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REVIEW ARTICLE

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Efficacy and safety of PCSK9 monoclonal antibodies: an evidence-based review and update

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ABSTRACT

Objective: Treatment of dyslipidemia lowers cardiovascular (CV) risk. Although statin use is a cornerstone therapy, many patients are not achieving their risk-specific low-density lipoprotein cholesterol (LDL-C) goals. The proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies have been extensively studied as lipid-lowering therapy (LLT). Herein, we present an updated evidence-based review of the efficacy and safety of PCSK9 monoclonal antibodies in the treatment of familial and non-familial hypercholesterolemia.
Methods: PubMed database was searched to review Phase III studies on PCSK9 monoclonal antibodies. Then, the US National Institutes of Health Registry and the WHO International Clinical Trial Registry Platform were searched to identify and present the ongoing research.
Results: PCSK9 monoclonal antibodies were investigated for the treatment of dyslipidemia, as a single therapeutic agent or as an add-on therapy to the traditional LLT. They proved effective and safe in the treatment of familial and non-familial hypercholesterolemia, and in the prevention of adverse CV events.
Conclusions: The use of PCSK9 monoclonal antibodies in the treatment of dyslipidemia is currently recommended to achieve risk-specific LDL-C goal to reduce adverse CV events. Future results of the ongoing research might expand their clinical generalizability to broader patient populations.

Introduction

It has been well established that lipid-lowering therapy (LLT) targeting low-density lipoprotein cholesterol (LDL-C) lowers cardiovascular (CV) risk. This is largely based on significant benefits observed with statin therapy in the prevention of primary and secondary atherosclerotic cardiovascular disease (ASCVD)[1,2]. Although statins remain the cornerstone of LLT, yet patients on statin therapy may still experience CV events[2], statin intolerance, or inability to achieve target LDL-C levels despite maximally-tolerated doses. Thus, alternative LLT to further decrease LDL-C levels and improve CV outcomes has been investigated[1]. Ezetimibe in combination with statin therapy has shown incremental lowering of LDL-C levels and improvement in CV outcomes. However, such improvements are modest and the overall outcome data on ezetimibe monotherapy are scarce[1,3]. Monoclonal antibodies are novel lipid-lowering agents that reduce LDL-C levels by inhibiting proprotein convertase subtilisin/kexin type 9 (PCSK9). The currently available antibodies, alirocumab and evolocumab, are fully human immunoglobulin-G (IgG) subtypes[4] and are 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).

Evolocumab is also indicated for homozygous familial hypercholesterolemia (HoFH)[5]. International guidelines have been updated to include PCSK9 antibodies in their recommendations[6–8]. The development of a third PCSK9 antibody, bococizumab, in advanced phase III clinical trials was abandoned in 2016. After the completion of six bococizumab studies, an unexpected attenuation of effect on LDL-C over time was observed, in addition to high rates of injection-site reaction due to high immunogenicity[9]. However, the development of new investigational monoclonal antibodies to inhibit PCSK9 is well under way with promising initial results[10–13]. This review will discuss the efficacy and safety profile of PCSK9 monoclonal antibodies or inhibitors in the treatment of familial and non-familial hypercholesterolemia. For the purpose of this review, PCSK9 monoclonal antibodies or inhibitors will be used interchangeably.

Materials and methods

Search strategy for studies on PCSK9 monoclonal antibodies

PubMed literature search was carried out on 31 December 2019 for original trials, using broad MeSH terms in the

