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Review Article

Alirocumab in Combination with Statins for CVD Risk Reduction: An Evidential Review

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ABSTRACT

Cardiovascular disorders have been one of the mainstay causes for the estimated rise in the incidences of mortality. In earlier times, treatment approach was initiated with statin therapy even though there were high reports of adverse events and failure to attain the target lipid concentration. In 2003, Proprotein Convertase subtilisin/kexin 9 was found to be responsible for the degradation and inactivation of LDL receptors. Ever since the concept was introduced, many researches have been conducted in this field for a better control in lipid management. Alirocumab was approved by FDA in the year 2015 as a PCSK9 inhibitor indicated for heterozygous familial hypercholesterolemia. The purpose of this review is to compile the available information on the LDL-C reduction capacity of Alirocumab in combination with statins and simultaneous cardiovascular risk reduction. It also aims at providing an evidential safety data associated with Alirocumab use.

Alirocumab is presently available in doses of 75 and 150mg subcutaneous injections once every two weeks. It is a monoclonal antibody directed against PCSK9 and evidential data provides an estimate of about 54% reduction in LDL-C concentrations. The application of Alirocumab as add on therapy to statins is the area of interest and the data suggests that there is a significant higher rate of LDL-C reductions in turn leading to a noteworthy cardiovascular risk reduction. However the appropriate dose of statins to incorporate a PCSK9 inhibitor requires further hypotheses. Additionally the safety profile of Alirocumab was found to be comparable with placebo or the control.

Key words: Alirocumab, Atherosclerotic cardio vascular disease, Hypercholesterolemia, LDL-cholesterol, LDL-receptor, PCSK9 inhibition.

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INTRODUCTION

Cardiovascular diseases are the prime cause of morbidity and mortality worldwide and research has been done to modify and for the prevention of its risk factors. It is well known and documented that, lowering of LDL cholesterol is the mainstay of therapy in the primary and secondary prevention of CVD.[1] Presently statins remain the cornerstone of lipid lowering therapy but conversely, there is widespread incidence of failure to achieve target lipid lowering goal even with the maximally tolerated dose of statins. This can be attributed to statin intolerance such as an injection site reaction, myalgia and myositis.[2-3]

Recent trends in medical diagnosis have led to the clear concept of the residual cholesterol levels and the high risk of cardio vascular events. To attain a better control and lowering of LDL-C, a new group of drugs called PCSK9 inhibitors have been recently approved by the FDA and the European Medical Agencies.[4]

PCSK9 inhibitors have been playing an overriding therapeutic role in the lipid homeostasis, ever since it was discovered in 2003. It is a proprotein found profusely in the human blood and moreover it has been found to be responsible for the degradation of LDL receptors and thereby increasing blood concentration of LDL-C, attributing to higher risk of adverse vascular events.[5] It is self-cleaved, secreted and tightly binds to the EGF-A–like domain of the LDLR which in turn causes the LDLR recycling leading to the down regulation of LDLR activity.[6-7] Lipid metabolism is also caused by degradation of endosomes and lysosomes in the cell surface. Furthermore, there is a link found between atherosclerosis and PCSK9 as vascular smooth muscle cells secrete PCSK9, which causes cutback in LDLR expression and LDL-C uptake of human and murine macrophages, ensuing vascular lipid build up and oxidation.[8]

Loss of function mutations in LDLR, heterozygous mutation in ApoB affecting the LDL receptor binding domain of ApoB or heterozygous gain-of-function mutations in PCSK9, are the identified genetic causes of Heterozygous Familial Hypercholesterolemia. Homozygous FH on the other hand, is a result of homozygous or frequently, from compound heterozygous mutations in either the LDLR or ARH genes. Additionally it has been proven that the incidence of CVD is considerably lower in patients having LOF mutation of PCSK9.[9] These present the ground data that offer strong rationale supporting the use of PCSK9 inhibitors. Alirocumab is a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, available in doses of 75 mg administered subcutaneously Q2W and the maximum dosage is 150 mg Q2W.[10]

The primary objective of this review is to compile the available information on the efficacy of Alirocumab in combination with statins, on LDL-C reduction and thus cardiovascular risk reduction, the secondary objective being to provide an evidential data on the safety associated with the use of Alirocumab.

