PCSK9 monoclonal antibodies are novel lipid-lowering therapy that have been extensively studied in patients with hypercholesterolemia either as monotherapy or as an add-on to other LLTs. PCSK9 monoclonal antibodies have significantly reduced the low-density lipoprotein cholesterol (LDL-C) plasma level resulting in a better LDL-C goal attainment. The commercially available PCSK9 monoclonal antibodies, alirocumab and evolocumab, have demonstrated reductions in major adverse cardiovascular events such as myocardial infarction, stroke, unstable angina, and the need for coronary revascularization but not mortality. PCSK9 monoclonal antibodies have demonstrated a favorable safety profile. The most reported side effects are mild injection site with no causal relationship proven between the inhibition of PCSK9 and neurocognitive or glycemic adverse events. In this overview, the efficacy and safety of PCSK9 monoclonal antibodies in the treatment of primary and familial hypercholesterolemia will be discussed.

Key words: Alirocumab, antidrug antibody, bococizumab, cardiovascular diseases, evolocumab, familial hypercholesterolemia, neurocognitive, proprotein convertase subtilisin-kexin type 9 inhibitors

INTRODUCTION

The reduction in low-density lipoprotein cholesterol (LDL-C) using statin therapy has shown significant benefits in terms of the prevention of primary and secondary atherosclerotic cardiovascular diseases (ASCVDs). Patients on maximally-tolerated statin doses may still suffer from cardiovascular (CV) events, inability to achieve target LDL-C, or intolerance to statin therapy. Subsequently, other lipid-lowering therapy (LLT) has been developed. Although ezetimibe has resulted in additional LDL-C-lowering effect when added to statins, the improvement in CV outcomes was not impressive.

Monoclonal antibodies directed against proprotein convertase subtilisin/kexin type 9 (PCSK9) are an innovative LLT that has the ability to substantially reduce LDL-C levels.

Alirocumab and evolocumab are currently approved by the Food and Drug Administration (FDA) for heterozygous familial hypercholesterolemia (HeFH) and for the prevention of CV events in patients with established cardiovascular disease (CVD). Evidence of PCSK9 monoclonal antibodies in homozygous familial hypercholesterolemia (HoFH) is limited with only evolocumab being labeled for this indication.

The American and the European guidelines have recently considered PCSK9 monoclonal antibody use in their recommendations. Although bococizumab development was stopped in 2016, trials on other potential monoclonal antibodies are ongoing with encouraging initial results. The efficacy and the safety of PCSK9 monoclonal antibodies in the treatment of hypercholesterolemia will be discussed in this overview.
MECHANISM OF ACTION

PCSK9 is a circulating plasma protein that is synthesized and secreted by hepatocytes.\textsuperscript{[12]} It regulates the LDL receptor (LDLR) located on the surface of hepatocytes. LDLR is the receptor responsible for clearing the circulating LDL-C particles from plasma by endocytosis. By binding to LDLR, PCSK9 prevents the release of LDLR from the endocytosed vesicle and causes LDLR lysosomal destruction, thus preventing its recycling.\textsuperscript{[4]} As a result, the LDLR density on the hepatocyte surfaces decreases affecting LDLR ability to eliminate LDL-C particles from the plasma, thus increasing their levels.\textsuperscript{[12]} By inhibiting PCSK9 from binding to LDLR with the use of monoclonal antibodies, LDL-C degrades and the LDLRs can be recycled and accumulate on the hepatocyte surface accelerating LDL-C particle clearance from plasma, thus reducing their levels.\textsuperscript{[4]}

HYPERCHOLESTEROLEMIA

The PCSK9 monoclonal antibodies were generally effective, safe and well-tolerated in early studies.\textsuperscript{[13‑26]} The PCSK9 monoclonal antibodies have been extensively studied in Phase III clinical trials in primary and familial hypercholesterolemia. In general, evolocumab was studied in two dosing regimens 140 mg every 2 weeks (Q2W) and 420 mg monthly (QM), whereas alirocumab was administered as 75 mg Q2w (75Q2W) increased to 150 mg Q2w (150Q2W) at week 12 if LDL-D was ≥1.8 mmol/L (70 mg/dL) at week 8. Both monoclonal antibodies were administered subcutaneously either alone or on top of other LLTs over periods of time ranging from 12 weeks up to 104 weeks.\textsuperscript{[27‑44]}

