.8 mmol/L (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ezetimibe 10 mg QD Patients continued to take statin therapy. Other lipid lowering therapy was not permitted. All patients were instructed to follow a stable Therapeutic Lifestyle Changes diet, as outlined by the ATP III or an equivalent diet for the duration of the study.	C ≥70 mg/dL and established heart disease or LDL-C ≥ 100 mg/dL and no established heart disease but at a high risk for CVE* and elevated LDL-C despite maximal doses of statins at maximum tolerated dosage for at least four weeks before screening		Absolute cholesterol change, percent of patients achieving goal of LDL-C <70 mg/dL, other lipoprotein evaluations and safety evaluations	As compared with the ezetimibe group, the alirocumab group had greater reductions from baseline to week 24 in levels of non–HDL-C, apoB, TC, lipoprotein(a) and had a modest increase in levels of HDL-C (P<0.0001 for all comparisons). TG were reduced from baseline to week 24 by 13.0 ± 1.5% in the alirocumab group and by 12.8 ± 2.0% in the ezetimibe group, but the difference between treatment arms was not statistically significant. Alirocumab was generally well tolerated, with no evidence of an excess of treatment-emergent adverse events. Adjudicated cardiovascular events were infrequent, occurring in 4.8% (n=23) of the alirocumab group vs 3.7% (n=9) in the ezetimibe group. Treatment-emergent local injection site reactions occurred in 2.5% of patients in the alirocumab arm vs 0.8% for ezetimibe arm.
Robinson et al[15] ODYSSEY LONG TERM Alirocumab 150 mg injected SQ every two weeks vs placebo Patients continued to take statin therapy with or without other lipid lowering agents. All patients were instructed to follow a stable Therapeutic	DB, MC, PC, RCT Patients ≥18 years of age at a high risk for CVE* (with HeFH or with established heart disease or CHD equivalent) with LDL ≥70 mg/dL receiving statins at maximum tolerated dosage for at least four weeks before	N=2,341 78 weeks	Primary: Percent change from baseline in LDL-C at week 24 Secondary: Absolute cholesterol change, percent of patients achieving goal of LDL-C <70 mg/dL, other lipoprotein evaluations, major	Primary: There was a significantly greater decrease in LDL-C with alirocumab from baseline at week 24 compared to placebo (−61.0% vs 0.08%;−62% placebo-corrected difference; P<0.0001). This effect remained consistent over 78 weeks. Secondary: The mean absolute LDL-C level at week 24 was 48 mg/dL in the alirocumab group and 119 mg/dL in the placebo group, corresponding to a mean absolute change from baseline of −74 mg/dL and −4 mg/dL, respectively (P<0.0001). The goal of an LDL-C level of <70 mg/dL at week 24 was met by 79.3% of the patients in the alirocumab group compared to 8.0% of the patients in the placebo group (P<0.001). As compared with the placebo group, the alirocumab group had greater

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lifestyle Changes diet, as outlined by the ATP III or an equivalent diet for the duration of the study.	screening		cardiovascular events (death from CHD, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization), adherence rates and safety evaluations	reductions from baseline to week 24 in levels of non–HDL-C, apoB, TC, lipoprotein(a) and triglycerides and had a modest increase in levels of HDL-C and apolipoprotein A1 (P<0.001 for all comparisons). In a post hoc analysis, the rate of major adverse cardiovascular events was lower with alirocumab than with placebo (1.7% vs 3.3%; HR, 0.52; 95% CI, 0.31 to 0.90; P=0.02). Adherence was 98.0% and 97.6% in the alirocumab group and the placebo group, respectively. The alirocumab group, as compared with the placebo group, had higher rates 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%).
Roth et al[16] ODYSSEY MONO Alirocumab 75 mg injected SQ every two weeks (dose increased to 150 mg at week 8 if LDL ≥70 mg/dL) vs ezetimibe 10 mg QD	DB, MC, PC, RCT Patients with primary hyper-cholesterolemia and moderate risk for CVE*† and LDL-C ≥100mg/dL and ≤190mg/dL	N=103 34 weeks	Primary: Percent change in calculated LDL-C from baseline to week 24 Secondary: Safety evaluations	Primary: There was a significantly greater decrease in LDL-C with alirocumab from baseline at week 24 compared to ezetimibe (47.2% vs 15.6%; P<0.0001). Secondary: Safety parameters and adverse events were similar between the two groups. The most common class of adverse events was infections (39.2% with ezetimibe vs 42.3% with alirocumab), which included nasopharyngitis, influenza, and upper respiratory tract infection. Injection-site reactions occurred in less than 2% of patients in both groups. Muscle-related adverse events occurred in 3.9% of patients treated with ezetimibe and 3.8% of patients treated with alirocumab.
Bays et al[17,18] ODYSSEY OPTIONS I Alirocumab 75 mg injected SQ every two weeks (dose increased to 150 mg at week 12 if LDL ≥70 mg/dL)	AC, DB, MC, PG, RCT Patients ≥18 years of age with LDL-C ≥70 mg/dL and	N=355 24 weeks	Primary: Percent change in calculated LDL-C from baseline to week 24	Primary: Among atorvastatin 20 and 40 mg regimens respectively, there was a significantly greater decrease in LDL-C with alirocumab add-on from baseline at week 24 compared to add-on ezetimibe, double dose atorvastatin and switching to rosuvastatin (44.1% and 54.0% vs 20.5% and 22.6%, 5.0% and 4.8%, and 21.4%; P<0.001 vs all comparators). Most alirocumab-treated patients (86%) maintained their 75 mg every