MATERIALS AND METHODS

Literature search

For the selection of studies, the approach used was to primarily choose randomized controlled trials that assess the PCSK9 inhibitors' efficacy when used in combination with statins, with or without Ezetimide and also the study should provide the data on the safety and adverse effect profile of Alirocumab. PubMed, BMC, Clinical key, Scopus, Science direct and the Cochrane CENTRAL were the databases that were searched, while using the search terms; 'PCSK9 inhibitors', 'PCSK9', 'AMG 145', 'Alirocumab', 'CVD risk reduction' and 'statins'. The finally extracted references were manually checked and the abstracts and non-English papers were excluded.

Study selection

The databases generated 790 articles and out of them 721 were excluded as they were abstracts, protocols or forum discussions. On further refining,

90 studies were excluded due unavailability of full text articles and duplication. After the final scrutiny, 9 studies met with the inclusion criteria and hence were included in the review.

All subjects included in the studies were screened for the eligibility criteria and being on a baseline statins with or without Ezetimibe was a must, but should have had a LDL-C concentration of ≥ 70mg/dl for those who had CVD and ≥100mg/dl for those who had coronary artery disease risk equivalents like diabetes mellitus with other risk factors or chronic kidney disease. Across the 9 studies, 2052 patients were randomized and treated: the intervention arm being of Alirocumab (50, 75 or 150mg) and the control arm consisting of placebo, Ezetimibe or doubling the statin dose. Characteristics of included studies are shown in Table 1.

RESULTS

LDL-C Reduction

Comparison of Alirocumab with other alternatives and its mean percentage changes in LDL-C reduction is shown in Table 2.

The study conducted by Kereiakes *et al.*[11] in the ITT analysis; the mean percent change of LDL-C from baseline to the 24th week for Alirocumab was −48.2% and −2.3% for placebo. On the other hand, for the on-treatment analysis, it was found −50.7% and −0.8% respectively (P≤ .0001). For the other lipid parameters, there was a significant reduction observed at the 24th week with Alirocumab (P ≤.0001 vs placebo). For non–HDL-C reduction it was observed −39.1% for Alirocumab and −1.6% for placebo. Others include apolipoprotein B −36.7% vs −0.9%, total cholesterol −27.9% vs −2.9 and lipoprotein (a) −20.5 −5.9%. Similarly in the study conducted by Teramoto *et al.*[12] Alirocumab resulted in a dose-dependent achievement in a ≥50% reduction in LDL-C which was not observed in any of the subjects in the placebo arm. Significant decline in the concentrations of total cholesterol, non HDL-C and apolipoprotein B were also observed (p <0.0001). Additionally as per Shahawy *et al.*[13] LDL-C levels showed significant reductions from baseline by 52% with Alirocumab whereas by 22% with the Ezetimibe group ([LS] mean difference of −31%, 95% confidence interval [CI] −35 to −26; p <0.0001).

Furthermore according to the study conducted by Farnier *et al.* LDL-C reductions were observed at about 36.3% in the Alirocumab arm and with 11.0% reductions observed in the Ezetimibe arm (p ≥0.0136).[14]

Moreover, as per the study conducted by Ginsberg *et al.* The {LS mean, [SE]} percent change in LDL-C was better in the Alirocumab arm with −45.7 [3.5] % whereas the placebo group with −6.6 [4.9] % for the subjects of ITT analysis group, associated with a statistically significant LS mean (SE) difference among the groups of −39.1 (6.0) % (P < 0.0001). A sensitivity analysis was also done and resultant demonstration of Alirocumab with −50.9 [3.4] % and placebo with −1.0 [4.7] % in LDL-C (P <0.0001).[15]

On top of the above outcomes, in the study by Cannon *et al.*[16] the assessment of the primary end point was 250.6 plus 1.4% {mean plus standard error (SE) decrease in LDL-C at the 24th week} in the interventional arm and 220.7 plus 1.9% in the Ezetimibe arm while both the arms were on a background of maximally tolerated statin therapy, with a statistically significant difference of the means + SE between groups of 229.8 (95% CI 234.4 to 225.3, P , 0.0001).

