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Review Article

Evolocumab and Alirocumab: A Review of the Emerging Role of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors in the Management of Hyperlipidaemia

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Abstract

This article reviews the emerging role of Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors in the management of hyperlipaedemia. Two PCSK9 inhibitors, Evolocumab and Alirocumab, have been recently approved by the National Institute for Health and Care Excellence (NICE) for patients who are at high risk of cardiovascular disease who cannot tolerate statins or those who fail to achieve appropriate levels of low density lipoprotein (LDL) despite maximum statin therapy. In this article we discuss the pathophysiology of PCSK9 Inhibitors as well as summarising the outcomes of the various clinical studies carried out on Evolocumab and Alirocumab. We also review the current NICE indications, contraindication, and the annual cost of each of these drugs.

Keywords: *PCSK9 Inhibitors; Evolocumab; Alirocumab; Hyperlipaedemia; Lipids; Cholesterol*

Abbreviations

TC: Total Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9; NICE: National Institute for Health and Care Excellence; LDLR: Low-Density Lipoprotein Receptor; Q2W: Every Two Weeks; QM: Every Month; heFH: Heterozygous Familial Hypercholesterolemia; LMT: Lipid Modifying Treatment; CVD: Cardiovascular Disease; QALY: Quality Adjusted Life Years; ICER: Incremental Cost Effectiveness Ratio; NHS: National Health Service; ACS: Acute Coronary Syndrome

Introduction

Cardiovascular disease accounts for the largest proportion in terms of the cause of death in advanced countries [1]. Most cardiovascular risk estimation systems and virtually all drug trials are based on total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C). The reduction of TC or LDL-C is associated with statistically and clinically significant reductions in cardiovascular events and mortality. The European Society of Cardiology recommends that LDL-C has to be used as the primary lipid analysis. The greater the LDL-C reduction, the greater the cardiovascular risk reduction. Statins remain the first line treatment of hyperlipidaemia while bile acid sequestrants, cholesterol absorption inhibitors, and nicotinic acid are usually used as a combination therapy in patients with very high cardiovascular risk or those who are statin intolerant or are not able to tolerate higher statin doses. Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors are a new class of drugs that have become available for LDL-C reduction [2]. Two PCSK9 inhibitors have recently been approved by the National Institute for Health and Care Excellence (NICE): Evolocumab and Alirocumab. We will summarise the history and development as well as the main clinical trials and characteristics of these drugs.

Genetics, Structure, and Physiological function

The human 22-kb gene PCSK9 is located on the small arm of chromosome 1p32 and contains 12 exons and 11 introns. The gene encodes a 692-amino acid (aa) proteinase K-like serine protease6 named PCSK9. In the adult, PCSK9 is highly expressed in liver hepatocytes and less so in the small intestine and kidney [3,4].

The 692-amino acid preproPCSK9 undergoes signal peptidase cleavage, then autocatalytic cleavage in the endoplasmic reticulum into two products: the prodomain and the mature PCSK9 containing the catalytic domain and the C-terminal domain. Cleavage of the prodomain is required for the maturation and secretion of PCSK9. After cleavage, the prodomain or prosegment remains associated by hydrogen bonds with the mature active form and the protein is finally secreted as an inactive dimer complex [4,5]. The major function of PCSK9 is the degradation of the low-density lipoprotein receptor (LDLR) by two possible ways: the first is for PCSK9 to be secreted and immediately get bound to LDL-R in the liver, and the second is to enter the systemic circulation. The binding of PCSK9 to LDLR induces modification of LDLR conformation and enhances the LDLR lysosomal degradation rather than the normal recycling to plasma membrane. Therefore leading to fewer numbers of LDL-R present on the cell surface and so less uptake of the LDL-C resulting in an elevated LCL-C concentration [4,5]. PCSK9 circulating in the plasma can bind to LDL-R in various organ systems such as the liver, intestines, kidneys, lungs, pancreas, and adipose tissue. This mechanism explains an inverse relationship between PCSK9 concentrations in plasma and LDL-R [4] (Figure 1).

