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# Alirocumab and Dyslipidemia: Heralding a New Therapeutic Era

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**Abstract**
*Prevention of cardiovascular diseases (CVDs) has been an insurmountable challenge for a clinician. The prevalence of CVDs has been consistently increasing. There is indisputable evidence that Low Density Lipoprotein cholesterol (LDLc) is a principal driver of ASCVD thus LDLc reduction is important to reduce risk of CVDs. LDLc reduction is critically related to improved plaque stability and reduction of atheroma volume. Low Density Lipoprotein cholesterol (LDLc), the primary driver of atherosclerosisis, is the key target for intervention for prevention of CVDs. Yet, despite best treatment by statins which are the first line drugs for the treatment of dyslipidemia, inadequate LDLc reduction can be problematic in high risk patients. PCSK9 antibody, alirocumab was approved by Food and Drug Administration (FDA) in 2015. The addition of alirocumab to statin or any other lipid lowering drug results in clinically significant as well as sustained LDLc reduction with fewer side effects in patients with suboptimal LDLc lowering. Thus, Based on its novel mechanism of action, aliorcumab can be very instrumental for filling the lacuna in the treatment of dyslipidemia.*
**Keywords:** *Alirocumab, Low-density Lipoprotein Cholesterol, Proprotein Convertase Subtilisin/Kexin type 9, PCSK9 inhibitors.*

## Introduction

Prevention of cardiovascular diseases (CVDs) has been an insurmountable challenge for a clinician. The prevalence of CVDs has been consistently increasing. There is indisputable evidence that Low Density Lipoprotein cholesterol (LDLc) is a principal driver of ASCVD thus LDLc reduction is important to reduce risk of CVDs. LDLc reduction is critically related to improved plaque stability and reduction of atheroma volume. Low Density Lipoprotein cholesterol (LDLc), the primary driver of atherosclerosisis, is the key target for intervention for prevention of CVDs. Yet, despite best treatment by statins which are the first line drugs for the treatment of dyslipidemia, inadequate LDLc reduction can be problematic in high risk patients. Thus, even in patients taking statins, there is enormous residual CVD risk. The development of Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9)

monoclonal antibodies (mab) have provided novel and mechanistic insights and can be an answer for such patients. PCSK9 antibody, alirocumab was approved by Food and Drug Administration (FDA) in 2015. Based on its novel mechanism of action, aliorcumab can be very instrumental for filling the lacuna in the treatment of dyslipidemia. This systematic review is an update on recent clinical trials of alirocumab from 2014 to 2017.

Alirocumab is an addendum to other lipid-lowering treatment like statins and ezetimibe. It also decreases lipoprotein(a), casual factor in ASCVD.[9,10,11] The ODYSSEY and PROFICIO (Programme to Reduce LDLc and Cardiovascular Outcomes Following Inhibition of PCSK9 In Different Populations) clinical trial programs have confirmed the consistency of the alirocumab on LDLc reduction, even with concomitant high-intensity statin or nonstatin therapy.[12,13]

**Odyssey Mono**

The ODYSSEY MONO study was the first alirocumab Phase III study to test a dose of 75 mg subcutaneously (SC), every 2 weeks (Q2W) in a population with hyperlipidemia on no lipid-lowering therapy.[14] A total of 103 patients were randomly assigned to alirocumab starting at 75 mg SC Q2W or ezetimibe 10 mg oral every day. Alirocumab dose uptitration was planned at 12 weeks (wks) based on achieved the LDLc level at wk 8 and followed to wk 24. The primary end point was the LDLc reduction at wk 24. The changes in LDLc at other time points, the effect of alirocumab on other lipid parameters, and the safety and tolerability of alirocumab were the secondary endpoints at the wk 24. The alirocumab intent-to-treat group showed a 47.2% reduction in LDLc compared with a 15.6% reduction with ezetimibe. In both groups safety parameters and adverse events were similar.