Some studies had to increase the dose of Alirocumab from 75 mg to 150mg at week 12 if the LDL-C ≥ 70mg/dl at week 8.[16-17] Subjects treated with add on Alirocumab showed higher reduction in LDL-C as compared to control arm in all the study pools. In addition to this, there was no association found between the type and dose of baseline statins and percentage change of LDL-C for Alirocumab and control arm. It was also found that the measured and the calculated values of LDL-C were consistent with each other. Efficacy of Alirocumab over time showed early and sustained reduction of LDL-C as compared to placebo and the reduction was found to be comparable. Teramoto *et al.* used three doses of Alirocumab i.e 50mg, 75mg and 150mg in their multiple dose study and it showed significant dose dependent LDL-C reduction. When the dose of Alirocumab was increased after week 12, additional decrease in the LDL-C was documented.

LDL-C goal attainment

The proportion of patients achieving the target LDL-C was significantly larger in Alirocumab arm as compared to placebo arm. Most of the patients (>80%) having high or very high cardiovascular risk achieved LDL-C <70 mg/dl and <100 mg/dl respectively in Alirocumab arm[18] and this proportion was much higher than any other add-on therapies of lipid lowering agents like Ezetimibe and doubling of statin dose. However there was association found between proportion of patients attaining the LDL goal and statin dose. The multiple dose study also showed a dose dependent increase in the proportions of patients achieving ≥50% LDL-C reduction.[12]

Other lipid parameters

There were marked reductions in non HDL-C, Apolipoprotein B, Lipoprotein (a), Triglycerides and total cholesterol associated with Alirocumab as compared to placebo or other controls. Relative to other parameters, triglycerides had a lesser degree of change when attributed to Alirocumab. Some studies also showed that the difference in Triglyceride levels between Alirocumab and Ezetimibe arm was not statistically significant.[13,15] Modest HDL-C elevation was also documented attributed to Alirocumab as compared to control. Other lipid parameters are shown in Table 3.

Safety Summary

The safety and adverse events associated with Alirocumab extracted from various studies are represented in Table 4. The treatment emergent adverse and serious adverse events were found to be comparable between intervention and control arm.

In the study conducted by Kereiakes *et al.* the incidence of TESAEs and TEAEs were comparable between the groups. TEAEs leading to discontinuation or death were also reported. 5.3% in the interventional group and 2.8% among the placebo arm, which demonstrated reports of local injection site reactions. Additionally, allergic reactions were reported in 8.7% subjects receiving Alirocumab and 6.5% for subjects receiving placebo patients. However, in the study by Teramoto *et al.* there were no reports of serious adverse events or drug discontinuations.

As per the study concluded by Shahawy *et al.* local injection-site reactions were reported about 2.5% in the interventional group and 0.8% in the Ezetimibe group for the first year, whereas it was reported about 0.2% in the interventional group for the second year.

In the study by Bays *et al.* TEAEs were reported in 65.4% of subjects with interventional add-on therapy, however discontinuation was reported in 6.7% of these subjects. Overall, TESAEs were reported for 5.4% of patients of which two subjects died during the study who were on Ezetimibe group.[18]

Additionally in the study by Cannon *et al.* the rate of TEAE leading to death was reported in 0.4% of subjects in the interventional group and in 1.7% of subjects in the Ezetimibe group. 18.8% of patients in interventional arm and 17.8% of subjects in Ezetimibe arm reported serious adverse events. However, a higher proportion of TEAEs leading to discontinuation was observed in the interventional arm (7.5% to 5.4%).[16]

In the study conducted by Leiter *et al.* cardiovascular events were reported in 8.8% and 2.6% of subjects with DM and 5.4% and 6.7% of subjects without diabetes mellitus for the interventional and Ezetimibe arms respectively.[17]

Table 1: Study characteristics.