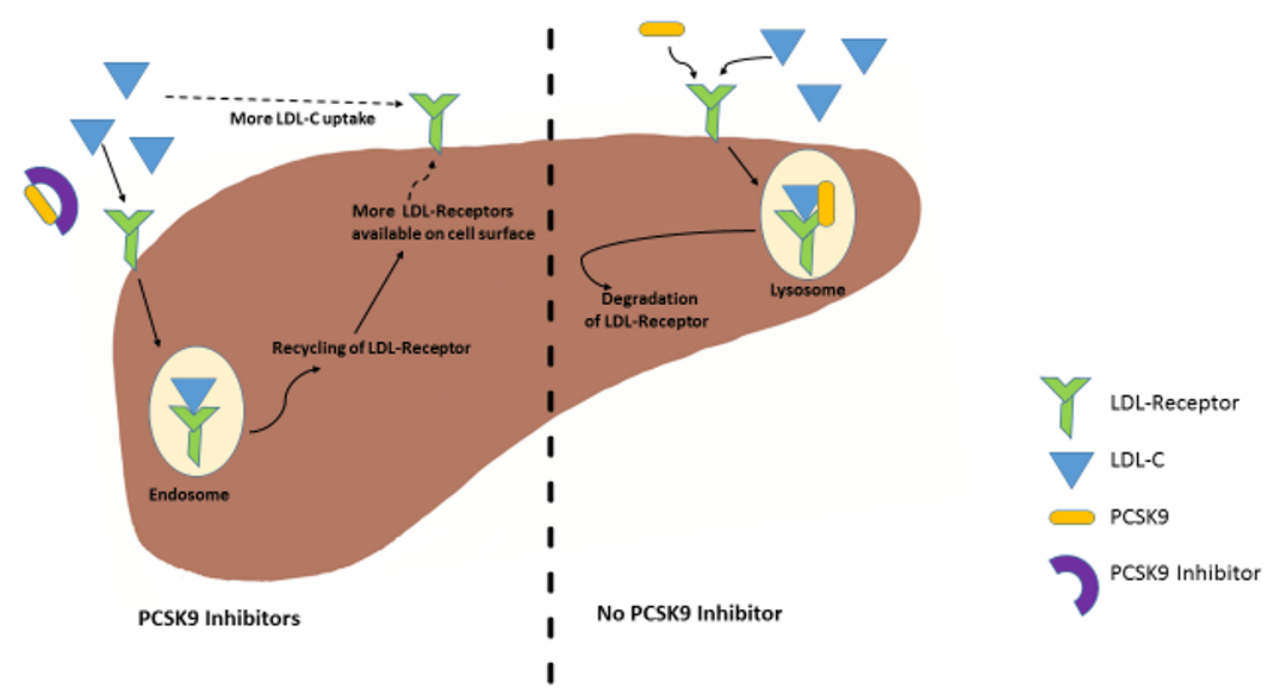

Figure 1: *The role of PCSK9 Inhibitors in lipids metabolism: PCSK9 binds to LDL-R at the surface of hepatocytes leading to the degradation of LDL-R and higher plasma LDL-L. PCSK9 Inhibitors interfere with this biding leading to recycling of LDL-R rather than degradation. This results in more LDL-R available at hepatocyte level leading to more LDL-C uptake and to reduction in plasma levels of LDL-C*

Discovery and early studies

In 2003 the ninth member of the protein convertase PCSK9 was identified [6]. In the same year, Abifadel., *et al.* reported two mutations in the gene PCSK9 causing autosomal dominant hypercholesterolemia (ADH) in two French families and with no detectable mutations in LDLR or ApoB. They were missense mutations favouring a gain-of-function or a dominant negative effect [7]. Further studies identified many PCSK9 gene mutations that have been classified as gain of function (GOF) resulting in high LDL-C levels or loss of function (LOF) when the lack of the gene resulted in low LDL-C levels [5,8]. The LOF association with hypocholesterolaemia made this protein an attractive target for the treatment of dyslipidaemia [8]. Animal studies in mice showed a direct relationship between PCSK9 and atherosclerosis as the overexpression of PCSK9 in mice resulted in an excess of atherosclerosis while mice lacking PCSK9 showed a marked reduction in aortic cholesteryl esters [9]. Also, administering statins to mice lacking PCSK9 was found to result in an exaggerated increase in LDLRs in their liver and enhanced LDL clearance from plasma [9].