Primary hypercholesterolemia

Evolocumab in the LAPLACE-2 study (2014) reduced LDL-C by 59% to 66% (Q2W) or 62% to 65% (QM) at week 12 when added to moderate-intensity statins in patients with primary hypercholesterolemia and mixed dyslipidemia. LDL-C reductions by 86% to 90% (Q2W) and 93% to 95% (QM) were reported when added to high-intensity statins. LDL-C levels of <1.8 mmol/L (70 mg/dL) were achieved in about 86% to 94% of the patients on evolocumab as compared to 17% to 62% on ezetimibe. In the DESCARTES trial (2014), a significant reduction of around 57% in LDL-C at week 12 and maintained through week 52 was observed with evolocumab (QM) when combined with diet alone or with atorvastatin 10 mg or 80 mg (in the absence or presence of ezetimibe).

The percentage of patients who achieved the LDL-C goal of < 1.8 mmol/L (70 mg/dL) was 82.3% with evolocumab versus 6.4% with placebo. In the diet-alone group, patients on evolocumab showed a least-square mean reduction in LDL-C of 55.7%. In the atorvastatin 10 mg group, atorvastatin 80 mg group, and atorvastatin 80 mg plus ezetimibe 10 mg group, the mean reductions in LDL-C were 61.6%, 56.8%, and 48.5%, respectively. All comparisons reached statistical significance.

Alirocumab when added to atorvastatin 20 mg and 40 mg in ODYSSEY OPTIONS II trial (2015) significantly lowered LDL-C by 44.1% and 54.0% as compared to 20.5% and 22.6% with ezetimibe, respectively. In a third arm where atorvastatin 40 mg was switched to rosuvastatin 40 mg, the reduction of LDL-C was by 21.4%. In the arm of doubling atorvastatin dose, the reduction in LDL-C was only of an average of 5%. In ODYSSEY OPTIONS II trial (2016), alirocumab when added to rosuvastatin 10 mg arm significantly reduced LDL-C by 50.6% compared to 14.4% of the patients on ezetimibe or 16.3% on double-dose rosuvastatin. When added to rosuvastatin 20 mg, alirocumab significantly decreased LDL-C by 36.3% compared to 11% with ezetimibe or to 15.9% with doubling the dose of rosuvastatin.

In both OPTIONS I and OPTIONS II trials, LDL-C reductions were observed at week 4 and maintained through the study duration, with an average of 80% of the patients on alirocumab achieving their LDL-C targets. ODESSEY COMBO trial (2015) showed an estimated mean difference in baseline LDL-C of − 45.9% (P < 0.0001) with alirocumab 75Q2W at week 24 which was maintained through week 52. The study enrolled patients with hypercholesterolemia at high CV risk and 75% of them achieved LDL-C target compared to 9% on placebo. A similar patient population was recruited in the ODESSEY COMBO II trial (2015) over a similar duration. At week 24, LDL-C mean reduction with alirocumab versus ezetimibe was 50.6% versus 20.7% with a significant difference of −29.8%. Seventy seven percent of patients on alirocumab achieved LDL-C <1.8 mmol/L (70 mg/dL) versus 45.6% on ezetimibe.

In 2016, the ODYSSEY CHOICE II\textsuperscript{[49]} and ODYSSEY CHOICE II\textsuperscript{[52]} studies were published. Both studies recruited patients with hypercholesterolemia and at moderate-to-very high CV risk. At week 24 in ODYSSEY CHOICE I trial (2016), alirocumab 300 mg Q4W without statins showed a mean LDL-C change from baseline of −52.7% compared to + 0.3% with placebo. With statins, alirocumab showed a mean change of −58.8% compared to − 0.1% with placebo. The mean LDL-C change was significant in both the groups, and LDL-C reduction was maintained through week 48. In ODYSSEY CHOICE II trial (2016), patients receiving fenofibrate or ezetimibe or diet alone were randomized to alirocumab 150 mg Q4W (150Q4W) or 75Q2W increased to 150Q2W at week 12 if LDL-C
target was not achieved. The least-square mean LDL-C changes were $-51.7\%$ and $-53.5\%$ versus placebo $+4.7\%$ ($P < 0.0001$, for both) with $63.9\%$ and $70.3\%$ of the patients on alirocumab achieving their CV risk-specific LDL-C goal versus $1.8\%$ on placebo, respectively.