Study	Place	Age (yrs)	Sample size	Selection Criteria	Study pool	Primary efficacy	Secondary efficacy
Shahawy *et al* [11]. (2017)		≥18	720	INCLUSION Hypercholesterolemia and known CHD or its equivalents For known CVD, LDL-C ≥70mg/dl For no history of CVD, LDL-C≥100mg/dl EXCLUSION Age <18 years Fasting sr TG >400 mg/dL Use of fibrates in the past 6 weeks prior to screening visit	Alirocumab Ezetimibe	Percentage change in calculated LDL-C from baseline to week 24	Percentage change in Apo B from baseline to week 24 Percentage change in non-HDL-C from baseline to week 24 Percentage change in total cholesterol from baseline to week 24 Proportion of patients reaching calculated LDL-C <70 mg/dL at week 24 Percentage change in Lp(a) from baseline to week 24 Percentage change in HDL-C from baseline to week 12
Ginsberg *et al* [12] (2016)	North America, Europe and South Africa	≥18	107	INCLUSION Heterozygous familial hypercholesterolemia poorly controlled by maximaly tolerated dose of statin LDL-C ≥70mg/dl EXCLUSION Not on stable dose of LLT Currently taking a statin Known history of homozygous FH Fasting sr TG >400 mg/dL Use of fibrates in the past 6 weeks prior to screening visit LDL-C <160 mg/dL the screening visit	Baseline statin therapy Alirocumab Placebo	Percent change in calculated LDL-C from baseline to Week 24	Percent change in calculated LDL-C from baseline to Week 24 Percent change in Apo B from baseline to Week 24 Percent change in non-HDL-C from baseline to Week 24 Percent change in total cholesterol from baseline to Week 24 Percent change in Lp(a) from baseline to Week 24 Percent change in HDL-C from baseline to Week 24 Percent change in fasting TG from baseline to Week 24
Leiter *et al* [13] (2016)				INCLUSION Hypercholesterolemia and known CHD or its equivalents For known CVD, LDL-C ≥70mg/dl EXCLUSION Age <18 years Fasting sr TG >400 mg/dL Use of fibrates in the past 6 weeks prior to screening visit eGFR<30 mL/min/1.73 m^2	Alirocumab Ezetimibe	percent change in calculated LDL-C from baseline to Week 24	Percent change from baseline in LDL-C at Week 12 Achievement of risk-based LDL-C goals at Week 24 Percent changes from baseline in HDL-C, TGs, non-HDL-C, apolipoprotein (Apo) B, Apo A1 and lipoprotein (a) [Lp(a)] at Week 24

Table 1: Con

M. Farnier *et al* [14] (2016)	Australia, Germany, Italy, Spain, the United Kingdom, Mexico, the United States, and Canada	≥18	300	INCLUSION Rosuvastatin (10 mg or 20 mg daily), ≥4weeks prior to screening visit LDL-C≥70mg/dl with a history of CVD LDL-C100mg/dl; with heFH; calculated CV risk≥5% or moderate CKD or with DM without target organ damage EXCLUSION Age <18 years Fasting sr TG >400 mg/dL taking ezetimibe Uncontrolled endocrine disease	Add-on Alirocumab Add-on ezetimibe Doubling of the rosuvastatin dose	Percent change from baseline in calculated LDL-C at Week 24	Percent change from baseline in calculated LDL-C on-treatment at Week 24 Percent change in LDL-C from baseline toWeek 12 Percent change in other lipid parameters Proportion of very-high and high CV risk patients reaching LDL-C <70 mg/dL
Teramoto *et al* [16](2016)	Japan	20-75	162	INCLUSION primary hypercholesterolemia(LDL-C≥100mg/dl) on Atorvastatin 5-20mg for ≥6 weeks	Alirocumab 50 mg Alirocumab 75 mg Alirocumab150mg	least-square mean (SE) reductions in calculated LDL-C concentrations from baseline to week 12	Percent change in lipid variables from baseline to week 12
Bays *et al* [17] (2015)	Australia, Canada, France, Germany, Italy, Mexico, Spain, the United Kingdom, and the United States	≥18	355	INCLUSION Hypercholestetrolemia 20 or 40 mg of atoevastatin with or without other LLT For known CVD, LDL-C ≥70mg/dl LDL-C100mg/dl; with heFH; calculated CV risk≥5% or moderate CKD or with DM without target organ damage EXCLUSION Age <18 years Fasting sr TG >400 mg/dL taking ezetimibe Uncontrolled endocrine disease On a statin that is not atorvastatin daily at 20 or40 mg	Add-on Alirocumab Add-on Ezetimibe Double Atorvastatin dose Switch to rosuvastatin40mg	Percent change in calculated LDL-C from baseline to week 24	Percent change in LDL-C frombaseline to week 24 Percent change in LDL-C at week 12 Percent change in other lipidparameters Proportion of patients achieving their target LDL-C goal(<70/100mg/dl) Proportion of patients reaching calculated LDL-C<70 mg/dL at week 24