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ezetimibe 10 mg QD vs atorvastatin (at double baseline dose) vs rosuvastatin 40 mg QD (atorvastatin 40 mg baseline dose cohort only) Prior to randomization, patients were stabilized on atorvastatin 20 mg to 40 mg QD.	established heart disease or LDL-C ≥ 100 mg/dL and risk factors for CVE*		Secondary: Safety evaluations	two weeks regimen. Secondary: Treatment-emergent adverse events occurred in 65.4% of alirocumab patients, compare to 64.4% ezetimibe and 63.8% double atorvastatin/switch to rosuvastatin (data pooled).
Blom et al[19] DESCARTES Evolocumab 420 mg SQ monthly vs placebo Patients received 1) diet alone, 2) diet with atorvastatin 10 mg QD, 3) diet with atorvastatin 80	DB, MC, PC, RCT Patients 18 to 75 years of age with an LDL-C≥75 mg/dL and TG≤400 mg/dL	N=901 52 weeks	Primary: LDL-C at 52 weeks Secondary: LDL-C at week 12 and percentage of patients with LDL-C <70 mg/dL at week 52, TC, HDL-C, non-HDL-C, VLDL, apoB, apoB/	Primary: At 52 weeks, the least-squares mean (±SE) reduction in LDL-C from baseline in the evolocumab group, taking into account the change in the placebo group, was 57.0 ± 2.1% at week 52. In the analysis according to background-therapy group, the least-squares mean reduction in LDL-C in the evolocumab group, taking into account the change in the placebo group, was 55.7 ± 4.2% in the diet-alone group, 61.6 ± 2.6% in the group receiving 10 mg of atorvastatin, 56.8 ± 5.3% in the group receiving 80 mg of atorvastatin and 48.5 ± 5.2% in the group receiving 80 mg of atorvastatin plus 10 mg of ezetimibe (P<0.001 for all comparisons). Secondary: The least-squares mean (±SE) reduction in LDL-C from baseline in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg QD, 4) or diet with atorvastatin 80 mg QD plus 10 mg of ezetimibe QD An initial four week run-in patients with CHD or risk equivalent and LDL-C ≥100 mg/dL or without CHD or risk equivalent and LDL-C ≥130 mg/dL were randomized to background treatment noted above. Treatment was continued in four-week increments with increases in background intensity for patients not at CHD-based goal noted above. Patients were randomized to treatment once at or below CHD-based goal.			apolipoprotein A1, lipoprotein (a), TG and safety evaluations	evolocumab group, taking into account the change in the placebo group, was 57.5 ± 1.6% at week 12. The level of LDL-C was reduced below 70 mg/dL in 82.3% of patients in the evolocumab group, as compared with 6.4% of those in the placebo group. Evolocumab treatment, as compared with placebo, also resulted in significant least-squares mean percent reductions from baseline in levels of apoB, non-HDL-C, lipoprotein(a) and TG (P values not reported). Evolocumab treatment resulted in a least-squares mean increase of 5.4 ± 1.1% in the HDL-C (P<0.001) and of 3.0 ± 0.8% in the apolipoprotein A1 (P<0.001). The most common adverse events were nasopharyngitis, upper respiratory tract infection, influenza and back pain.
Stroes et al[20] GAUSS-2 Evolocumab SQ 140 mg every two weeks vs evolocumab SQ 420 mg monthly vs	AC, DB, MC, RCT Patients 18 to 80 years of age with an LDL-C above ATP III goal and a previous intolerance to ≥2 statins	N=307	Primary: LDL-C at week 12 and mean of weeks 10 and 12 Secondary: Percentage of patients with LDL-C <70 mg/dL, non HDL-C, apoB, apoB/apolipoprotein A1,	Primary: Evolocumab reduced LDL-C from baseline by 53% (every two weeks) to 56% (monthly), corresponding to treatment differences versus ezetimibe of 37 to 39% (P<0.001). Mean percent reductions from baseline and treatment differences at week 12 were similar (P<0.001). Secondary: Evolocumab-treated patients were more likely to achieve LDL-C target levels than ezetimibe-treated patients. Compared with ezetimibe, evolocumab led to significant reductions in apoB, lipoprotein(a), non–HDL-C and the apoB/apolipoprotein A-I and TC/HDL-C ratios (P<0.001)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ezetimibe 10 mg QD			lipoprotein (a), TG, TC/HDL-C, VLDL and safety evaluations.	Muscle adverse events occurred in 12% of evolocumab-treated patients and 23% of ezetimibe-treated patients. Treatment-emergent adverse events and laboratory abnormalities were comparable across treatment groups.
Robinson et al[21] LAPLACE-2 Evolocumab SQ 140 mg every two weeks vs evolocumab SQ 420 mg monthly ezetimibe 10 mg QD (atorvastatin group only) vs placebo During a four-week run in period, patients were initially randomized to a moderate-intensity (atorvastatin 10 mg QD, simvastatin 40 mg QD or rosuvastatin 5 mg QD) or high-intensity (atorvastatin 80 mg QD or rosuvastatin 40 mg QD) statin.	AC, DB, MC, PC, RCT Patients 18 to 80 years of age with LDL-C ≥150 mg/dL (not on statin), ≥100 mg/dL (non-intensive statin) or ≥80 mg/dL (intensive statin [defined as daily atorvastatin (40mg or greater), rosuvastatin (20mg or greater), simvastatin (80 mg), or any statin plus ezetimibe]) and TG<400 mg/dL	N=2,067 12 weeks	Primary: LDL-C at week 12 and mean of weeks 10 and 12 Secondary: Mean at weeks 10 and 12 and at week 12 for the change from baseline in LDL-C level, the percent change from baseline in additional lipid parameters, the proportion of patients achieving LDL-C levels less than 70mg/dL, and safety evaluations.	Primary: Evolocumab reduced LDL-C levels by 66% (95% CI, 58 to 73%) to 75% (95% CI, 65 to 84%) (every two weeks) and by 63% (95% CI, 54 to 71%) to 75% (95% CI, 67 to 83%) (monthly) compared to placebo at the mean of weeks 10 and 12 in the moderate- and high-intensity statin-treated groups. Secondary: For moderate-intensity statin groups, evolocumab every two weeks reduced LDL-C from a baseline mean of 115 to 124 mg/dL to 39 to 49 mg/dL; monthly evolocumab reduced LDL-C from a baseline mean of 123 to 126 mg/dL to 43 to 48 mg/dL. For high-intensity statin groups, evolocumab every two weeks reduced LDL-C from a baseline mean of 89 to 94 mg/dL to 35 to 38 mg/dL; monthly evolocumab reduced LDL-C from a baseline mean of 89 to 94 mg/dL to 33 to 35 mg/dL. Evolocumab administered every two weeks and monthly resulted in significant reductions in non-HDL-C, apoB and lipoprotein(a) for all statin groups. Ninety four percent and 93 to 95% of patients receiving evolocumab every two weeks and monthly reached an LDL-C of <70 mg/dL, respectively. The most common adverse events in evolocumab-treated patients were back pain, arthralgia, headache, muscle spasms and pain in extremity (all <2%).
Koren et al[22]	AC, DB, MC,	N=614	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
MENDEL-2 Evolocumab SQ 140 mg every two weeks vs evolocumab SQ 420 mg monthly vs ezetimibe 10 mg QD vs placebo	PC, RCT Patients 18 to 80 years of age with LDL-C≥ 100 mg/dL, <190 mg/dL and Framingham risk scores ≤10%	12 weeks	LDL-C at week 12 and mean of weeks 10 and 12 Secondary: Proportion of patients achieving LDL-C <70 mg/dL, other lipid parameters and safety endpoints	Evolocumab treatment reduced LDL-C from baseline, on average, by 55 to 57% more than placebo and 38 to 40% more than ezetimibe (P<0.001 for all comparisons). At 12 weeks, LDL-C levels had decreased from baseline, on average, by 57.0% (95% CI, 59.5 to 54.6%) with biweekly evolocumab compared with 0.1% (95% CI, 3.2 to 3.4%) for placebo and 17.8% (95% CI, 21.0 to 14.5%) for ezetimibe (P<0.001). For patients administered monthly evolocumab, the mean 12-week LDL-C reduction was 56.1% (95% CI, 58.3% to 53.9%) compared to 1.3% (95% CI, 4.4%to 1.7%) for placebo and 18.6% (95%CI, 21.6% to 15.5%) for ezetimibe (P<0.001). LDL-C percent changes from baseline for the mean of weeks 10 and 12 and the absolute mean reductions in LDL-C levels were significant in all evolocumab groups compared with placebo and ezetimibe (P<0.001). Secondary: Patients in the evolocumab groups achieved a level of LDL-C <70 mg/dl at much higher rates (72% and 69%) than placebo (0% and 1%) or ezetimibe (2% and 1%) group patients for the mean of weeks 10 and 12 and at week 12, respectively. Evolocumab significantly decreased levels of apoB, lipoprotein (a), and non–HDL-C, TC/HDL-C and apoB/apolipoprotein A1. Significant HDL-C increases were observed with evolocumab (P<0.05). TG and VLDL were significantly lowered with monthly evolocumab vs placebo or ezetimibe and in some comparisons in the biweekly group. Evolocumab treatment also favorably altered other lipoprotein levels. Treatment-emergent adverse events, muscle-related adverse events and laboratory abnormalities were comparable across treatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				groups.
Sabantine et al[23] OSLER-1/2 Evolocumab SQ 140 mg every two weeks (OSLER-2) or 420 mg monthly (OSLER 1 or 2 [based upon patient preference]) vs standard therapy alone Evolocumab was administered in combination with other standard therapies based upon local guidelines for cholesterol treatment.	ES, MC, OL, RCT (extension study of five phase II trials (OSLER-1) or seven phase III trials (OSLER-2) Patients with hyperlipidemia (trials included patients on monotherapy, combination with statin with or without ezetimibe, statin intolerant patients, patients with HeFH)	N=4,465 56 weeks randomized followed by ongoing non-randomized open-label evaluation (OSLER-1) 48 weeks by ongoing non-randomized open-label evaluation (OSLER-2)	Primary: Safety endpoints Secondary: LDL-C, non–HDL-C, HDL-C, TC, TG, apolipoprotein A1 and apoB, lipoprotein(a). and CVE	Primary: Most adverse events occurred with similar frequency in the two groups, although neurocognitive events were reported more frequently in the evolocumab group. The risk of adverse events, including neurocognitive events, did not vary significantly according to the achieved level of LDL-C. Secondary: As compared with standard therapy alone, evolocumab reduced the level of LDL-C by 61%, from a median of 120 mg/dL to 48 mg/dL at 12 weeks (P<0.001). At 12 weeks, the LDL-C was reduced to ≤100 mg/dL in 90.2% of patients and to ≤70 mg/dL in 73.6% of patients in the evolocumab group, as compared with 26.0% and 3.8%, respectively, in the standard-therapy group. In the evolocumab group, as compared with the standard-therapy group, changes in related atherogenic lipid measures were similar to those observed for LDL-C, with reductions of 52.0% in non-HDL-C, 47.3% in apoB, 36.1% in TC, 12.6% in TG, and 25.5% in lipoprotein(a) (P<0.001 for all comparisons) Evolocumab also raised levels of HDL-C and apolipoprotein A1 by 7.0% and 4.2%, respectively (P<0.001 for both comparisons). The rate of CVE at one year was reduced from 2.18% in the standard-therapy group to 0.95% in the evolocumab group (HR in the evolocumab group, 0.47; 95% CI, 0.28 to 0.78; P=0.003).
Raal et al[24] RUTHERFORD-2 Evolocumab SQ 140 mg every two weeks	DB, PC, MC, RCT Patients 18 to 80 years age who met clinical	N=331 12 weeks	Primary: LDL-C at week 12 and mean of weeks 10 and 12	Primary: Compared with placebo, evolocumab at both dosing schedules led to a significant reduction in mean LDL-C at week 12 (biweekly dose: 59.2% reduction [95% CI, 53.4% to 65.1%], monthly dose: 61.3% reduction [53.6% to 69.0%]; both P<0.0001) and at the mean of weeks 10 and 12 (60.2% reduction [95% CI, 54.5% to 65.8%] and 65.6% reduction