Both monoclonal antibodies were studied as monotherapy. In the MENDEL-2\cite{50-52} trial (2014), baseline LDL-C was significantly decreased by an average of $57\%$ and $56.1\%$ with biweekly and monthly evolocumab compared to $17.8\%$ and $18.6\%$ with ezetimibe or $0.1\%$ and $1.3\%$ with placebo, respectively. In the evolocumab groups, $69\%$ of the patients achieved LDL-C $<1.8$ mmol/L (70 mg/dL) versus $1\%$ in either the ezetimibe or placebo group. O DYSSSEY MONO\cite{47} study (2015) reported that alirocumab (75Q2W) led to a significant $47.2\%$ reduction in LDL-C compared with $15.6\%$ with ezetimibe. Furthermore, both agents were studied in specified patient populations, such as Japanese or diabetic patients.

In a Japanese\cite{28} study (2016), evolocumab on top of atorvastatin 5 or 20 mg reduced LDL-C by an average of $67\%$ to $76\%$. O DYSSSEY KT\cite{35} trial (2018) included patients from South Korea and Taiwan. Alirocumab versus placebo, on top of atorvastatin 40-80 mg, rosuvastatin 20, or simvastatin 40 mg, showed the least-square mean percentage change in LDL-C from baseline of $-57.1\%$ versus $+6.3\%$, with a statistically significant difference between the groups of $-63.4\%$. Patients with diabetes mellitus (DM) on insulin therapy with either type 1 or 2 (T1DM or T2DM) were enrolled in the O DYSSSEY DM-INSULIN\cite{53} trial (2017). Alirocumab 75Q2W as an add-on to statins with or without other LLTs yielded a least-square mean percentage change in baseline LDL-C of $-50.1\%$ versus $-1.3\%$ of the patients on placebo with a significant difference between the diabetic groups of $-49.0\%$ in type 2 DM (T2DM) and $-47.8\%$ in T1DM. The O DYSSSEY DM-DYSLIPIDEMIA\cite{34} study (2018) tested alirocumab 75Q2W in patients with T2DM and mixed dyslipidemia and CV risk factors. In the alirocumab group compared to the usual care group, there was a mean of $-37.3\%$ reduction in mean nonhigh-density lipoprotein cholesterol (non-HDL-C) versus $-4.7\%$ (difference of $-32.5\%, P < 0.0001$) and LDL-C reduction by $43\%$. More than $66\%$ of the patients achieved their non-HDL-C goals.

Evolocumab was studied in T2DM patients in the B E R S O N\cite{48} trial (2019). Evolocumab combined with atorvastatin showed a significant reduction in LDL-C by $\geq 70\%$ in both regimens (Q2W and QM). In a two-dose regimen, the E V O P A C S\cite{49} trial (2019) investigated evolocumab 420 mg QM in patients during hospitalization due to acute coronary syndrome (ACS). Evolocumab on top of high-dose statin showed a difference in mean percentage change from baseline LDL-C of $-40.7\%$ with $95.7\%$ of the patients who achieved LDL-C $<1.8$ mmol/L (70 mg/dL) versus $37.6\%$ on placebo. Finally, PCKS9 monoclonal antibodies are considered effective and safe in statin-intolerant patients, as reported in at least three\cite{50-52} trials. Evolocumab in the GAUSS-2\cite{50} (2014) and GAUSS-3\cite{51} (2016) studies significantly reduced LDL-C by $53\%$–$56\%$ and $52.8\%$, respectively. Moreover, a significant LDL-C reduction by $45\%$ was achieved with alirocumab use in the O DYSSSEY ALTERNATIVE\cite{52} trial (2015) at week 24. The aforementioned trials\cite{50-52} defined statin intolerance as the inability to tolerate two or more statins at the lowest available dosage.