Human studies

After performing phase I and phase II studies, both Evolocumab and Alirocumab underwent multiple phase 3 studies. Tables 1 and 2 summarise the major phase 3 studies performed on Evolocumab and Alirocumab respectively.

Study Name	Type	Design	Number of Patients	Study duration (Weeks)	Number of centres	Outcome
LAPLACE-2 [11]	Double-blind, Randomized, Placebo and Ezetimibe Controlled	Evolocumab Q2W* or QM** in combination to a statin in patients with Primary Hypercholesterolemia and Mixed Dyslipidaemia	2067	12	Multinational	Evolocumab added to moderate- or high-intensity statin therapy resulted in additional LDL-C lowering
GAUSS-2 [12]	Double-blind, Randomized	Evolocumab Q2W* and QM** vs Ezetimibe in hypercholesteraemic adults unable to tolerate an effective dose of a statin	307	12	Multicentre multinational	Evolocumab resulted in a significant reduction in LDL-C in hypercholesteraemic patients who were unable to tolerate effective doses of at least 2 statins
GAUSS-3 [13]	Randomized, double-blind, ezetimibe-controlled, parallel group study	Evolocumab vs Ezetimibe in patients with muscle related statin intolerance	511	24	Multicentre multinational	Evolocumab resulted in a significantly greater reduction in LDL-C levels after 24weeks
RUTHERFORD-2 [14]	Double-blind, Randomized, Placebo-controlled	Evolocumab Q2W* or QM** vs Placebo Q2W or QM in patients with heFH on a statin with or without ezetimibe	331	12	Multicentre multinational	Evolocumab administered either biweekly or monthly yielded significant reductions in LDL-C with no notable difference in the adverse events profile compared with placebo
Descartes [15]	Double-Blind, Randomized, Placebo-controlled	Evolocumab vs placebo in patients on lipid lowering therapy	905	52	Multicentre multinational	Evolocumab added to diet alone, to low-dose atorvastatin, or to high dose atorvastatin with or without ezetimibe significantly reduced LDL cholesterol levels in patients with a range of cardiovascular risks.
FOURIER [16]	Randomized, double blind, placebo controlled	Evolocumab vs placebo in patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 1.8 mmol/l or higher on statin therapy	27564	26	Multicentre multinational	The addition of Evolocumab was associated with a 59% reduction in LDL cholesterol levels. This was associated with a significant reduction of the risk of cardiovascular event. Apart from a higher rate of injection-site reactions, there was no significant difference in the rate of adverse effects.

Table 1: *Phase 3 clinical trials of Evolocumab.*

Q2w: Every two weeks; QM: Every month; LDL-C: Low Density Lipoprotein Cholesterol.