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs evolocumab SQ 420 mg monthly vs placebo	criteria for HeFH and were on stable lipid-lowering therapy for at least four weeks, with LDL-C≥ 100 mg/dL		Secondary: Other lipid parameters and safety endpoints	[59.8% to 71.3%]; both P<0.0001). Secondary: Mean reductions in lipoprotein(a) and apoB at week 12 were significantly greater in both evolocumab groups than in the placebo groups (P<0.05 for all comparisons). At week 12, evolocumab 140 mg every two weeks reduced TG concentrations compared with placebo, whereas the 420 mg monthly evolocumab dose resulted in a smaller, but still significant, decrease compared with placebo (P<0.05 for all comparisons). Both doses of evolocumab led to significant increases in HDL-C compared with placebo (P<0.05 for all comparisons). The most common adverse events occurring more frequently in the evolocumab-treated patients than in the placebo groups were nasopharyngitis (19 patients [9%] vs five [5%], respectively) and muscle-related adverse events (ten patients [5%] vs one [1%], respectively).
Raal et al[25] TESLA-B Evolocumab SQ 420 mg monthly vs placebo Evolocumab was administered in combination with other standard therapies based upon local guidelines for cholesterol treatment.	DB, MC, PC, RCT Patients aged ≥12 years with HoFH diagnosed either by genetic analysis or clinical criteria and LDL-C >3.4 mmol/L (61.2 mg/dL) after at least four weeks of a stable, low-fat diet and baseline lipid-	N=50 12 weeks	Primary: LDL-C at week 12 Secondary: Other lipid parameters and safety endpoints	Primary: Compared with placebo, evolocumab significantly reduced LDL-C at 12 weeks by 30.9% (95% CI, –43.9% to –18.0%; P<0.0001). The least-squares mean absolute reduction in LDL-C with evolocumab versus placebo at week 12 was 2.4 mmol/L (43.2 mg/dL; 95% CI, –3.7 to –1.1). Secondary: Evolocumab treatment led to a significant least-squares mean reduction in apoB at week 12 compared to placebo (P=0.0002). No differences between the two treatment groups were recorded in HDL-C or TG at week 12 (P values not reported). Treatment-emergent adverse events occurred in ten (63%) of 16 patients in the placebo group and 12 (36%) of 33 in the evolocumab