**Odyssey Combo II**

COMBO II trial was a double-blind, double-dummy, active-controlled, parallel-group, 104 wks, conducted at 126 sites, study of alirocumab vs. ezetimibe in high cardiovascular risk patients. It was published in European Heart Journal in Feb. 2015.[15] Patients (n= 720) were randomized to either SC alirocumab 75 mg Q2W plus oral placebo daily or 10 mg oral ezetimibe daily plus placebo SC Q2W with their background statin therapy. Mean baseline reduction in LDLc for alirocumab 50.6% ± 1.4% vs 20.7 ± 1.9% for ezetimibe. LDLC <1.8 mmol/L ($p < 0.0001$) was achieved by 77.0% of patients with alirocumab and 45.6% with ezetimibe. LDLc levels were 1.3± 0.04 mmol/L at wk 24 with alirocumab and 2.1 + 0.05 mmol/L with ezetimibe which were maintained at wk 52. Alirocumab was well tolerated.

**Odyssey Long Term**

Odyssey Long Term, "The Long-term safety and tolerability of alirocumab in high cardiovascular risk patients with hypercholesterolemia not adequately controlled with their lipid-modifying therapy" was a multicentre, randomized, double-blind, placebo-controlled phase 3 study published in the New England Journal of Medicine in April 2015.[16] A total of 2341 patients with heterozygous familial hypercholesterolemia (HeFH), established coronary heart disease (CHD), or a family history of premature CHD were included in the study if they had an LDLc level ≥ 70 mg/dL despite receiving maximum tolerated dose of statin therapy. Eligible patients were randomly assigned in a 1:2 ratio to receive placebo or SC alirocumab (150 mg) Q2W for 78 wks. The percent change in calculated LDLc level from baseline to wk 24 was the primary end point. Patients assigned to alirocumab had 62% reduction in LDLc level at wk 24 compared to 0.8% increase in LDLc in the placebo group ($p<0.001$). There was 58% LDLc reduction at 78 wks. The alirocumab group had a modest increase in levels of High-Density Lipoprotein cholesterol (HDLc) level (4.6%) and significant greater reduction from baseline in serum triglycerides level (217.3%) as compared to placebo group. There was a significant reduction in levels of lipoprotein (a) in alirocumab group as compared to placebo (229.3% vs. 23.7%

respectively, p <0.001). The alirocumab group had higher rates of myalgia (5.4% vs. 2.9%), injection site reactions (5.9% vs. 4.2%), neurocognitive events (1.2% vs. 0.5%), and ophthalmologic events (2.9% vs. 1.9%) as compared to placebo.. The rate of incidences of major adverse cardiovascular event was lower with alirocumab than with placebo (1.7% vs. 3.3%).

**Odyssey Alternative**

Odyssey Alternative was a multicenter, randomized, double-blind, phase 3 study in statin-intolerant patients. Patients unable to tolerate more than 2 statins due to muscle symptoms are known as statin-intolerant. This study evaluated efficacy and safety of alirocumab in patients with well-documented statin intolerance and moderate to very high cardiovascular risk. The study was published in Journal of lipid cardiology in Aug, 2015.[17] Patients first received single-blind SC and oral placebo for 4 wks, and were withdrawn if they developed muscle-related AEs after the placebo treatment. Then patients were randomized to alirocumab 75 mg self-administered via single 1 mL prefilled pen Q2W and oral placebo or ezetimibe 10 mg/day and SC placebo or atorvastatin 20 mg/day (rechallenge) and SC placebo, for 24 wks in a ratio of 2:2:1. Then dose of alirocumab was increased to 150 mg Q2W at wk 12 depending on week 8 LDLc level. The percent change in LDLc from baseline to wk 24 was the primary endpoint. Alirocumab reduced mean LDLc by 45.0% vs 14.6% with ezetimibe (mean difference 30.4% [3.1%], P < .0001). Incidences of skeletal muscle-related events were less frequent with alirocumab than atorvastatin.