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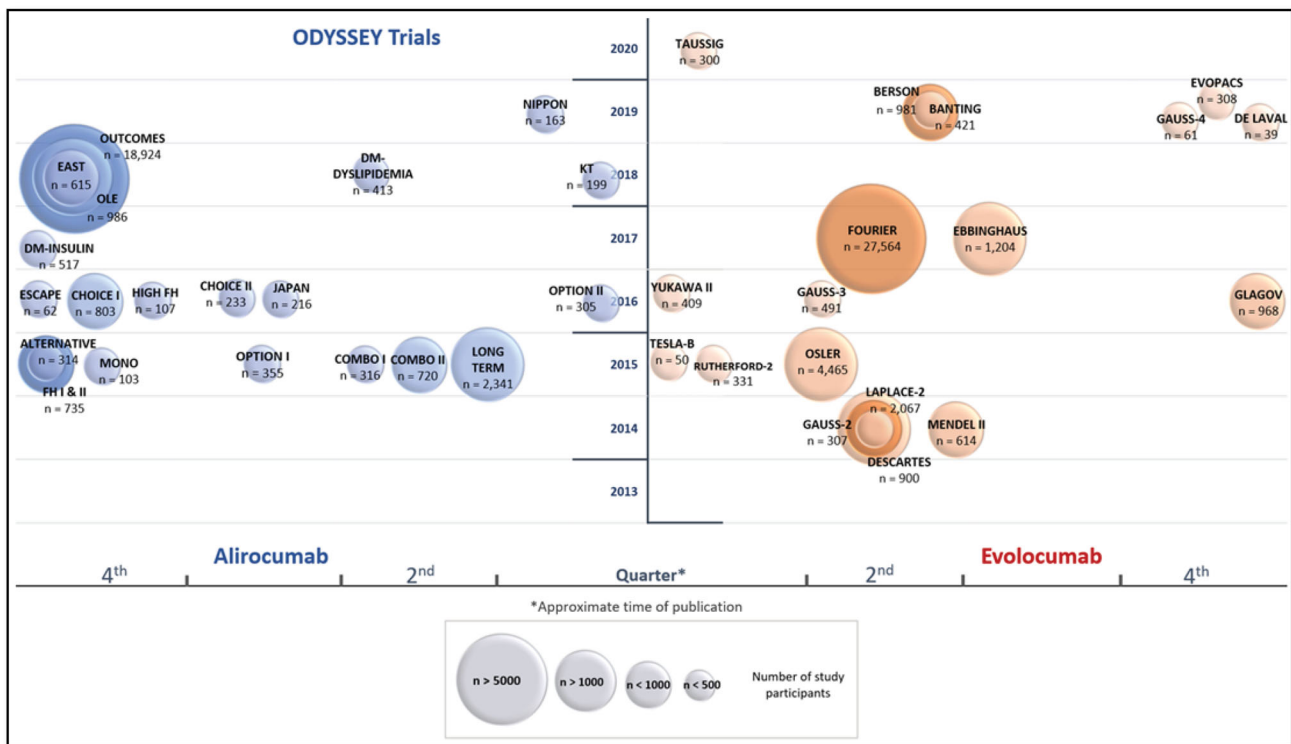
Figure 1. Timeline of phase III studies of alirocumab and evolocumab.

following search thread: ("alirocumab" [Supplementary Concept] OR "evolocumab" [Supplementary Concept] OR "bococizumab" [Supplementary Concept]). The search was limited to "Humans" and "Clinical Trial". The references' lists of the identified trials were manually searched to identify further potentially useful articles. Several meta-analyses, pre-specified, post hoc and pooled analyses of PSCK9 inhibitors trials have been included to emphasize their findings. The literature search was updated on March 1, 2020. Figure 1 presents the approximate publication period of time of Phase III clinical trials discussed in the review.

Search strategy for registered clinical trials (ReCTs)

Literature search on the ongoing active research on PCSK9 monoclonal antibodies was conducted on 15 March 2020. The search strategy included the individual agents separately: alirocumab and evolocumab. The United States (US) National Institutes of Health Registry (http://clinicaltrials.gov/) was searched for Phase III trials and recruitment status of "Active, not recruiting", "Recruiting" and "Not yet recruiting" and the World Health Organization (WHO) International Clinical Trial Registry Platform (ICTRP) (http://www.who.int/ictrp/network/en/) for Phase III trials.

Mechanism of action of PCSK9 monoclonal antibodies

The PCSK9 is a low-abundance circulating plasma protein that is synthetized and secreted by hepatocytes[14]. PCSK9 regulates LDL receptor (LDLR) on hepatocytes surfaces, which is the primary receptor that is responsible for clearing the circulating LDL particles by endocytosis. PCSK9 binds to LDLR, stabilizes the LDL/LDLR complex and prevents LDLR from being released from the endocytosed vesicle causing lysosomal destruction of the LDLR and thus preventing its recycling[5,15]. Subsequently, there is reduction in the LDLR density on the hepatocytes surfaces which affects the ability to eliminate the circulating LDL particles leading to an elevated plasma cholesterol level[14]. Preclinical trials have shown that PCSK9 has direct proinflammatory action on the vessel walls which could be explained by its effect on LDLR-related protein 1 (LRP1) which regulates plaque macrophages[5]. PCSK9 circulating in the plasma has also been postulated to flow through the arterial plaque adding up to the plaque PCSK9 concentration which controls LDLR expression in the atheroma and reduces levels of LRP1[5]. Increased LDLR expression through the inhibition of PCSK9 will result in profound uptake of lipoprotein cholesterol into the atheroma theoretically while the reduction of LRP1 levels results in induction of inflammation[4,5]. Monoclonal antibodies such as alirocumab and evolocumab, self-administered subcutaneously every two or four weeks, bind to PCSK9 preventing its binding to LDLR. When PCSK9 is absent or its binding to LDLR is inhibited, LDL is degraded while the LDLR can be recycled then accumulate on the hepatocyte's membrane leading to an accelerated LDL clearance and reduced levels in blood[5]. Accordingly, PCSK9 inhibition have two counteracting actions with a net effect of reduction of LDL-C levels and atheroma volume[4]. An injection of monoclonal antibodies can completely inactivate all the circulating PCSK9 within hours[5,14], and all the newly secreted PCSK9 after several days[5]. Marked reduction in LDL-C levels starts one day after an injection[14]. Inhibition of PCSK9 can also be achieved by