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	lowering therapies, fasting TG <81 mg/dL and body weight ≥40 kg			group. No serious clinical or laboratory adverse events occurred, and no anti-evolocumab antibody development was detected during the study.

* In this trial, high risk for cardiovascular events was defined as: ischemic stroke, peripheral artery disease, moderate chronic kidney disease, or diabetes mellitus plus ≥2 additional risk factors (hypertension; ankle–brachial index of ≤0.90; microalbuminuria, macroalbuminuria, or a urinary dipstick result of >2+ protein; preproliferative or proliferative retinopathy or laser treatment for retinopathy; or a family history of premature coronary heart disease)
Drug regimen abbreviations: QD=once daily, SQ=subcutaneously
Study abbreviations: AC=active-controlled, DB=double-blind, DD=double-dummy, ES=extension study, MC=multicenter, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial
apoB=apolipoprotein B, ATP=Adult Treatment Program, CHD=coronary heart disease, CI=confidence interval, CVE=cardiovascular events, CRP= C-reactive protein, HDL-C=high density lipoprotein, HeFH=heterozygous familial hypercholesterolemia, HR=hazard ratio, LDL-C=low density lipoprotein cholesterol, SE=standard error, TC=total cholesterol, TG=triglyceride, VLDL=very low density lipoprotein

Special Populations

Table 5. Special Populations [1-2]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Alirocumab	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	No dose adjustment required for mild or moderate impairment. Not studied in severe impairment.*	No dose adjustment required for mild or moderate impairment. Not studied in severe impairment.*	No data	Unknown; use with caution
Evolocumab	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Approved for use in children 13 years of age and older (HoFH). Safety and efficacy in children have not been established for HeFH or primary hyperlipidemia.	No dose adjustment required for mild or moderate impairment. Not studied in severe impairment.*	No dose adjustment required for mild or moderate impairment. Not studied in severe impairment.*	No Data	Unknown; use with caution