**Options I**

This study was a parallel-group, randomized, double-blind, double-dummy, multicenter, phase 3 trial in patients with hypercholesterolemia, carried out at 85 sites, published in The Journal of Clinical Endocrinology & Metabolism (JCEM) in 2015.[18] A total of 355 patients of more than 18 years of age at very high CVD risk, already on atorvastatin 20 mg or 40 mg/d were randomized to alirocumab add-on, ezetimibe add-on, or atorvastatin dose increase/switch to rosuvastatin. Add-on alirocumab reduced LDLc levels at wk 24 by 44.1% and 54.0%, add-on ezetimibe, 20.5% and 22.6%; doubling of atorvastatin dose, 5.0% and 4.8%; and switching atorvastatin 40 mg to rosuvastatin 40 mg, 21.4% among atorvastatin 20 and 40 mg regimens respectively. Alirocumab significantly reduced apolipoprotein B and non high-density lipoprotein cholesterol (non-HDL-C) from baseline to wk 24 and also reduced Lp(a) by 23.6%–30.8% as compared to all groups. Treatment- Emergent Adverse Event (TEAEs) are comparable in all treatment groups

**Odyssey Options II**

Odyssey Options II was a double-dummy, randomized, double-blind, Phase 3 study, and patients were enrolled in 79 sites. This study was published in Atherosclerosis in Sep. 2015.[19] Patients already on rosuvastatin regimens 10 or 20 mg were randomized to add-on alirocumab 75 mg Q2W; add-on ezetimibe 10 mg/day; or double-dose rosuvastatin. In the alirocumab group, dose was blindly increased at wk 12 to 150 mg Q2W in patients not achieving their LDLc target. The percent change in LDLc from baseline to wk 24 was the primary endpoint. A total of 305 patients were randomized. LDLc reductions with add-on alirocumab were 50.6% vs ezetimibe 14.4% and with double-dose rosuvastatin it was 16.3% in the baseline rosuvastatin 10 mg. LDLc reduction with add-on alirocumab was 36.3% compared to 11.0% with ezetimibe and 15.9% with double-dose rosuvastatin in the baseline rosuvastatin 20 mg group. TEAEs occurred in 56.3% of alirocumab vs. 53.5% ezetimibe and 67.3% double-dose rosuvastatin.

**Odyssey FH I and FH II**

Odyssey FH I and FH II were placebo controlled, double-blind, multicentre, randomized, phase 3 studies with similar designs.[20] FH I was conducted at across North America, Europe, and South Africa at 89 sites; FH II was conducted in Europe at 26 sites. Patients (n=486 in FH I and n=249 in

FH II) with Heterozygous Familial Hypercholesterolaemia (HeFH) having inadequate lipid control were randomized in 2:1 ratio to alirocumab 75 mg Q2W or placebo Q2W. The increment in the dose of alirocumab was done at wk 12 to 150 mg Q2W if at wk 8 LDLc was ≥1.8 mmol/L (70 mg/dL). The percent change in LDLc from baseline to wk 24 was the primary endpoint. In FH I, LDLc reduction was 144.7 mg/dL at baseline to 71.3 mg/dL at wk 24 in patients randomized to alirocumab (placebo-corrected LDLC reduction of 57.9%; $p < 0.0001$). In FH II, LDLc reduction was 134.6 mg/dL at baseline to 67.7 mg/dL at wk 24 in patients randomized to alirocumab (placebo-corrected LDLC reduction of 51.4%; $p < 0.0001$). These reductions were maintained through wk 78. Approximately 3% of alirocumab-treated patients discontinued the treatment because of adverse events in FH I (vs. 6.1% placebo) and 3.6% (vs. 1.2% placebo) in FH II. In alirocumab-treated patients (vs. placebo), rates of injection site reactions were 12.4%(vs 11%) in FH I and 11.4%(vs. 7.4%) in FH II.