targeting PCSK9 synthesis in hepatocytes. Inclisiran, a long-acting small interfering RNA (siRNA), that inhibits translation of PCSK9 mRNA leading to a reduced PCSK9 synthesis. Inclisiran is a valid alternative to PCSK9 inhibitors with an advantage of twice-a-year injection to produce an LDL-C reduction by 50% or more[16]. Bempedoic acid is another promising agent that could be a potential alternative to statins. It is an oral once-daily molecule that acts as an inhibitor to adenosine triphosphate (ATP) citrate lyase. The latter is an enzyme that upstream from 3-hydroxy-3-methylglutaryl-coenzyme A. Thus, reducing cholesterol synthesis[16,17].

Efficacy of PCSK9 monoclonal antibodies

The Phase I studies of evolocumab, alirocumab, and bococizumab have shown reduction in LDL-C levels in healthy volunteers and patients with familial and non-familial hypercholesterolemia. They were generally effective, safe and well-tolerated[18–20]. Similar results have been obtained from Phase II studies, which are usually dose-finding, of alirocumab[21–24], bococizumab[25–27], and evolocumab[28–31]. The PCSK9 monoclonal antibodies have been studied in Phase III clinical trials for lipid, cardiovascular, and safety outcomes. Data in HoFH are limited in general.

Lipid outcomes

For the purpose of Figure 2, when the monoclonal antibody was tested in several arms i.e. in different strengths and/or in combination with other LLT, the LDL-C values were averaged using the values of different arms of the Phase III trials presented in the review.

Primary hypercholesterolemia
Primary hypercholesterolemia is defined as blood cholesterol measurement >5.17 mmol/L (200 mg/dL) that could be attributed to genetics, obesity, or dietary intake[32]. In patients with primary hypercholesteremia in the absence or presence of various CV risk levels, who have not reached their CV risk-specific LDL-C goals, the effect of PCSK9 inhibitors on LDL-C levels has been extensively studied as monotherapy, in statin intolerance, or as an add-on to diet-alone or other LLT such

as statins, ezetimibe, fenofibrate. Several studies have shown that alirocumab and evolocumab significantly reduce LDL-C levels at Weeks 12[33–37], 24[38–42], 52[43–45], 56[46], 78[47,48], 96[49], and 104[50] of therapy. In most trials[38,46,50–52], authors adopted the 2011[53] and 2012[54] European guidelines' definitions of CV risk categories. Patients with very high CV risk are defined, as per studies, to have a documented coronary heart disease (CHD) or CHD risk equivalents such as type 1 (T1DM) or 2 (T2DM) diabetes mellitus (DM) with target organ damage, ischemic stroke, peripheral artery disease (PAD), or carotid artery occlusion >50% without symptoms, carotid endarterectomy or carotid artery stent procedure, or renal artery stenosis or renal artery stent procedure. High CV risk are defined as patients with no history of CVD or CHD but with other risk factors such as calculated 10-year risk of fatal CVD using the European Systematic Coronary Risk Evaluation (SCORE) score of ≥5% (although the guidelines specified ≥5% and <10%), T1DM or T2DM without target organ damage, moderate chronic kidney disease (CKD). Moderate CV risk is defined as SCORE score of ≥1 and <5%[38,46]. On the other hand, the 2018 American guidelines[7] defined very high-risk patients to have a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions such as age ≥65 years, HeFH, history of coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s), DM, hypertension, CKD (eGFR 15–59 mL/min/1.73 m^2), current smoking persistently elevated LDL-C (LDL-C ≥2.6 mmol/L (100 mg/dL) despite maximally tolerated statin therapy and ezetimibe or history of congestive heart failure. It is worth nothing that the 2019 European guidelines[8] re-defined very high risk CV category to include family history with ASCVD or with another major risk factor, and moderate risk CV category to include young patients (T1DM <35 years, T2DM <50 years) with DM duration of <10 years and without other risk factors.

Short-term trials (≤12 weeks)