** The dose for Evolocumab twice weekly is 140mg subcutaneously.*

*** The dose for Evolocumab once a month is 250mg subcutaneously.*

Study Name	Type	Design	Number of Patients	Study duration	Location and centres	Outcome
Odyssey Mono [17]	Randomised double blind, active -controlled, Parallel group study	Alirocumab vs Ezetimibe	103	24 weeks	Multicentre Multinational	%47.2 reduction in LDL compared to %15.6 with Ezetimibe
Odyssey Combo 1 [18]	Randomised double blind, placebo-controlled, Parallel Group study	Alirocumab vs placebo in patients on maximally tolerated statin therapy in high CVD risk patients	316	24 weeks	Multicentre USA	Alirocumab treatment achieved a significantly greater reduction in LDL-C compared to placebo %45.9 vs %2.3
Odyssey Combo II [19]	Double blind, double-dummy, active controlled parallel group trial	Alirocumab vs Ezetimibe in patients on maximal tolerated statin therapy, and high CVD risk	720	24 weeks	Multicentre Multinational	Alirocumab achieved a significantly greater reduction in LDL-C compared with Ezetimibe (%50.6 vs %20.7) with a similar safety profile
Odyssey FH I [20]	Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study	Alirocumab vs Placebo in Patients With heFH Not Adequately Controlled With Their Lipid-Modifying Therapy	486	24 weeks	Multicentre Multinational	Alirocumab achieved a significantly greater reduction in LDL-C compared with Placebo The difference in mean percent change from baseline in LDL-C level at 24 weeks (with possible up-titration) was −57.9% ($p < 0.0001$) with Alirocumab compared with placebo
Odyssey FH II [20]	randomized, double-blind, placebo-controlled, parallel-group	Alirocumab vs Placebo in patients with heFH who are not adequately controlled with their LMT.	249	24 weeks	Multicentre Multinational	Alirocumab achieved a significantly greater reduction in LDL-C compared with Placebo. The difference in mean percent change from baseline in LDL-C level at 24 weeks (with possible up-titration) was −57.9%.
ODYSSEY HIGH FH [21]	Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study	Alirocumab vs Placebo in Patients with heFH and LDL-C Higher or Equal to 160mg/dL	107	24 weeks	Multicentre Multinational	Alirocumab achieved significantly greater reduction in LDL-C compared with Placebo. The difference in mean percent change from baseline in LDL-C level at 24 weeks was −57.9% ($p < 0.0001$)

Table 2: *Published Phase 3 Clinical trials of Alirocumab.*

heFH: Heterozygous Familial Hypercholesterolemia; LMT: Lipid Modifying Treatment; CVD: Cardiovascular Disease; LDL-C: Low Density Lipoprotein Cholesterol

Indications

NICE recommends using Evolocumab and Alirocumab in specific situations as follows:

Evolocumab:

Evolocumab is recommended, only if:

- The dosage is 140 mg every 2 weeks and
- The person has primary non-familial hypercholesterolaemia or mixed dyslipidaemia and:
    - A history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; chronic heart disease; ischaemic stroke; or peripheral arterial disease and
    - A low-density lipoprotein cholesterol (LDL-C) concentration persistently above 4.0 mmol/litre
- The person has primary non-familial hypercholesterolaemia or mixed dyslipidaemia and
    - Recurrent cardiovascular events or cardiovascular events in more than1 vascular bed (that is, polyvascular disease) and
    - An LDL-C concentration persistently above 3.5 mmol/litre
- The person has primary heterozygous-familial hypercholesterolaemia and
    - A history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation), coronary or other arterial revascularisation procedures, chronic heart disease, ischaemic stroke, or peripheral arterial disease and
    - An LDL-C concentration persistently above 3.5 mmol/litre
- The person has primary heterozygous-familial hypercholesterolaemia and
    - No cardiovascular disease (CVD) and
    - An LDL-C concentration persistently above 5.0 mmol/litre
- The company provides Evolocumab with the discount agreed in the patient access scheme [22].

Alirocumab

Alirocumab in combination with other lipid-lowering therapies:

- Is not recommended for treating non-familial hypercholesterolaemia or mixed dyslipidaemia in adults without a history of cardiovascular disease.
- Is recommended for treating primary non-familial hypercholesterolaemia or mixed dyslipidaemia in adults with a high risk of cardiovascular disease and persistent LDL-C levels of at least 4.0 mmol/l despite having the maximum tolerated lipid-lowering therapy.
- Is recommended for treating primary non-familial hypercholesterolaemia or mixed dyslipidaemia in adults with a very high risk of cardiovascular disease and persistent LDL-C levels of at least 3.5 mmol/l despite having the maximum tolerated lipid-lowering therapy.
- Is recommended for treating heterozygous-familial hypercholesterolaemia in adults without a history of cardiovascular disease and persistent LDL-C levels of at least 5.0 mmol/l despite having the maximum tolerated lipid-lowering therapy.
- Is recommended for treating heterozygous-familial hypercholesterolaemia in adults with a history of cardiovascular disease and persistent LDL-C levels of at least 3.5 mmol/l despite having the maximum tolerated lipid-lowering therapy.
- In all cases, Alirocumab is recommended only if the company provides the drug with the discount agreed in the patient access scheme [23].