**Odyssey Choice II**

Odyssey Choice II was a placebo-controlled, randomized, double-blind, phase 3 multinational study including 233 patients from 43 study sites, published in Journal of the American Heart Association in June, 2016.[21] This evaluated alirocumab 150 mg Q4W in patients with inadequately controlled hypercholesterolemia and not on statin, receiving treatment with fenofibrate, ezetimibe, or diet alone. Patients were randomly assigned to alirocumab 150 mg every 4 wks (Q4W) or 75 mg Q2W, and placebo. The LDLc percentage change from baseline to wk 24 was the primary efficacy endpoint. Mean baseline LDLc levels were 163.9 mg/dL (alirocumab 150 mg Q4W, n=59), 154.5 mg/dL (alirocumab 75 mg Q2W, n=116), and 158.5 mg/dL (placebo, n=58). Mean LDLc changes from baseline to wk 24 were 51.7% and 53.5% in alirocumab 150 mg Q4W and 75 mg Q2W groups respectively vs placebo [+4.7%]; both groups $p<0.0001$ versus placebo). TEAEs occurred in 77.6% (alirocumab 150 mg Q4W), 73.0% (alirocumab 75 mg Q2W), and 63.8% (placebo) of patients, with injection-site reactions among the most common TEAE.

**Odyssey Choice I**

Odyssey Choice I was a randomized, placebo-controlled, double-blind, phase 3 multinational study which enrolled 803 patients from 105 study sites, published in Atherosclerosis in August, 2016.[22] CHOICE I evaluated 300 mg Q4W in patients on either maximally tolerated statin or no statin, both with or without other lipid-lowering therapies. Patients with hypercholesterolemia at moderate-to-very-high cardiovascular risk, were randomized to alirocumab 300 mg Q4W, 75 mg Q2W, or placebo for 48 weeks, with dose adjustment for either alirocumab arm to 150 mg Q2W at wk 12 if at wk 8 LDLc levels were >70/100 mg/dL depending on cardiovascular risk or LDLc reduction was <30% from baseline. Approximately two-thirds of randomized patients were receiving statins. Significant reductions of LDLc from baseline were observed with alirocumab 300 mg Q4W at wk 24: mean differences were 52.7% in patients not receiving statin vs. 0.3% with placebo and patients receiving statin 58.8% vs 0.1% with placebo. The LDLc reductions were maintained at wk 48 with alirocumab 300mg vs placebo. Thus, there was higher LDLc reduction seen with the statin and alirocumab given together than alirocumab alone. TEAEs rates ranged from 61.1 to 75.0% (placebo) and 71.5 to 78.1% (alirocumab 300 mg Q4W). TEAE were 79.2 to 83.6% in the alirocumab 300Q4W group and 73.2 to 77.8% in the placebo groups, depending on statin status. Most of them were mild in intensity. Only injection site reactions were higher than placebo in the alirocumab group.

**Odyssey Escape**

Odyssey Escape was a randomized, double-blind, placebo-controlled, parallel-group, phase 3 study, conducted at 14 sites in patients with HeFH undergoing regular weekly or Q2W lipoprotein apheresis. It was published in European Heart

Journal in Aug. 2016.[23] A total of 62 patients were randomly assigned to receive alirocumab 150mg or placebo Q2W SC for 18 wks (in a 2:1 ratio). The primary endpoint was rate of apheresis treatments over 12 wks. Apheresis rates were fixed from day 1 to wk 6 then adjusted based on LDLc from 7 to 16 wks. When LDLc levels are ☐>30% lower than the baseline (pre-apheresis value) apheresis was not performed. In the alirocumab group, percentage reduction in pre-apheresis LDLc from baseline at wk 6 was ☐53.7 ± 6 2.3 and it was 1.6 ± 3.1 in placebo group. In the alirocumab group, 75% additional reduction in rate of apheresis treatment vs placebo group. Lipoprotein apheresis was not required anymore in 63.4 % patients and halved in 92.7% patients on alirocumab. Incidences of adverse drug reactions were similar in both groups.

**Odyssey High FH**

This study was a randomized, double-blind, placebo-controlled, phase 3, multicenter trial conducted at 33 sites, published in Cardiovasc Drugs Therapeutics in 2016.[24] A total 107 eligible patients with heterozygous familial hypercholes-terolemia (HeFH) who continue to have elevated LDLc levels were randomized to SC alirocumab 150 mg (n = 72) or placebo (n = 35) Q2W for 78 wks. The change in percentages of LDLc from baseline to wk 24 was the primary endpoint. The reductions in LDLc from baseline to wk 24 were observed with alirocumab −45.7 % vs. placebo −6.6%, a difference of −39.1% (p< 0.0001). The reductions in LDLc were maintained upto week 78. All TEAEs were comparable between groups. Only injection-site reactions were more frequent in the alirocumab group (8.3 %) as compared to placebo (5.7 %).