The LAPLACE-2[33] study (n = 2067) enrolled patients with primary hypercholesterolemia and mixed dyslipidemia. Evolocumab 140 mg every 2 weeks (Q2W) or 420 mg monthly (QM), on top of moderate-intensity statins reduced LDL-C by 59–66% or by 62–65%, respectively. When added to
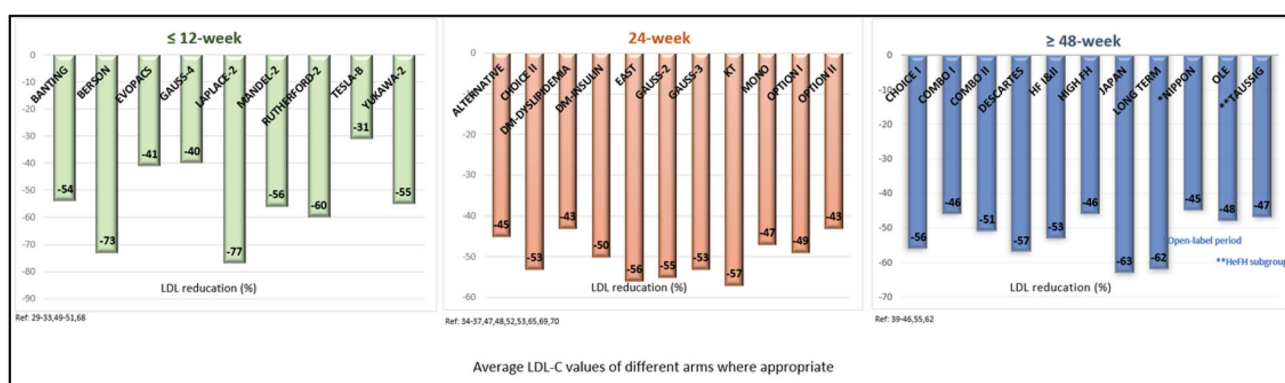

Figure 2. Approximate LDL-C reductions in phase III trials.

high-intensity statins, Q2W dose reduced LDL-C by 86–90%, while QM dose reduced the levels by 93–95%. Around 86–94% of the patients on evolocumab and 17–62% on ezetimibe achieved LDL-C level < 1.8 mmol/L (70 mg/dL) regardless of the statin therapy used. In the large MENDEL-2[37] monotherapy trial ($n = 612$), the biweekly and monthly evolocumab decreased LDL-C levels from baseline by an average of 57 and 56.1% compared to 17.8 and 18.6% for ezetimibe or to 0.1 and 1.3% for placebo ($p < .001$, all comparisons), respectively. There were higher rates in patients achieving LDL-C level < 1.8 mmol/L (70 mg/dL) in the evolocumab groups (69%) than ezetimibe (1%) or placebo (1%) groups. Kiyosue et al.[34] in the Japanese YUKAWA II study ($n = 409$), recruited high CV risk patients with hyperlipidemia and mixed dyslipidemia. Evolocumab 140 mg Q2W or 420 mg QM on top of atorvastatin 5 or 20 mg reduced LDL-C by an average of 67–76%. When studied in patients during hospitalization due to acute coronary syndrome (ACS) in the EVOPACS[55] study ($n = 308$), evolocumab 420 mg QM for 2 doses added to high-dose statin resulted in a difference in mean percentage change from baseline of −40.7% ($p < .001$). In the evolocumab group, around 95.7% of patients achieved LDL-C levels < 1.8 mmol/L (70 mg/dL) by Week 8 versus 37.6% in the placebo group. The BERSON[56] trial ($n = 981$) evaluated the efficacy and safety of evolocumab (140 mg Q2W or 420 mg QM) combined with atorvastatin in T2DM patients with hyperlipidemia and mixed dyslipidemia. Evolocumab was well-tolerated and significantly decreased LDL-C levels by ≥70% in both dosing regimens ($p < .0001$). In a similar patient population in the BANTING[57] trial ($n = 421$), evolocumab (420 mg QM) on top of statins reduced LDL-C by a mean of 54.3% compared to 1.1% in placebo group ($p < .0001$) with significantly more patients achieved LDL-C < 1.8 mmol/L (70 mg/dL); 84.5 versus 15.4%, respectively. Evolocumab had no negative impact on glycemic parameters in both trials after 12 weeks of treatment[56,57].

24-Week trials

In ODYSSEY EAST[58] ($n = 615$), ODYSSEY KT[41] ($n = 199$), ODYSSEY OPTIONS I[51] ($n = 355$) and ODYSSEY OPTIONS II[52] ($n = 305$) trials, alirocumab 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, was studied in patients with very high CV risk and LDL-C levels ≥1.8 mmol/L (70 mg/dL) or with high CV risk and LDL-C levels ≥2.6 mmol/L (100 mg/dL) despite maximumly tolerated statin therapy. In ODYSSEY EAST[58] trial that was conducted in three Asian countries (China, India, Thailand), there were reductions in LDL-C levels by 56 versus 20.3% with alirocumab versus ezetimibe ($p < .0001$). The ODYSSEY KT[41] trial enrolled patients from South Korea and Taiwan who were on atorvastatin 40 to 80 mg, rosuvastatin 20, or simvastatin 40 mg. The least-squares mean percentage change in LDL-C from baseline was −57.1% in alirocumab group and +6.3% in placebo group, with a difference between groups of −63.4% ($p < .0001$). In ODYSSEY OPTIONS I[51] trial, alirocumab as an