Table 3 compares the main characteristics of Evolocumab and Alirocumab.

	Evolocumab	Alirocumab
Dose	140 mg every two weeks or 420 mg once a month by subcutaneous injection* [22]	75 mg or 150 mg every two weeks [23]
Annual cost per patient	£4,422.60 for 140 mg every 2 weeks, and £6,123.60 for 420 mg monthly [22]	£4,383 for 75 mg or 150 mg every 2 weeks [23]
Contraindications	Hypersensitivity [24]	Hypersensitivity [25]
Common Side effects-nice	Nasopharyngitis, upper respiratory tract infection, influenza, back pain, arthralgia (joint pain), and nausea [24]	Local injection site reactions, upper respiratory tract signs and symptoms, and pruritus [25]
Pregnancy	Avoid unless the clinical condition of the woman requires treatment with Evolocumab [24]	Not recommended unless the clinical condition of the woman requires treatment with Alirocumab [25].
Breast feeding	It is unknown whether Evolocumab is excreted in human milk. Risk to breastfed newborns/ infants cannot be excluded [24].	Not recommended in breast-feeding women in colostrum. For the remaining duration of breast-feeding the effects of Alirocumab on the breast-fed infant are unknown [25]
Renal impairment	Use with caution in severe renal impairment [24]	Use with caution in severe impairment [25]
Hepatic impairment	Use with caution in severe impairment [24]	Use with caution in severe impairment [25]

Table 3: *Comparison of the main characteristics of Evolocumab and Alirocumab.*

**Only the 140 mg every two weeks is recommended by NICE.*

Role of PCSK9 Inhibitors in different types of dyslipidemia

In patients with heterozygous familial hypercholesterolemia, both Evolocumab and Alirocumab achieved a higher LDL-C reduction in patients on maximum statin dose plus Ezetimibe compared to placebo [14,20,29].

In patients with homozygous familial hypercholesterolemia who took a maximum statin dose and Ezetimibe; Evolocumab reduced LDL-C significantly more than placebo at 12 weeks [26,29]. There were no studies of Alirocumab in patients with homozygous familial hypercholesterolemia [29].

In patients with Statin intolerance, The GAUSS and GAUSS-2 studies showed that Evolocumab, led to a greater reduction LDL -C than placebo [12,27,29] with similar changes in HDL- C and harm. The GAUSS study also showed that the combination of Evolocumab 420mg every 4 weeks, plus Ezetimibe was superior to Ezetimibe in LDL-C reduction [27,29]. There was no evidence for Alirocumab in patients who were intolerant to statins [29].

When considering the role of PCSK 9 inhibitors in patients with high cardiovascular risk, the initial studies were based on LDL-C reduction. These trials showed that Alirocumab resulted in a higher proportion of patients with high cardiovascular risk reaching an LDL-C Target of less than 70 mg/dl at 24 weeks compared to Ezetimibe [ODYSSEY COMBO II [19]] and to placebo [ODYSSEY COMBO I [18]]. Similar results were found when comparing the usage of Evolcumab with statins to Ezetimibe with statins [11].

More recent studies have addressed cardiovascular events and mortality and morbidity reduction. The FOURIER study concluded that the addition of Evolocumab to statin therapy in patients with atherosclerotic cardiovascular disease and LDL cholesterol levels of 1.8 mmol/l or higher was associated with a 59% reduction in LDL cholesterol levels. This was associated with a significant reduction of

the risk of cardiovascular event when compared to placebo [16]. More recently, the ODYSSEY OUTCOMES study that was presented at the American College of Cardiology Annual Scientific Session ACC 2018) showed that the use of Alirocumab significantly reduced ischemic events, including all-cause mortality and myocardial infarctions, compared with placebo among patients with an ACS event within the preceding 1 - 12 months [28].