**Familial hypercholesterolemia**

Evolocumab in the R U T H E R F O R D - 2\cite{30} trial (2015), which recruited patients with HeFH and LDL-C of $\geq 2.58$ mmol/L (100 mg/dL), significantly reduced baseline LDL-C by $61.3\%$ (QM) and $59.2\%$ (Q2W) at week 12. In O DYSSSEY FH I and FH II\cite{42} (2015), alirocumab as an add-on therapy to statins in patients with HeFH significantly reduced LDL-C by $57.9\%$ and $51.4\%$, respectively, at week 24 through week 78. With a longer follow-up, the reported LDL-C reductions were $51.8\%$ and $52.1\%$ and the percentages of patients who achieved target LDL-C were $59.8\%$ and $68.2\%$, respectively. Patients with HeFH and LDL-C $\geq 4.14$ mmol/L (160 mg/dL) when started on alirocumab 150Q2W on top of statin in O DYSSSEY HIGH FH\cite{41} trial (2016) had a percent change in baseline LDL-C of $-45.7\%$ compared to $-6.6\%$ on placebo with a significant least square mean difference of $-39.1\%$ at week 24 which maintained through week 78. The percentage of patients on alirocumab who achieved LDL-C targets was $41\%$ as compared to $5.7\%$ on placebo.

In the O DYSSSEY OLE\cite{43} study (2018), alirocumab led to an LDL-C reduction by $44.2\%$ at week 8 that increased to $47.9\%$ by week 96. The T A U S S I G\cite{53} trial (2020) recruited patients with HoFH (35\%) or severe HeFH (65\%) who completed Part A or B of the T E S L A study and administered evolocumab over 4 years. At weeks 12 and 216, patients with HoFH showed smaller relative reductions in LDL-C ($-21.2\%$ and $-4\%$, respectively) when compared to that in patients with severe HeFH ($-54.9\%$ and $-47.2\%$, respectively). In the T E S L A-B\cite{29} trial (2015), evolocumab (QM) on top of LT significantly decreased LDL-C by $30.9\%$ in HoFH patients after 12 weeks of therapy.

In patients with HeFH and/or coronary heart disease (CHD) on LLT and baseline LDL-C of $\geq 4.14$ mmol/L (160 mg/dL), alirocumab 150Q2W reduced LDL-C levels by $55\%$ at week 24 in the alirocumab expanded use program (2018).\cite{36} Moreover, in Japanese patients with HeFH or non-FH and high CV risk on statins, i.e., O DYSSSEY J AP AN\cite{39} trial (2016), there was a least-square mean change...
in baseline LDL-C of −62.5% in the alirocumab group versus + 1.6% in the placebo group at week 24 through 52 weeks with 96.7% of the patients achieving their LDL-C goals. In a pooled analysis of four evolocumab 12-week trials (LAPLACE-2,[27] RUTHERFORD-2,[30] MENDEL-2,[31] and GAUSS-2[60]) including mixed patient populations, i.e., familial and primary hypercholesterolemia with different CV risks and prior statin intolerance, evolocumab as compared to placebo led to mean percent changes in LDL-C of −65.7% (Q2W) and −65.0% (QM). When compared to ezetimibe, the mean percent changes in LDL-C were −38.9% (Q2W) and −40.3% (QM).

**CARDIOVASCULAR BENEFIT**

PCSK9 inhibition is an important process in controlling lipid levels to prevent primary or secondary CV incidents. The ODYSSEY LONG TERM[58] trial (2015) showed that alirocumab significantly lowered LDL-C by 62%, and the rate of major adverse CV events (MACE) by 48% [hazard ratio (HR), 0.52; 95% confidence interval (CI), 0.31–0.90; nominal \( P = 0.02 \)]. Similarly, evolocumab in the OSLER[56] study (2015) significantly reduced LDL-C by 61% and adverse CV events rate by 53% (HR, 0.47; 95% CI, 0.28–0.78; \( P = 0.003 \)).

The multicenter double-blind FOURIER[57] trial, a large-scale CV outcome trial was published in 2017. The study enrolled 27,564 patients with ASCVD and LDL-C level of ≥1.8 mmol/L (70 mg/dL) who were on statin therapy across 49 countries. It investigated the effect of evolocumab (140 mg Q2W or 420 mg QM) in addition to statin therapy on CV events against matched placebo. In the evolocumab group, patients achieved a mean 59% reduction in LDL-C at 48 weeks and had a significantly reduced risk of the primary composite endpoint (HR, 0.85; 95% CI, 0.79–0.92; \( P < 0.001 \)) at a median duration of follow-up of 26 months. The primary endpoint was a composite of CV death, myocardial infarction (MI), stroke, hospitalization for unstable angina (UA), or coronary revascularization. There was also a statistically significant reduction in the secondary endpoint of CV death, MI, or stroke (HR, 0.80; 95% CI, 0.73–0.88; \( P < 0.001 \)) but not in CV death as an individual component.