add-on to atorvastatin 20 mg and 40 mg reduced LDL-C levels by 44.1 and 54.0% compared to 20.5 and 22.6% with ezetimibe ($p < .001$, both comparisons), respectively. Switching atorvastatin 40 mg to rosuvastatin 40 mg in a third arm resulted in 21.4% reduction, while doubling atorvastatin dose in the fourth arm yielded an average of 5% reduction in baseline LDL-C levels. In ODYSSEY OPTIONS II[52] trial, alirocumab was added to either rosuvastatin 10 mg or 20 mg. In rosuvastatin 10 mg arm, alirocumab reduced LDL-C levels by 50.6% compared to 14.4% in ezetimibe group or 16.3% by doubling rosuvastatin dose ($p < .0001$). In rosuvastatin 20 mg arm, alirocumab reduced LDL-C levels by 36.3% compared to 11% in ezetimibe group ($p = .0136$) or to 15.9% in double-dose rosuvastatin group ($p = .0453$). In the four aforementioned studies[41,51,52,58], the reductions were observed at Week 4 and maintained through the study duration with an average of 80% or more of the patients on alirocumab achieving LDL–C < 1.8 mmol/L (70 mg/dL). ODYSSEY DM-INSULIN[39] trial ($n = 517$), in diabetics (types 1 and 2) with hypercholesterolemia and high CV risk on insulin and statins with or without other LLT, showed a least-squares mean percentage change in baseline LDL-C of −50.1% with alirocumab (75Q2W) versus −1.3% with placebo ($p < .0001$). The difference between the groups was −49.0% in T2DM and −47.8% in T1DM ($p < .0001$). The reductions were similar regardless of disease state or age. In ODYSSEY DM-DYSLIPIDEMIA[40] trial ($n = 413$), patients with T2DM and mixed dyslipidaemia with ASCVD or at least one additional CV risk factor were randomized to alirocumab (75Q2W) or usual care (maximally tolerated statins with other LLT; fenofibrate, ezetimibe, omega-3 fatty acid, nicotinic acid). The mean non-high-density lipoprotein cholesterol (non-HDL-C) reduction was −37.3% in alirocumab group versus −4.7% (difference of −32.5%, $p < .0001$) with >66% of patients achieving non-HDL-C level of 2.6 mmol/L (100 mg/dL). Alirocumab also reduced LDL-C levels by 43%. In the trials that evaluated the every-4-week (Q4W) dose, alirocumab has shown similar outcomes. In ODYSSEY CHOICE II[38] trial ($n = 233$), moderate, high, and very high CV risk patients with hypercholesterolemia receiving fenofibrate or ezetimibe or diet-alone, were randomized to alirocumab 150 mg Q4W (150Q4W) or 75Q2W increased to 150Q2W at Week 12, if target LDL-C was not achieved at Week 8 (75/150 mg). The least-squares mean LDL-C changes was −51.7% (150Q4W) and −53.5% (75Q2W) versus placebo +4.7% ($p < .0001$, both comparisons). The reductions were observed at Week 4 and maintained through the study duration with 63.9% (150Q4W) and 70.3% (75Q2W) of patients on alirocumab achieving LDL–C target versus 1.8% on placebo. ODYSSEY MONO[59] trial ($n = 103$), the first study to test alirocumab in patients on no LLT, showed that patients on alirocumab (75Q2W) had a 47.2% reduction in LDL-C compared with a 15.6% with ezetimibe ($p < .0001$). A post-hoc pooled analysis[60] from nine randomized, double-blind, placebo- or ezetimibe-controlled, 24- to 104-week ODYSSEY Phase III trials evaluated add-on alirocumab to statins in regimens of 150Q2W and 75/150 mg. The observed change in LDL-C level was −61.5% with alirocumab 150Q2W versus −1.0% with placebo, −46.4% with

alirocumab 75/150 mg versus +6.3% with placebo, and −48.7% with alirocumab 75/150 mg versus −20.6% with ezetimibe. Without statins, an LDL-C change of −54.9% was observed with alirocumab versus +4% with ezetimibe. Patients on alirocumab were more likely to achieve LDL-C < 1.8 mmol/L (70 mg/dL) and < 1.42 mmol/L (55 mg/dL). At Week 8, around 16.3% of patients on alirocumab 75Q2W and statins required dose increase to 150Q2W, while 34.8% alirocumab 75Q2W without statins required dose adjustment.