*No adequate or well-controlled trials.
HeFH=heterozygous familial hyperlipidemia, HoFH=homozygous familial hyperlipidemia

Adverse Drug Events

Table 6. Adverse Drug Events [1-2]

Adverse Event	Reported Frequency	
	Alirocumab	Evolocumab
Bronchitis	4.3	-
Contusion	2.1	-
Cough	2.5	4.5
Back Pain	-	6.2
Diarrhea	4.7	-
Headache	-	4.0
Influenza	5.7	7.5
Injection site reactions	7.2	5.7
Muscle spasms	3.1	-
Musculoskeletal pain	2.1	-
Myalgia	4.2	4.0
Nasopharyngitis	11.3	10.5
Sinusitis	3.0	4.2
Upper respiratory tract infection	-	9.3
Urinary tract infection	4.8	4.5

Contraindications

Table 7. Contraindications[1-2]

Contraindication	Alirocumab	Evolocumab
Known serious hypersensitivity to the active ingredient or any component.	a	a

Warnings/Precautions

Table 8. Warnings and Precautions[1-2]

Warning/Precaution	Alirocumab	Evolocumab
Hypersensitivity reactions (e.g., pruritus, rash, urticaria), including some serious events, have been reported with use.	a	a

Drug Interactions

There are no known clinically significant drug interactions with alirocumab or evolocumab. However, a 20% decrease in are under the curve (AUC) of evolocumab occurs when administered with a statin. In addition, the median apparent half-life of alirocumab is reduced to 12 days when administered with a statin. These interactions are not considered to be clinically meaningful and do not impact dosing recommendations.[1,2]

Dosage and Administration

Table 9. Dosing and Administration[1-2]

Generic Name	Adult Dose	Pediatric Dose	Availability
Alirocumab	Clinical atherosclerotic cardiovascular disease, HeFH, or Primary Hyperlipidemia: Injection: initial, 75 mg SQ every two weeks; maintenance and maximum, 150 mg SQ every two weeks	Safety and efficacy in children have not been established.	Prefilled Pen: 75 mg 150 mg Prefilled Syringe: 75 mg 150 mg
Evolocumab	Clinical atherosclerotic cardiovascular disease, HeFH, or Primary Hyperlipidemia: Injection: initial, maintenance and maximum, 140 mg SQ every two weeks or 420 mg monthly (three 140 mg injections administered within 30 minutes) HoFH: Injection: initial, maintenance and maximum, 420 mg SQ monthly (three 140 mg injections administered within 30 minutes)	Safety and efficacy in children <13 years of age have not been established.	Prefilled Pen: 140 mg/mL Prefilled Syringe: 140 mg/mL

Drug regimen abbreviations: SQ=subcutaneous
Other abbreviations: HeFH=heterozygous familial hyperlipidemia, HoFH=homozygous familial hyperlipidemia

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
American College of Cardiology/American Heart Association Task Force on Practice Guidelines: **Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2013)**[3]	Statin treatment · The panel makes no recommendations for or against specific LDL-C or non-HDL-C targets for the primary or secondary prevention of ASCVD. · High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age that have clinical ASCVD, unless contraindicated. · In individuals with clinical ASCVD in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated. · In individuals with clinical ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it. · Adults ≥21 years of age with primary LDL-C ≥190 mg/dL should be treated with statin therapy (ten-year ASCVD risk estimation is not required): use high-intensity statin therapy unless contraindicated. For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity. · For individual's ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% LDL-C reduction. · For individual's ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, after the maximum intensity of statin therapy has been achieved, addition of a non-statin drug may be considered to further lower LDL-C. Evaluate the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions and consider patient preferences. · Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus. · High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated ten-year ASCVD risk unless contraindicated. · In adults with diabetes mellitus, who are <40 or >75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy. · Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL, without clinical ASCVD or diabetes and an estimated ten-year ASCVD risk ≥7.5% should be treated with moderate- to high-intensity statin therapy. · It is reasonable to offer treatment with a moderate intensity statin to adults 40 to 75 years of age, with LDL-C 70 to 189 mg/dL, without clinical ASCVD or diabetes and an estimated ten-year ASCVD risk of 5.0 to <7.5%. · Before initiating statin therapy for the primary prevention of ASCVD in adults with LDL-C 70 to 189 mg/dL without clinical ASCVD or diabetes it is reasonable for clinicians and patients to engage in a discussion which considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions and patient preferences for treatment. · In adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group, or for whom after quantitative risk assessment a risk based

Clinical Guideline	Recommendations
	treatment decision is uncertain, additional factors may be considered to inform treatment decision making. In these individuals, statin therapy for primary prevention may be considered after evaluating the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and discussion of patient preference. Statin safety · To maximize the safety of statins, selection of the appropriate statin and dose in men and non-pregnant/non-nursing women should be based on patient characteristics, level of ASCVD risk, and potential for adverse effects. · Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin associated adverse effects are present. · Characteristics predisposing individuals to statin adverse effects include, but are not limited to: o Multiple or serious comorbidities, including impaired renal or hepatic function. o History of previous statin intolerance or muscle disorders. o Unexplained alanine transaminase elevations >3 times upper limit of normal. o Patient characteristics or concomitant use of drugs affecting statin metabolism. o >75 years of age. · Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to: o History of hemorrhagic stroke. o Asian ancestry. · Creatinine kinase should not be routinely measured in individuals receiving statin therapy. · Baseline measurement of creatinine kinase is reasonable for individuals believed to be at increased risk for adverse muscle events based on a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk for myopathy. · During statin therapy, it is reasonable to measure creatinine kinase in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue. · Baseline measurement of hepatic transaminase levels should be performed before initiating statin therapy. · During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark colored urine or yellowing of the skin or sclera). · Decreasing the statin dose may be considered when two consecutive values of LDL-C levels are <40 mg/dL. · It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily. · Individuals receiving statin therapy should be evaluated for new-onset diabetes mellitus according to the current diabetes screening guidelines. Those who develop diabetes mellitus during statin therapy should be encouraged to adhere to a heart healthy dietary pattern, engage in physical