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"Efficacy, safety, LDLc lowering, and calculated 10-year cardiovascular risk reduction of alirocumab and evolocumab in addition to maximal tolerated cholesterol lowering therapy": a post-commercialization study by Shah Parth et al was published in BioMed Central in 2017.[25] Patients with HeFH and CVD with suboptimal LDLc lowering on maximal tolerated lipid lowering therapy were divided in three groups. Patients received alirocumab 75mg, alirocumab 150mg, evolocumab 140mg Q2W. At 24-wks, the median LDLc reduction with alirocumab 75 mg was from 117 to 62 mg/dL (−54%), with alirocumab 150 mg from 175 to 57 mg/dL (−63%), and with evolocumab 140 mg from 165 to 69 mg/dL (−63%), p <0.0001 for all. Absolute and percent LDLc reduction did not differ (p >.05) between alirocumab 150 and evolocumab 140 mg, but were less on alirocumab 75 mg vs alirocumab 150 mg and evolocumab 140 mg (p <.05). Percent reductions in 10-year CVD risks by American Heart Association (AHA) and National Institute of Health (NIH) calculators, respectively were alirocumab 75 mg −22 and −44%, alirocumab 150 mg −31 and −50%, and evolocumab 140 mg −29 and −56%, p ≤.002 for all groups (Table 1.). The three most common adverse events were flu-like myositis (10%), respiratory tract symptoms (8%), and injection site reactions (6%).

**Table 1** Percent reductions in 10-year CVD risks

| Drug | AHA | NIH |
|---|---|---|
| Alirocumab 75 mg | -22% | -44% |
| Alirocumab 150 mg | -31% | -50% |
| Evolocumab 140 mg | -29% | -56% |

**Odyssey Outcomes trial**

Odyssey Outcomes trial 'Effect of Alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes (ACS)"[26] is an international, multicen-ter, randomized, double-blind, placebo-controlled study in approximately 18,000 patients with a recent ACS, conducted at >1,000 sites worldwide. Primary endpoints are CHD death, non-fatal myocardial infarction, ischemic stroke, unstable angina requiring hospitalization. Results of this trial are still awaited.

**Table 2.** LDLc Percent reductions by different trials

| | Alirocumab (Dose, frequency) | Placebo | Ezetimibe |
|---|---|---|---|
| **ODYSSEY MONO** | 47.2% (75 mg,Q2W) | | 15.6% |
| ODESSEY LONG TERM | 62% (150 mg,Q2W) | 0.8% (increase) | |
| ODESSEY COMBO II | 50.6% (75 mg,Q2W) | | 20.7% |
| ODESSEY ESCAPE | 53.7% (150 mg,Q2W) | 1.6% | |
| ODESSEY ALTERNATIVE | 45% (75 mg,Q2W) | | 14.6% |
| ODESSEY HIGH FH | 45.7 150 mg,Q2W) | 6.6% | |
| OPTION I | 54% (75 mg,Q2W) | | 22.6% |
| OPTION II | 50.6% (75 mg,Q2W) | | 14.4% |
| CHOICE I | 58.8% (300 mgQ4W) | 0.1% | |
| **Shah Parth et al** | 54% (75 mg,Q2W) | | 63% (Evolocumab Q2W) |

## Discussion

In this study, we reviewed eleven randomized controlled studies which included overall 6000 patients belonging to different strata. Most of these studies were analyzed for the dose of alirocumab sc 75 mg Q2W and 150 mg Q2W for the reduction of LDLc. Only one study has analyzed for the dose of 300 mg, Q4W.