Longer-term trials (≥48 weeks)

Evolocumab 420 mg Q4W combined with diet-alone or with atorvastatin 10 mg or 80 mg (with or without ezetimibe), showed an average of 57% (p < .001) reduction in LDL-C at Week 12 maintained through Week 52 when studied in hyperlipidemic patients with CV risk in the DESCARTES[44] trial (n = 900). Around 82.3% of patients on evolocumab achieved LDL-C level < 1.8 mmol/L (70 mg/dL) versus 6.4% on placebo. In the diet-alone group, the least-square mean reduction in LDL-C was 55.7%, in the atorvastatin 10 mg group was 61.6%, in the atorvastatin 80 mg group was 56.8% and in the atorvastatin 80 mg plus ezetimibe 10 mg group was 48.5% (p < .001, all comparisons). The ODYSSEY COMBO I[43] trial (n = 316) in hypercholesterolemic patients at high CV risk, showed estimate mean difference in baseline LDL-C of −45.9% (p < .0001) with alirocumab 75Q2W at 24 weeks. Furthermore, 75% of patients achieved LDL-C < 1.8 mmol/L (70 mg/dL) in alirocumab group compared to 9% in the placebo group. The reductions were sustained till Week 52. In ODYSSEY CHOICE I[46] trial (n = 803) in hypercholesterolemic patients at moderate-to-very-high CV risk, alirocumab 300 mg Q4W without statins showed mean LDL-C change from baseline by −52.7% compared to +0.3% with placebo (p < .0001) at Week 24. While those on statins showed a mean change of −58.8% compared to −0.1% with placebo (p < .0001). The results were maintained through Week 48 in both groups. When compared to ezetimibe in hypercholesterolemic patients at high CV risk in the ODYSSEY COMBO II[50] trial (n = 720), alirocumab 75Q2W reduced LDL-C by a mean of 50.6% as compared to a mean of 20.7% with a difference of −29.8% (p < .0001) at Week 24. The reductions were sustained till Week 52 and the percentage of patients who achieved LDL-C < 1.8 mmol/L (70 mg/dL) was 77% on alirocumab versus 45.6% on ezetimibe (p < .0001).

Familial hypercholesterolemia

Alirocumab 150Q2W when added to statin therapy in ODYSSEY HIGH FH[47] trial (n = 107) in patients with HeFH and LDL-C ≥ 4.14 mmol/L (160 mg/dL), resulted in a percent change in LDL-C from baseline of −45.7% compared to −6.6% by placebo with least-square mean difference between the groups of −39.1% (p < .0001). Forty one percent of the patients on alirocumab achieved LDL-C risk-specific goals versus 5.7% in the placebo group at Week 24. These reductions were maintained through the treatment phase of 78 weeks. At a dose of 75/150 mg in patients with

HeFH in ODYSSEY FH I and FH II[48], alirocumab on top of maximally tolerated statins led to 57.9 and 51.4% (p < .0001) reduction in LDL-C at Week 24, respectively, and were maintained up to week 78. After 78 weeks, the reductions were 51.8 and 52.1% from baseline LDL-C levels. The percentage of patients who achieved LDL-C levels < 1.8 mmol/L (70 mg/dL) was 59.8 and 68.2% versus 0.8 and 1.2% in placebo, respectively. Evolocumab 420 mg Q4W on top of stable LLT, reduced baseline LDL-C by 30·9% (p < .0001) in 50 patients with HoFH at 12 weeks in the TESLA-B trial[35]. In an open-label single-arm TAUSSIG[61] trial (n = 300), evolocumab over 4 years was well-tolerated and effective in patients with HoFH (35%) and severe HeFH (65%) who completed Part A or B of the TESLA study. At Week 12 and 216, relative reductions in LDL-C were smaller in patients with HoFH (-21.2 and −24%, respectively) as compared with that in patients with severe HeFH (-54.9 and −47.2%, respectively). When studied in RUTHERFORD-2[36] trial (n = 331) which recruited patients with HeFH and LDL-C ≥ 2.6 mmol/L (100 mg/dL), evolocumab reduced baseline LDL-C by 61·3% with 420 mg QM and 59·2% with 140 mg Q2W (p < .0001, for both against placebo) at Week 12. In an analysis[62] of patients with HeFH (n = 1257) in 4 double-blind, randomized, placebo-controlled, 78-week ODYSSEY studies (HIGH FH[47], FH I and II[48], and LONG TERM[63]) a mean percent change in baseline LDL-C of −43.6% was observed with alirocumab 75Q2W at Week 12, increased to −48.8% with alirocumab (75/150 mg) at Week 24. Mean changes of −57.1% at Week 12 and −55.0% at Week 24 were observed with 150Q2W (p < .0001). Around 75.3% (75/150 mg) or 64.5% (150 mg) of patients achieved their LDL-C goal of 1.8 or 2.6 mmol/L (70 or 100 mg/dL) based on CV risk by Week 24 and maintained it up to Week 78. In ODYSSEY OLE[49] trial (n = 986), the mean LDL-C level reduction of 44.2% was observed in patients in alirocumab groups (75 mg or 150 mg Q2W) by Week 8 which increased to 47.9% by Week 96. Alirocumab use for 18 weeks in apheresis-treated patients with HeFH was safe and effective in ODYSSEY ESCAPE[64] trial (n = 62). Lipoprotein apheresis can decrease lipoproteins' levels but is an invasive procedure. As compared to the placebo, there was a 75% additional reduction in the standardized rate of apheresis. A percentage of 63.4% of patients avoided all and 92.7% avoided at least half of the lipoprotein apheresis treatment. The open-label DE LAVAL[65] study (n = 36) showed that evolocumab significantly reduced apheresis requirement as well. The patients were randomized to either discontinue pheresis and receive evolocumab (140 mg Q2W) or continue pheresis frequency. At Week 6, 84% versus 10% avoided apheresis (treatment difference, 74%, 95% confidence interval (CI) 45 − 87; p < .0001). Furthermore, in the recent TAUSSIG[61] trial (n = 300), lipoprotein apheresis was used by 61 patients. Of the 34 patients with HoFH and the 27 with HeFH 9% and 48% were able to stop apheresis treatment when evolocumab was used, respectively.