Clinical Guideline	Recommendations
	activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events. · For individuals taking any dose of statins, it is reasonable to use caution in individuals >75 years of age, as well as in individuals that are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (e.g., those who have undergone solid organ transplantation or are receiving treatment for HIV) . A review of the manufacturer's prescribing information may be useful before initiating any cholesterol-lowering drug). · It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following management algorithm: o To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy. o If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating creatinine kinase, creatinine, and a urinalysis for myoglobinuria. · If mild to moderate muscle symptoms develop during statin therapy: o Discontinue the statin until the symptoms can be evaluated. o Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases). o If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy. o If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin. o Once a low dose of a statin is tolerated, gradually increase the dose as tolerated. o If, after two months without statin treatment, muscle symptoms or elevated creatinine kinase levels do not resolve completely, consider other causes of muscle symptoms listed above. o If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose. · For individuals presenting with a confusional state or memory impairment while on statin therapy, it may be reasonable to evaluate the patient for non-statin causes, such as exposure to other drugs, as well as for systemic and neuropsychiatric causes, in addition to the possibility of adverse effects associated with statin drug therapy. <u>Monitoring and optimizing statin therapy</u> · Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within four to 12 weeks after initiation or dose adjustment, and every three to 12 months thereafter. Other safety measurements should be measured as clinically indicated. · The maximum tolerated intensity of statin should be used in individuals for

Clinical Guideline	Recommendations
	whom a high- or moderate-intensity statin is recommended, but not tolerated. · Individuals who have a less-than anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy, the following should be performed: o Reinforce medication adherence. o Reinforce adherence to intensive lifestyle changes. o Exclude secondary causes of hyperlipidemia. · It is reasonable to use the following as indicators of anticipated therapeutic response to the recommended intensity of statin therapy. Focus is on the intensity of the statin therapy. As an aid to monitoring: o High-intensity statin therapy generally results in an average LDL-C reduction of ≥50% from the untreated baseline; o Moderate-intensity statin therapy generally results in an average LDL-C reduction of 30 to <50% from the untreated baseline; o LDL-C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards. · Individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less than-anticipated therapeutic response, addition of a non-statin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. · Higher-risk individuals include: o Individuals with clinical ASCVD <75 years of age. o Individuals with baseline LDL-C ≥190 mg/dL. o Individuals 40 to 75 years of age with diabetes mellitus. o Preference should be given to non-statin cholesterol-lowering drugs shown to reduce ASCVD events in controlled trials. · In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use non-statin cholesterol lowering drugs that have been shown to reduce ASCVD events in controlled trials if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. <u>Non statin safety</u> · Baseline hepatic transaminases, fasting blood glucose or hemoglobin A1c, and uric acid should be obtained before initiating niacin, and again during up-titration to a maintenance dose and every six months thereafter. · Niacin should not be used if: o Hepatic transaminase elevations are higher than two to three times upper limit of normal. o Persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout or unexplained abdominal pain or gastrointestinal symptoms occur. o New-onset atrial fibrillation or weight loss occurs. · In individuals with adverse effects from niacin, the potential for ASCVD benefits and the potential for adverse effects should be reconsidered before reinitiating niacin therapy. · To reduce the frequency and severity of adverse cutaneous symptoms, it is reasonable to: o Start niacin at a low dose and titrate to a higher dose over a period of weeks as tolerated. o Take niacin with food or premedicate with aspirin 325 mg 30 minutes

Clinical Guideline	Recommendations
	before niacin dosing to alleviate flushing symptoms. o If an extended-release preparation is used, increase the dose of extended-release niacin from 500 mg to a maximum of 2,000 mg/day over four to eight weeks, with the dose of extended release niacin increasing not more than weekly. o If immediate-release niacin is chosen, start at a dose of 100 mg three times daily and up-titrate to 3 g/day, divided into two or three doses. · Bile acid sequestrants should not be used in individuals with baseline fasting TG levels ≥300 mg/dL or type III hyperlipoproteinemia, because severe TG elevations might occur. · A fasting lipid panel should be obtained before bile acid sequestrants are initiated, three months after initiation, and every six to 12 months thereafter. · It is reasonable to use bile acid sequestrants with caution if baseline triglyceride levels are 250 to 299 mg/dL, and evaluate a fasting lipid panel in four to six weeks after initiation. Discontinue the bile acid sequestrants if triglycerides exceed 400 mg/dL. · It is reasonable to obtain baseline hepatic transaminases before initiating ezetimibe. When ezetimibe is coadministered with a statin, monitor transaminase levels as clinically indicated, and discontinue ezetimibe if persistent alanine transaminase elevations >3 times upper limit of normal occur. · Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis. · Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are >500 mg/dL, are judged to outweigh the potential risk for adverse effect. · Renal status should be evaluated before fenofibrate initiation, within three months after initiation, and every six months thereafter. Assess renal safety with both a serum creatinine level and an estimated glomerular filtration rate based on creatinine. · Fenofibrate should not be used if moderate or severe renal impairment, defined as estimated glomerular filtration rate <30 mL/min per 1.73 m^2, is present. · If estimated glomerular filtration rate is between 30 and 59 mL/min per 1.73 m^2, the dose of fenofibrate should not exceed 54 mg/day. · If, during follow-up, the estimated glomerular filtration rate decreases persistently to ≤30 mL/min per 1.73 m^2, fenofibrate should be discontinued. · If eicosapentaenoic acid and/or docosahexanoic acid are used for the management of severe hypertriglyceridemia, defined as triglycerides ≥500 mg/dL, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding.
National Cholesterol Education Program: **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III**	· TLC remain an essential modality in clinical management. · When LDL-C lowering drug therapy is employed in high risk or moderately high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction. · Standard HMG-CoA reductase inhibitors (statins) doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, plant stanols/sterols).