Cost effectiveness

In the United States, a study looking at the cost-effectiveness of PCSK9 inhibitors in patients with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease. Found that PCSK9 inhibitors did not meet generally acceptable incremental cost-effectiveness thresholds for this group of patients and was estimated to increase US health care costs substantially. The study suggested that the cost of PCSK9 inhibitors needed to be reduced from $14.350 to $4,536, or less, per patient per annum for PCSK9 inhibitors to be cost effective at less than $100,000 per QALY [30].

Further cost - effectiveness analysis of PCSK9 inhibitors based on the results of the FOURIER trial suggested a 71% price reduction was required to make PCSK9 inhibitors therapy cost effective [31].

In the United Kingdom, the price of PCSK9 inhibitors is cheaper (Evolocumab costs £4,422.60 for 140 mg every 2 weeks, and £6,123.60 for 420 mg monthly and Alirocumab costs £4,383) but so is the maximum acceptable ICER considered to represent a cost effective use of NHS resources (£20,000- 30,000) [22,23]. The specific conditions under subheading 8 where NICE recommends the use of PCSK9 inhibitors represent conditions where usage of Evolocumab and Alirocumab resulted in an acceptable QALY gained below the maximum ICER. Reducing the cost of PCSK9 inhibitors could potentially reduce the QALY of using Evolocumab and Alirocumab in other lipid disorders to below the acceptable ICER.

Conclusion

This review summarises the rapid evolution of PCSK9 inhibitors with large clinical outcome trials along with future utilisation of these exciting new drugs. While clinical trials are showing promising results, the high costs of PCSK9 inhibitors is currently limiting their use in clinical practice to the highest risk patients who are most likely to benefit. If the cost of PCSK9 inhibitors was to be reduced, this would potentially result in a huge increase in their market.

As these are all injectable medications; compliance can be a significant limitation in daily practice. It would be useful to gather post launch registry data to understand what proportion of patients can manage with self-injections in a real world setting. The long term safety data on PCSK9 inhibitors is also awaited with eagerness as well as further trials to further assess their efficacy on clinical outcomes. Despite these limitations, a 50 - 70% reduction in LDL appears to be an exciting prospect in certain high risk patients. PCSK9 inhibitors could well represent the start of a new era in lipids management.

Conflict of Interest

None of the authors have a financial interest or any conflict of interest.

Bibliography

1. Agarwal SK., *et al*. "Sources of variability in measurements of cardiac troponin T in a community-based sample: the atherosclerosis risk in communities study". *Clinical Chemistry* 57.6 (2011): 891-897.

2. Catapano AL., *et al*. "2016 ESC/EAS guidelines for the management of Dyslipidaemias". *European Heart Journal* 37.39 (2016): 2999-3058.

3. Seidah NG., *et al*. "PCSK9 A Key Modulator of Cardiovascular Health". *Circulation Research* 114.6 (2014): 1022-1036.

4. Yuishi J., *et al*. "PCSK9 (Proprotein convertase subtilisin/kexin type 9) inhibitors: past, present, and the future". *European Heart Journal* 36.36 (2015): 2415-2424.

5. Farnier M. "PCSK9: From discovery to therapeutic applications". *Archives of Cardiovascular Diseases* 107.1 (2014): 58-66.

6. Seidah NG., *et al*. "The secretory proprotein convertase neural apoptosis-regulated convertase 1 (NARC-1): liver regeneration and neuronal differentiation". *Proceedings of the National Academy of Sciences of the United States of America* 100.3 (2003): 928-933.

7. Abifadel M., *et al*. "Mutations in PCSK9 cause autosomal dominant hypercholesterolemia". *Nature Genetics* 34.2 (2003): 154-156.