Mixed populations

In Alirocumab expanded-use program[42], an open-label single arm trial, in patients with HeFH and/or CHD and baseline

LDL-C of ≥ 4.14 mmol/L (160 mg/dL) on LLT, a reduction of 55% in LDL-C level was observed with alirocumab 150Q2W arm by Week 24. The single-arm ODYSSEY APPRISE[66] study ($n = 955$) is the first study in a real life setting prior commercial availability of alirocumab in subjects (63% with HeFH; 68% with a history of CVD) inadequately controlled on their maximally-tolerated LLT. In the interim data of the first 843 patients, LDL-C level reduction from baseline was 56% at Week 12. The ODYSSEY JAPAN[45] trial ($n = 216$) was a randomized double-blind trial in Japanese patients with HeFH or non-FH and at high CV risk who were on stable statins. Alirocumab (75/150 mg) at Week 24, showed a least-square mean change in baseline LDL-C of -62.5% versus $+1.6\%$ in placebo with 96.7% of patients achieving their LDL-C goals. An average reduction of 62.5% was maintained for 52 weeks. A *post hoc* analysis[67] of the diabetic patients in ODYSSEY JAPAN showed a least-square mean change in baseline LDL-C of -63.1% in DM versus -60.8% in non-DM at Week 24, which was maintained for 52 weeks with similar percentage of patients attaining their LDL-C goals as in the parent trial. The ODYSSEY NIPPON[68] trial ($n = 163$) was another one conducted in Japanese patients with either HeFH or non-HeFH with CHD who were on lowest-strength atorvastatin (5 mg per day) or non-statin LLT. At Week 12, the least-square mean percent change in LDL-C from baseline was -43.8% with alirocumab 150Q4W, -70.1% with 150Q2W, and -4.3% with placebo. The study continued as 52-week open-label treatment period and the patients received 150Q4W with possible up-titration to 150Q2W at Week 24. The mean LDL-C change from baseline was -45.1% at Week 20, with a further reduction at Week 36, with achieved levels maintained to Week 64. In a pooled analysis[69] of eight ODYSSEY Phase III trials ($n = 4629$) in patients with HeFH at high CV risk on maximally tolerated statin therapy, LDL-C reduction by 48.9% was observed in 75/150 mg arms versus 9.3% with ezetimibe and 60.4% in 150Q2W arms versus 0.5% increase with placebo ($p < .0001$, all comparisons) at Week 24. The LDL-C reductions appeared as early as Week 4 and maintained up to the studies' durations. The percentage of patients who achieved risk-based LDL-C goals of 1.8 or 2.6 mmol/L (70 or 100 mg/dL) by Week 24 was 75–79% on alirocumab versus 52% on ezetimibe and 6–8% on placebo. In PROFICIO[70] ($n = 3146$), a pooled analysis of four randomized Phase III evolocumab 12-week trials (LAPLACE-2[33], RUTHERFORD-2[36], MENDEL-2[37], GAUSS-2[71]) that included patients with FH, primary hypercholesterolemia with different CV risks and prior statin intolerance, evolocumab as compared to placebo resulted in mean percent changes in LDL-C of -65.7% for the Q2W dose and -65.0% for the QM dose. Compared to ezetimibe, the mean percent changes in LDL-C was -38.9% for Q2W and -40.3% for QM. There were no differences between evolocumab and placebo or ezetimibe across the various subgroups i.e. age, gender, race, ethnicity, region, glucose tolerance status, or risk categories. In an analysis[72] of the efficacy of biweekly and monthly evolocumab in hypercholesterolemic patients ($n = 1148$) from four Phase III randomized trials; LAPLACE-2[33], RUTHERFORD-2[36], MENDEL-2[37], GAUSS-2[71]) who had fasting

triglyceride (TG) levels of ≥ 1.7 mmol/L (150 mg/dL), a mean percentage change in LDL-C of -67% versus placebo and -42% versus ezetimibe was observed ($p < .001$, all comparisons), which was similar to the observed LDL-C reductions in patients without elevated TG levels.