Table 1: Con

Cannon *et al* [18] (2015)	Europe, Israel, North America, South Africa, South Korea	≥18	720	INCLUSION Hypercholesterolemia and known CHD or its equivalents For known CVD, LDL-C ≥70mg/dl EXCLUSION Age <18 years Fasting sr TG >400 mg/dL Use of fibrates in the past 6 weeks prior to screening visit	Alirocumab Ezetimibe	percent change in calculated LDL-CfrombaselinetoWeek 24	Percent change in calculated LDL-C frombaseline to Week 24 Percentage of change in other lipid parameters proportion of patients reaching calculatedLDL-C at week 24
Kereiakes *et al* [20] (2015)	US	≥18	316	INCLUSION Hypercholesterolemia or known CHD or its equivalents on maximaly tolerated daily dose of statin for known CVD, LDL-C ≥70mg/dl For no history of CVD, LDL-C≥100mg/dl EXCLUSION Age <18 years Fasting sr TG >400 mg/dL Use of fibrates, other than fenofibrate, within 6 weeks prior to the screening visit (week −2)	Alirocumab Placebo	Percent change in LDL-C from baseline to week 24	Percent change in LDL-C from baseline toweek 24 Percent change in LDL-C at other defined time points Percent changes in other lipid parameters
Roth *et al* [21] (2012)	The United States	18-75	92	INCLUSION 18-75 years Primary hypercholesterolemia(LDL-C≥100mg/dl) EXCLUSION Type I or type II DM treated with insulin TG>350mg/dl Hepatic aminotransferase levels more than twice the upper limit Cardiovascular or Cerebrovascular events or procedure within 6 months before screening On statins other than atorvastatin	Atorvastatin 80 mg+Alirocumab Atorvastatin 10mg+Alirocumab Atorvastatin 80mg+Placebo	Percent reduction in LDL-C from baseline	Percent of patients achieving the LDL-C target Percent change from baseline to week 8 in other lipid and apolipoprotein levels

Table 2: Comparison of Alirocumab with other alternatives and its mean percentage changes in LDL-C reduction