Statins up regulate the expression of LDLR which is a desirable change but they also upregulate the PCSK9 expresssion which may limit their effectiveness through increased degradation of LDLR.[27,28] Alirocumab, by inactivation of PCSK9, overcomes this compensatory effect of statins. Patients having inadequate reduction of LDLc with statins, addition of alirocumab was found to have greater reduction of LDLc as compared to statins alone. This can be attributed to their different mechanism of action resulting in additional therapeutic effects without causing cumulative toxicity. Although increased circulating PCSK9 levels by statins may limit the durability of effect of alirocumab, this effect can be mitigated by increasing the dose of alirocumab.[29] Studies have shown the efficacy of PCSK9 antibodies in patients with hyperlipidemia.[19,24] Therefore, these antibodies can be useful choice in statin intolerant or statin resistant patients of hypercholesterolemia.

For reduction of LDLc, statins are the first line of drugs. Factors predisposing for statin-associated myopathy are the older age, frailty, renal insufficiency, and co-administration of drugs that interfere with the metabolism of statins, such as erythromycin and related antibiotics, antifungal agents, immunosuppressive drugs, and fibric acid derivatives.[30] There appears to be lacunae in the treatment of LDLc reduction of the patients who are statin intolerant. In statin intolerant patients, alirocumab was associated with significantly higher reduction of LDLc as compared to ezetimibe.[17]

Candidates for LDL apheresis are the severely hypercholesterolemic patients despite optimally tolerated drug therapy. Candidates for every-other week apheresis are the having CHD and a plasma LDLc level >200 mg/dL despite maximally tolerated combination drug therapy and those who do not have CHD but have a and a plasma LDLc level >300 mg/dL.[25] Alirocumab decreases the

rate of lipoprotein apheresis in patients with HeFH.[23] In one study done in Germany, the costs of PCSK9 inhibitor therapy and apheresis amount to approximately €9,650 per year and €50,000 per year respectively.[31] Patients treated with apheresis have lower quality-of-life scores regarding mental aspects and equal scores regarding physical aspects as compared to the general population.[32] Further studies are needed to evaluate the potential benefits of alirocumab over apheresis in terms of cost and quality of life.

In addition to significant reduction of calculated 10-year cardiovascular risk, [24] alirocumab has additional beneficial effects on multiple lipid parameters. Apart from reduction of LDLc, alirocumab causes reduction in lipoprotein (a) and increment in HDL-C.[33] Alirocumab is well tolerated. It has fewer skeletal-muscle adverse events as compared to statins. Only injection site reactions are higher than placebo.

In Odyssey Outcomes, stipulated background statin therapy is concordant with new guideline recommendations. The trial result will determine whether further reduction in cardiovascular risk can be achieved by addition of the monoclonal PCSK9 antibody, alirocumab, resulting in further reduction of LDLC and other atherogenic lipoproteins

Despite the proven effectiveness of alirocumab, the lack of long term safety data and its high cost are the factors which have been detrimental for approval of alirocumab as first line therapy.[34]

## Conclusion

The addition of alirocumab to statin or any other lipid lowering drug results in clinically significant as well as sustained LDLc reduction with fewer side effects in patients with suboptimal LDLc lowering. In HeFH patients, alirocumab was found to reduce the frequency for the apheresis. In statin intolerant patients, alirocumab demonstrated statistically significant and sustained reduction in LDLc in patients with hypercholesterolemia as compared to other lipid lowering therapy. Reported adverse events were minimal and tolerable. In terms of CVD reduction, with long-term safety and cardiovascular outcomes are yet to be determined. Alirocumab is useful addendum as add on and substitute to the statins for the treatment of dyslipidemia.

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**Abbreviations**

ASCVD- Atherosclerotic Cardiovascular Disease
CHD
CVD- Cardiovascular disease
HDLc-High Density Lipoprotein cholesterol
PCSK9- Proprotein Convertase Subtilisin/Kexin type 9
Q2W-every 2 weeks
Q4W-every 4 weeks
HeFH-Hereditary Familial Hypercholesterolemia
LDLC--Low Density Lipoprotein Cholesterol
LDLR-Low Density Lipoprotein Receptor
SC-Subcutaneous