8. Tibolla G, *et al*. "Proprotein convertase subtilisin/kexin type 9 (PCSK9): from structure-function relation to therapeutic inhibition". *Nutrition, Metabolism and Cardiovascular Diseases* 21.11 (2011): 835-843.

9. Denis M., *et al*. "Gene inactivation of proprotein convertase subtilisin/kexin type 9 reduces atherosclerosis in mice". *Circulation* 125.7 (2012): 894-901.

10. Rashid S., *et al*. "Decreased plasma cholesterol and hypersensitivity to statins in mice lacking Pcsk9". *Proceedings of the National Academy of Sciences of the United States of America* 102.15 (2005): 5374-5379.

11. Robinson JG., *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". *Journal of the American Medical Association* 311.18 (2014): 1870-1882.

12. Stroes E., *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". *Journal of the American College of Cardiology* 63.23 (2014): 2541-2548.

13. Nissen SE., *et al*. "Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance: The GAUSS-3 Randomized Clinical Trial". *Journal of the American Medical Association* 315.15 (2016): 1580-1590.

14. Raal FJ., *et al*. "PCSK9 Inhibition With Evolocumab (AMG 145) in Heterozygous Familial Hypercholesterolemia (RUTHERFORD-2): A Randomised, Double-Blind, Placebo-Controlled Trial". *Lancet* 385.9965 (2015): 331-340.

15. Blom DJ., *et al*. "A 52-Week Placebo-Controlled Trial of Evolocumab in Hyperlipedemia". *New England Journal of Medicine* 370.19 (2014): 1809-1819.

16. Sabatirne MS., *et al*. "Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease". *New England Journal of Medicine* 376.18 (2017): 1713-1722.

17. Roth EM and McKenney JM. "ODYSSEY MONO: effect of alirocumab 75 mg subcutaneously every 2 weeks as monotherapy versus ezetimibe over 24 weeks". *Future Cardiology* 11.1 (2015): 27-37.

18. Kereiakes DJ., *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". *American Heart Journal* 169.6 (2015): 906-915.

19. Cannon CP., *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". *European Heart Journal* 36.19 (2015): 1186-1194.

20. Kastelein JJ., *et al*. "ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia". *European Heart Journal* 36.43 (2015): 2996-3000.

21. Ginsberg HN., *et al*. "Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia and LDL-C of 160 mg/dl or Higher". *Cardiovascular Drugs and Therapy* 30.5 (2016): 473-483.

22. National Institute for Health and Care Excellence. Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. London. Nice (2016).

23. National Institute for Health and Care Excellence. Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. London. Nice (2016).

24. "Repatha PFS - Summary of Product Characteristics (SPC) - (Emc)". Medicines.org.uk. N.p. (2016).

25. "Praluent solution for injection in pre-filled pen - Summary of Product Characteristics (SPC) - (Emc)". Medicines.org.uk. N.p., (2016).

26. Raal FJ., *et al*. "Inhibition of PCSK9 with Evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial". *Lancet* 385.9965 (2015): 341-350.

27. Sullivan D., *et al*. "Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: the GAUSS randomized trial". *Journal of the American Medical Association* 308.23 (2012): 2497-2506.

28. Steg PG. "Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY OUTCOMES)". Presented at: ACC, Orlando (2018).

29. McDonagh M., *et al*. "A systematic review of PCSK9 Inhibitors Alirocumab and Evolocumab". *Journal of Managed Care and Specialty Pharmacy* 22.6 (2016): 641-653.

30. Kazi DS., *et al*. "Cost-effectiveness of PCSK9 Inhibitor Therapy in Patients With Heterozygous Familial Hypercholesterolemia or Atherosclerotic Cardiovascular Disease". *Journal of the American Medical Association* 316.7 (2016): 743-753.

31. Kazi DS., *et al*. "Updated Cost-effectiveness Analysis of PCSK9 Inhibitors Based on the Results of the FOURIER Trial". *Journal of the American Medical Association* 318.8 (2017): 748-750.

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