Study	Study Pool	N	Reduction in LDL-C(%)	% of subjects reaching the Goal
Shahawy *et al*[11]	At week 24			
(2017)	Alirocumab	479	-52%	-
	Ezetimibe	241	-22%	-
	At 2 years			
	Alirocumab	479	-49%	-
	Ezetimibe	241	-17%	-
Ginsberg *et al*[12]	Alirocumab	71	-45.7%	41%
(2016)	Placebo	35	-6.6%	5.7%
Leiter *et al*[13] (2016)	With DM	225		
	Alirocumab	148	49.1%	77.9%
	Ezetimibe	77	18.4%	50.1%
	Without DM	495		
	Alirocumab	331	51.2%	77.3%
	Ezetimibe	164	21.8%	45.1%
M. Farnier *et al*[14] (2016)	Rosuvastatin 10mg group			
	Add-on Alirocumab			
	Add-on ezetimibe	48	-50.6%	84.9%
	Doubling of the rosuvastatin dose	47	-14.4%	57.2%
	Rosuvastatin 20mg group	48	-16.3%	45.0%
	Add-on Alirocumab			
	Add-on ezetimibe			
	Doubling of the rosuvastatin dose			
		53	-36.3%	66.7%
		50	-11.0%	52.2%
		52	-15.9%	40.1%
Teramoto *et al*[16]	Alirocumab50 mg	25	-54.8%	100%
(2016)	Alirocumab 75 mg	25	-62.3%	100%
	Alirocumab150 mg	25	-71.7%	100%
Bays *et al*[17]	Atorvastatin 20 mg group			
(2015)	Add-on Alirocumab			
	Add-on Ezetimibe	55	44.1%	-
	Double Atorvastatin dose	53	20.5%	-
	Atorvastatin 40 mg group	53	5.0%	-
	Add-on Alirocumab			
	Add-on Ezetimibe			
	Double Atorvastatin dose			
	Switchto rosuvastatin40mg	46	54.0%	-
		46	22.6%	-
		47	4.8%	-
		45	21.4%	-
Cannon *et al*[18] (2015)	Alirocumab	479	-50.6%	77%
	Ezetimibe	241	-20.7%	45.6%
Kereiakes *et al*[20]	Alirocumab	205	-48.2%	75%
(2015)	Placebo	106	−2.3%	9%
Roth *et al*[21] (2012)	Atorvastatin	30	73.2%	90%
	80 mg+Alirocumab			
	Atorvastatin 10mg+Alirocumab	31	66.2%	97%
	Atorvastatin 80mg+Placebo			
		31	17.3%	17%

Table 3: Comparison of Alirocumab and other alternatives with mean percentage changes in other lipid parameters

		Non HDL-C	Apo-B	Lipoprotein (a)	Triglyceride	HDL-C	Total Cholesterol
Shahawy *et al*[11] (2017)	Alirocumab	-39.4	-35.8	-23.1	-11.4	1.2	-
	Ezetimibe	-14.6	-10.2	4.8	-8.2	8.7	-
Ginsberg *et al*[12] (2016)	Alirocumab	-41.9	-39.0	-23.5	-10.5	7.5	-33.2
	Placebo	-6.2	-8.7	-8.7	-1.9	3.9	-4.8
Leiter *et al*[13] (2016)	With DM						
	Alirocumab	-40.8	-39.0	-28.1	-15.3	8.4	-
	Placebo	-15.3	-14.8	-4.3	-11.4	1.3	-
	Without DM						
	Alirocumab	-42.7	-41.4	-27.7	-12.0	8.7	-
	Placebo	-20.9	-19.8	-6.9	-13.3	0.2	-
M. Farnier *et al*[14] (2016)	Rosuavstatin 10mg						
	Add-on Alirocumab	-42.7	-36.5	-27.9	-11.2	9.1	-
	Add-on ezetimibe	-13.4	-9.7	-4.3	-8.3	4.0	-
	Doubling of the rosuvastatin dose	-11.3	-7.3	-4.0	-1.8	1.7	-
	Rosuavstatin 20mg						
	Add-on Alirocumab	-31.4	-28.3	-22.7	-8.7	7.2	-
	Add-on ezetimibe	-12.9	-11.2	-5.8	-11.1	1.8	-
	Doubling of the rosuvastatin dose	-11.2	-9.8	-5.2	-9.9	1.5	-
Teramoto *et al*[16](2016)	Alirocumab 50 mg	-46.4	-43.7	-35.6	-21.1	3.4	-31.6
	Alirocumab 75 mg	-53.5	-48.9	-40.2	-10.7	5.7	-36.4
	Alirocumab150mg	-62.1	-60.2	-43.3	-15.0	2.0	-41.8
	Placebo	-1.2	-2.8	-3.7	1.3	2.1	-0.6
Bays *et al*[17] (2015)	Atorvastatin 20mg						
	Add-on Alirocumab	-36.7	-33.7	-23.6	-12.0	4.8	-
	Add-on Ezetimibe	-15.1	-10.1	-10.6	-3.3	-0.1	-
	Atorvastatin 40mg	-6.3	-4.4	-20.2	-6.7	1.9	-
	Atorvastatin 40mg						
	Add-on Alirocumab	-47.6	-41.9	-30.8	-19.1	7.7	-
	Add-on Ezetimibe	-21.0	-14.3	0.2	-13.9	2.0	-
	Atorvastatin 80mg	-6.5	-3.5	-9.7	-7.3	4.7	-
	Rosuvastatin 40mg	-17.4	-10.9	-4.9	-0.5	5.7	-
Cannon *et al*[18] (2015)	Alirocumab	-42.1	-40.7	-27.8	-13.0	8.6	-29.3
	Ezetimibe	-19.2	-18.3	-6.1	-12.8	0.5	-14.6
Kereiakes *et al*[20] (2015)	Alirocumab	-39.1	-36.7	-20.5	-6.0	3.5	-27.9
	Placebo	-1.6	-0.9	-5.9	-5.4	-3.8	-2.9
Roth *et al*[21] (2012)	Atorvastatin 80 mg+Alirocumab	-63.9	-58.0	-31.0	-24.7	5.8	-47.2
	Atorvastatin 10 mg+Alirocumab	-58.3	-54.4	-34.7	-4.0	2.6	-40.5
	Atorvastatin 80mg+Placebo	-22.3	-12.0	-2.7	-11.9	-3.6	-16.6