Clinical Guideline	Recommendations
Guidelines (2004)[4]	· When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. · Fibrates may have an adjunctive role in the treatment of patients with high TG and low HDL-C, especially in combination with statins. · In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent. · Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of CHD risk, both when used alone and in combination with statins. The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C. <u>Treatment of heterozygous familial hypercholesterolemia</u> · Begin LDL-C lowering drugs in young adulthood. · TLC indicated for all persons. · Statins, first line of therapy (start dietary therapy simultaneously). · Bile acid sequestrants (if necessary in combination with statins). · If needed, consider triple drug therapy (statins and bile acid sequestrants and nicotinic acid). <u>Treatment of homozygous familial hypercholesterolemia</u> · Statins may be moderately effective in some persons. · LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). <u>Treatment of familial defective apolipoprotein B-100</u> · TLC indicated. · All LDL-C lowering drugs are effective. · Combined drug therapy required less often than in heterozygous familial hypercholesterolemia. <u>Treatment of polygenic hypercholesterolemia</u> · TLC indicated for all persons. · All LDL-C lowering drugs are effective. · If necessary to reach LDL-C goals, consider combined drug therapy.

<u>Conclusions</u>

Praluent® (alirocumab) and Repatha® (evolocumab) are Food and Drug Administration (FDA)-approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).[1,2] Evolocumab is also indicated as an adjunct to diet and other lipid lowering therapies (statins, ezetimibe, LDL-C apheresis) in patients with homozygous familial hypercholesterolemia (HoFH). [2] Although both agents have demonstrated a benefit in reducing various measures of cholesterol, the extent of benefit on cardiovascular morbidity and mortality has not been determined. In addition, both were only approved as adjunctive therapy to maximally-dosed statin therapy, not in statin intolerant patients.[1,2] Alirocumab and evolocumab are both dosed every two weeks; however, evolocumab also has the option to be dosed once monthly.[1,2]

Across the clinical trial programs, both agents were generally associated with a 40% to 60% reduction in LDL-C from baseline. There was also a significant decrease in other lipid parameters compared to placebo. In addition, the agents were generally well tolerated. [1,2,7-25] Both agents have preliminary data supporting their cardiovascular risk reduction. In a post-hoc analysis of one key study, ODYSSEY LONG-TERM, investigators observed a decreased risk of cardiovascular events compared to placebo (1.7% vs 3.3%; HR 0.52; 95% CI, 0.31 to 0.90; P=0.02).[15] In addition, in an extension study of a phase II and III clinical trial program (OSLER 1 and 2), the rate of cardiovascular events at one year was reduced from 2.18% in the standard-therapy group to 0.95% in the evolocumab group (HR in the evolocumab group, 0.47; 95% CI, 0.28 to 0.78; P=0.003).[23] Additional cardiovascular data is expected upon completion of the ODYSSEY OUTCOMES and FOURIER trials.[26,27]

Currently available consensus treatment guidelines do not address the place in therapy of PCSK9 inhibitors. The 2013 consensus guidelines from the AHA/ACC emphasize the use of statin therapy with intensity stratified by risk level.[3] This differed significantly from the previous gold standard guidelines from the National Cholesterol Education Program that emphasized the use LDL-C to monitor response to therapy.[4]