In 2017, the combined analysis of SPIRE-1 and SPIRE-2 trials was also published. The SPIRE-1 and SPIRE-2 trials were parallel multicenter, double-blind, randomized control trials that tested bococizumab in addition to statin therapy on CV events in patients at high risk for CV events. The primary endpoint was a composite of CV death, nonfatal MI, nonfatal stroke, and hospitalization for UA needing urgent revascularization. Patients in the SPIRE program developed high rates of antidrug antibodies (ADAs), and the combined analysis of the SPIRE-1 and SPIRE-2 trials did not show any benefit with regards to MACE rates. As a consequence, both SPIRE trials were discontinued prematurely by the sponsor in November 2016.[7,58]

The ODYSSEY OUTCOMES trial (2018) was a multicenter, double-blind, randomized control trial that investigated the effect of alirocumab (75 mg or 150 mg Q2W) on top of statin therapy on CV events. The study recruited 18,924 patients with LDL-C >1.8 mmol/L (70 mg/dL) and on a maximally tolerated dose of statin who had a recent ACS event across 57 countries. Alirocumab significantly lowered the primary endpoint of a composite of CV death, MI, stroke, hospitalization for UA, or coronary revascularization (HR, 0.85; 95% CI, 0.78–0.93; \( P < 0.001 \)) over a median follow-up of 48 months with the absolute benefit among patients with baseline LDL-C of ≥2.58 mmol/L (100 mg/dL). The CV benefit of the PCSK9 monoclonal antibodies was related in part to the reduction in the levels of atherogenic lipids such as LDL-C, non-HDL-C, lipoprotein (a) (Lp(a)), and apolipoprotein B.[60] In addition, evolocumab on top of statin therapy in the GLAGOV study (2016) lowered the atheroma volume and led to plaque regression.

**ADVERSE EFFECTS**

Findings from PCSK9 monoclonal antibodies research did not find excess in muscle adverse symptoms or rise in creatinine kinase or liver enzyme levels which are commonly associated with statin therapy.[1-60] Nasopharyngitis and mild self-limited injection site reactions (e.g., itching, redness, and swelling) are considered the most frequent adverse reactions.[4,59,62]

Anti-drug antibodies (ADAs) can be generated in response to monoclonal antibodies either with the fully human (e.g., alirocumab and evolocumab) or the humanized (e.g., murine-derived bococizumab) type. Alirocumab and evolocumab did not lead to a significant ADAs generation unlike bococizumab which generated high-titer ADAs due to its high immunogenic property.[58,63] The aforementioned difference explains the higher injection site reaction rate reported with bococizumab.[58] The very low LDL-C levels achieved with PCSK9 monoclonal antibodies have raised a concern about the association of their use with cognitive impairment,[64] such as delirium, attention disorders, amnesia, dementia, disturbances in thinking and perception, or mental impairment disorders.[4,63]

Findings from the published literature did not find a statistically significant difference in terms of neurocognitive adverse events with alirocumab and evolocumab use when compared with the control.[1,55,57,59,60,64] As previously suggested that a significant reduction in LDL-C levels with statin use may influence the glycemic status of the body and lead to an
increase in diabetes incidence,[58,65] the current body of evidence[1,60,65] did not prove that alirocumab-b[33,55,59,66] nor evolocumab[48,57,67-70] use would significantly increase the incidence of new-onset diabetes or worsen the preexisting diabetic condition.

Finally, there were no clinically meaningful changes in the levels of fat-soluble vitamins (e.g., Vitamin E & K) and steroid hormones in the studies that measured their levels as part of a prespecified safety analysis.[58,71]

**SUMMARY**

The currently available PCSK9 monoclonal antibodies, alirocumab and evolocumab, are proved effective and safe when used alone or in addition to other LLTs in patients with hypercholesterolemia in the presence or absence of CV risk. The significant reduction in baseline LDL-C observed early with PCSK9 monoclonal antibodies therapy has been associated with positive CV outcomes but not mortality benefit. The safety profile of PCSK9 monoclonal antibodies is good since most of the reported adverse effects are mild and the reported neurocognitive adverse events in some studies are not statistically significant. PCSK9 monoclonal antibodies offer a safe and effective therapeutic option for patients who are intolerant to statin therapy or who have not achieved their LDL-C goals.

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**Conflicts of interest**

There are no conflicts of interest.

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