Table 4: Safety and adverse event outcomes of Alirocumab

	TEAEs	TESAEs	TEAE leading to death	TEAE leading to discontinuation	Injection site reactions
Shahawy *et al*[11] (2017) N=479	391	124	6	44	13
Ginsberg *et al* [12] (2016) N=72	51	10	0	3	6
Leiter *et al*[13] (2016)					
With DM(N=148)					
Without DM(N=331)	120	39	2	15	1
	271	85	4	29	12
M. Farnier *et al*[14] (2016) N=103	58	6	0	5	4
Teramoto *et al*[16] (2016) N=75	41	1	0	2	7
Bays *et al*[17] (2015) N=104	68	4	0	7	3
Cannon *et al*[18] (2015) N=479	341	90	2	36	12
Kereiakes *et al*[20] (2015) N=207	157	26	2	13	11
Roth *et al*[21] (2012) N=61	32	1	0	1	-

DISCUSSION

The Food and Drug Administration, USA approved Alirocumab in the year 2015 for use in patients with clinical ASCVD and HeFH receiving maximally tolerated statin therapy and still requiring further LDL-lowering. The dose of Alirocumab being 75 mg administered subcutaneously once every 2 weeks, adjusted upto 150mg subcutaneously once every 2 weeks based on the patients Lipid control.[21]

However, since the recent approval of the drug in the market, further epidemiological data may be necessary to elucidate the risk versus benefit outcomes of Alirocumab use. It may be applied in instances where only limited options remain in the control of dyslipidemias and in patients with statin intolerance.

Data and clinical outcomes are implicating the efficacy of Alirocumab in reduction of LDL being far greater than any of the existing lipid lowering therapies. Studies have shown that monotherapy of PCSK9 inhibitors cause 50-58% of LDL-C reduction.[22] This review briefs on the hypothesis that the LDL-C lowering capability of Alirocumab is further amplified when used with statins. To justify this, Stroes E *et al.*[32] studied the effect of monotherapy of Alirocumab on LDL reduction and it was found to be -51.7% and -53.5% for 150mg Q4W and 75mg Q2W respectively, whereas Teramoto *et al.*[12] studied the effect of same but in combination with background statins and found that the LDL reduction from baseline was -62.3% and -71.7% for the same doses. Hence, when the patients' cholesterol level is poorly controlled by baseline low, moderate or high intensity statin, it can be brought well within the range by adding Alirocumab.[23]