References

1. Praluent® [package insert]. Bridgewater (NJ): Sanofi-Aventis U.S.; 2015 Jul.
2. Repatha® [package insert]. Thousand Oaks (CA): Amgen Inc.; 2015 Aug.
3. Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PWF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2013;00:000–000. DOI: 10.1161/01.cir.0000437738.63853.7a.
4. Grundy SM, Cleeman JI, Merz NB, Brewer Jr B, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation. 2004;110:227-39.
5. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015 Jun 18;372(25):2387-97. doi: 10.1056/NEJMoa1410489.
6. FDA Approves First of Novel Cholesterol-Lowering Drugs [press release on the Internet]. American College of Cardiology: 2015 July 24 [cited 2015 Jul 29]. Available from: http://www.acc.org/latest-in-cardiology/articles/2015/07/24/16/01/fda-approves-first-of-novel-cholesterol-lowering-drugs?w_nav=Tab
7. Moriarty PM, Jacobson TA, Bruckert E, Thompson PD, Guyton JR, Baccara-Dinet MT et al. Efficacy and safety of alirocumab, a monoclonal antibody to PCSK9, in statin-intolerant patients: design and rationale of ODYSSEY ALTERNATIVE, a randomized phase 3 trial. J Clin Lipidol. 2014 Nov-Dec;8(6):554-61. doi: 10.1016/j.jacl.2014.09.007.
8. Regeneron and Sanofi Announce New Results from Six Phase 3 Trials Showing that Alirocumab Significantly Reduced LDL Cholesterol [press release on the Internet]. Tarrytown (NY): Regeneron Pharmaceuticals: 2015 Nov 19 [cited 2015 Apr 15]. Available from: http://investor.regeneron.com/releaseDetail.cfm?ReleaseID=883807.
9. Stroes E, Guyton JR, Farnier M, Rader D, Moriarity PM, Bergeron J, et al. Efficacy and safety of alirocumab 150 mg and 300 mg every four weeks in patients with poorly controlled hypercholesterolemia: the ODYSSEY CHOICE I and CHOICE II studies. Presented at American College of Cardiology Annual Meeting. March 2015.
10. Kereiakes DJ, Robinson JG, Cannon CP, Lorenzato C, Pordy R, Chaudhari U et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: The ODYSSEY COMBO I study. Am Heart J. 2015 Jun;169(6):906-915.e13. doi: 10.1016/j.ahj.2015.03.004.
11. Colhoun HM, Robinson JG, Farnier M, Cariou B, Blom D, Kereiakes DJ et al. Efficacy and safety of alirocumab, a fully human PCSK9 monoclonal antibody, in high cardiovascular risk patients with poorly controlled hypercholesterolemia on maximally tolerated doses of statins: rationale and design of the ODYSSEY COMBO I and II trials. BMC Cardiovasc Disord. 2014 Sep 20;14:121. doi: 10.1186/1471-2261-14-121.
12. Cannon CP, Cariou B, Blom D, McKenney JM, Lorenzato C, Pordy R et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. Eur Heart J. 2015 Feb 16. pii: ehv028.
13. Kastelein JJ, Robinson JG, Farnier M, Krempf M, Langslet G, Lorenzato C et al. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia not adequately controlled with current lipid-lowering therapy: design and rationale of the ODYSSEY FH studies. Cardiovasc Drugs Ther. 2014 Jun;28(3):281-9. doi: 10.1007/s10557-014-6523-z.
14. Ginsberg HN, Rader DJ, Raal FJ, Guyton JR, Lorenzato C, Marzarin C, et al. ODYSSEY HIGH FH: Efficacy and Safety of alirocumab in patients with severe heterozygous familial hypercholesterolemia. Available from : http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_469616.pdf.
15. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M et al. Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events. N Engl J Med. 2015 Mar 15.

16. Roth EM, McKenney JM. ODYSSEY MONO: effect of alirocumab 75 mg subcutaneously every 2 weeks as monotherapy versus ezetimibe over 24 weeks. Future Cardiol. 2015;11(1):27-37. doi: 10.2217/fca.14.82.
17. Bays H, Gaudet D, Weiss R, Ruiz JL, Watts GF , Gouni-Berthold I et al. Alirocumab as Add-on To Atorvastatin Versus Other Lipid Treatment Strategies: ODYSSEY OPTIONS I Randomized Trial. J Clin Endocrinol Metab. 2015 Jun 1:jc20151520.
18. Robinson JG, Colhoun HM, Bays HE, Jones PH, Du Y, Hanotin C et al. Efficacy and safety of alirocumab as add-on therapy in high-cardiovascular-risk patients with hypercholesterolemia not adequately controlled with atorvastatin (20 or 40 mg) or rosuvastatin (10 or 20 mg): design and rationale of the ODYSSEY OPTIONS Studies. Clin Cardiol. 2014 Oct;37(10):597-604. doi: 10.1002/clc.22327.
19. Blom DJ, Hala T, Bolognese M, Lillestol MJ, Toth PD, Burgess L et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med. 2014 May 8;370(19):1809-19. doi: 10.1056/NEJMoa1316222.
20. Stroes E, Colquhoun D, Sullivan D, Civeira F, Rosenson RS, Watts GF et al. Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. J Am Coll Cardiol. 2014 Jun 17;63(23):2541-8. doi: 10.1016/j.jacc.2014.03.019.
21. Robinson JG, Nedergaard BS, Rogers WJ, Fialkow J, Neutel JM, Ramstad D et al. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. JAMA. 2014 May 14;311(18):1870-82. doi: 10.1001/jama.2014.4030
22. Koren MJ, Lundqvist P, Bolognese M, Neutel JM, Monsalvo ML, Yang J et al. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol. 2014 Jun 17;63(23):2531-40. doi: 10.1016/j.jacc.2014.03.018.
23. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. 2015 Apr 16;372(16):1500-9. doi: 10.1056/NEJMoa1500858.
24. Raal FJ, Stein EA, Dufour R, Turner T, Civeira F, Burgess L et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet. 2015 Jan 24;385(9965):331-40. doi: 10.1016/S0140-6736(14)61399-4.
25. Raal FJ, Honarpour N, Blom DJ, Hovingh GK, Xu F, Scott R et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet. 2015 Jan 24;385(9965):341-50. doi: 10.1016/S0140-6736(14)61374-X.
26. ClinicalTrials.gov. NCT01764633: Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) (http://ClinicalTrials.gov/show/NCT01764633).
27. FDA Approves Amgen's New Cholesterol-Lowering Medication Repatha™ (evolocumab) [press release on the Internet]. Amgen Inc: 2015 August 27 [cited 2015 August 29]. Available from: http://www.amgen.com/media/media_pr_detail.jsp?releaseID=2082837.