It was also found that, LDL-C reduction was increased in Alirocumab arm irrespective of and unaffected by the dose of statin, which indicates that even though Statins as well as PCSK9 monoclonal antibody therapy causes upregulation of LDL receptors, their mechanisms for LDL reduction are different.[23] Studies done on add on Alirocumab with different doses of statins showed that there is a lesser degree of reduction in LDL-C in higher doses of statin as compared to their lower doses. This effect can be attributed to the fact that statin treatment increases the activity of sterol regulatory element binding protein 2(SREBP-2) causing amplification of PCSK9 expression leading to reduced uptake of LDL-C and this happens dose dependently. But this effect is not significant with Ezetimibe.[24]

LDL reduction is attained at 4 weeks and remains considerably constant through 12 and 24 weeks,[25] and this is consistent with the study done by Shahawy *et al.*[13] which showed constant LDL reduction for upto 2 years. LDL reduction is shown to be accompanied by percent and absolute decrease in calculated 10 year cardiovascular risk calculated by both ACC/AHA and NIH calculators.[25]

In statin intolerance, Ezetimibe is the recommended alternative to statins but causes only 15-20% of LDL reduction.[26] In the absence of statins, a higher magnitude of LDL reduction is required and this need can be addressed by Alirocumab.[27]

Majority of patients with ASCVD and/or HeFH in Alirocumab arm, reached their target LDL levels in this pooled data. The additional LDL-C reduction caused by increasing the dose of Alirocumab from 75mg to 150mg at week 12 was around 14% in COMBO II and FH 1 study. The dose increase was more likely done in patients having higher baseline LDL-C.[18,19, 28]

Addition of Ezetimibe to baseline statin showed additional 12-18% reduction of LDL but only a 6% decrease in Apo B[23] but add on Alirocumab arm showed significantly higher reduction in ApoB.

For selection of candidates for PCSK9 inhibitors, it is highly beneficial for patients who have ASCVD with LDL-C ≥ 140mg/dl or LDL-C ≥ 100mg/dl for patients who are at high risk of retracting ASCVD.[29]

The safety and adverse effect profile of Alirocumab was found to be similar to that of Ezetimibe, hence Alirocumab can be effectively used instead of Ezetimibe in statin intolerant patients.[30] The treatment emergent adverse effects and serious adverse events are comparable with the previous studies.

Researchers have studied the various biological pathways underlining the lipid pathways, which includes association of males and the relation between PCSK9 and lipoprotein sub fractions and this interaction, may be attributed to a novel mechanism for gender disparity.[31] However this needs further exploration into the field.

The major limitation of this review is thes mall number of studies are included in the study. In some studies, the specifics of the baseline statins are not mentioned and there is no data on the adherence of the statins. This can cause information bias in the analysis. Another important limitation is that, as the drug is just few years into the market, there are not much post marketing data available for the drug.

CONCLUSION

This review states that there is additional LDL-C reduction when Alirocumab is added to baseline statins hence reducing the cardiovascular risk significantly. It was well established that this reduction due to Alirocumab is independent by type and dose of statins as compared to placebo. But as the dose of statins increases (high intensity) the degree of LDL-C reduction decreases. But high intensity statin as well as PCSK9 inhibitors are said to decrease CVD risk, hence further research is required to refine this concept. Research on PCSK9 inhibitors should be extended to explore its long term effects emphasizing on the cardiovascular morbidity and mortality.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ApoB: Apolipoprotein B; **ASCVD:** Atherosclerotic Cardio Vascular Disease; **FDA:** Food and Drug Administration, USA; **HDL-C:** High Density Lipoprotein Concentration; **HeFH:** Heterozygous Familial Hypercholesterolemia; **HoFH:** Homozygous Familial Hypercholesterolemia; **LDL-C:** Low Density Lipoprotein Concentration; **LDLR:** Low Density Lipoprotein-Receptor; **PCSK9:** Proprotein Convertase Subtilisin/Kexin Type 9; **TEAEs:** Treatment Emergent Adverse Events; **TGs:** Triglycerides; **TESAEs:** Treatment Emergent Serious Adverse Events; **VLDL:** Very Low Density Lipoproteins.

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