Statin intolerance

It is estimated that about 10 of patients[73,74] may be unable to tolerate any dose of statins (i.e. complete intolerance) or the dose that effectively reduces LDL-C (i.e. partial intolerance). More than half of the patients who experience statin-related adverse effects, discontinue their statin therapy. Thus, this precludes patients from achieving the target LDL-C level[4], and exposing high CV risk patients to increased risk of mortality or adverse CV events[5]. Statin adverse muscle symptoms are considered the most predominant cause for statin discontinuation[4,5].

Therapy with PCSK9 inhibitors has been effective and well tolerated in statin-intolerant patients in the short-term (12–24 weeks)[71,74–77] or longer-term (up to two years)[78] pivotal trials. Statin-intolerance in such trials was defined as the inability to tolerate two or more statins at the lowest available dosage[71,76,77]. Evolocumab therapy in three randomized double-blind trials, the 12-week Phase II (GAUSS; $n = 236$)[74], the Japanese 12-week Phase III (GAUSS-4; $n = 61$)[75] and the 24-week Phase III (GAUSS-2; $n = 307$)[71], significantly reduced LDL-C levels and was associated with short-term tolerability. The efficacy and safety persisted over 24 weeks then up to two years, as shown in the two-stage GAUSS-3[76] ($n = 491$) trial and the subset analysis[78] of the OSLER open-label extension studies, respectively. In GAUSS-2[71] and GAUSS-3[76] trials, evolocumab reduced LDL-C by 53 to 56 and 52.8% ($p < .001$, both comparisons), respectively. Adverse muscle events occurred in 12 and 20.7% of patients on evolocumab as compared to 23 and 28.8% of patients on ezetimibe, respectively. In the GUASS-4[75] trial, the percent change in mean LDL-C was -40.1% as compared to ezetimibe (adjusted $p < .0001$) with diarrhea (9.5%) and nasopharyngitis (12.5%) being the most common adverse events. Similarly, alirocumab in the ODYSSEY ALTERNATIVE[77] trial ($n = 314$) was well-tolerated and produced significant reductions in LDL-C levels by 45% ($p < .0001$) at Week 24 in patients with statin intolerance due to muscle symptoms. Skeletal muscles adverse events were less frequent with alirocumab as compared to ezetimibe (hazard ratio (HR), 0.71, 95% CI $0.47 - 1.06$, $p = .096$).

Cardiovascular outcomes

The use PCSK9 inhibitors has been associated with a benefit in CV outcomes. One interpretation of the potential mechanism is their ability to lower the atherogenic lipids levels (namely LDL-C, non-HDL-C, lipoprotein(a) (Lp(a))[79]. A number of studies has shown that PCSK9 inhibitors had significant reduction in atherogenic lipid fractions i.e. LDL-C, non-HDL-C, apolipoprotein-B (apo-B), and Lp(a) levels. In a post hoc analysis of a Phase II trial, alirocumab reduced total LDL particle

(LDL-P) and very-low-density lipoprotein (VLDL), and increased HDL particles by 63.3, 36.4, and 11.2% ($p < .01$, all), respectively[80]. Evolocumab in the BERSON[56] trial, BANTING trial[57] and a post hoc analysis[81] of the DESCARTES trial significantly decreased the serum levels and size of the lipoprotein particles. Both alirocumab and evolocumab caused significant reduction in LDL-apoB[58,82,83] by 56.3% each[82] and Lp(a)[58,84–86] by 23.0–30.30%[84,85] and 24.5–29.5%[86], respectively. In a recent pre-specified analysis[87] of the ODYSSEY OUTCOMES trial, a reduction in Lp(a) was an independent factor of lowering the risk of major adverse CV events (MACE), and that a 1 mg/dL reduction in Lp(a) was associated with an HR of 0.994 (95% CI, $0.990 - 0.999$, $p = .0081$). In addition, there has been a positive correlation between plasma levels of PCSK9 and the carotid intima media wall thickness[88], the platelet count in patients with coronary artery disease (CAD)[89], and the necrotic core tissue fraction within the coronary plaques[90], suggesting that the PCSK9 protein may have a key modulating effect in atherosclerosis[91]. The GLAGOV[92] trial ($n = 968$) has confirmed that evolocumab in addition to statin therapy led to significant reduction in atheroma volume and induced plaque regression in higher percentage of patients. Alirocumab was evaluated in the Japanese Phase IV ODYSSEY J-IVUS[93] study ($n = 206$) which enrolled hypercholesterolemic patients recently hospitalized with ACS. Using intravascular ultrasound imaging analysis, there was a numerically more percent reduction in normalized total atheroma volume which did not reach the statistical significance. It remains to be established whether PCSK9 inhibition has important clinical effects on arterial stiffness, endothelial function, and inflammatory responses. Circulating PCSK9 was significantly associated with arterial stiffness[94] and drove a pro-inflammatory response on macrophage that stimulates cytokines[95]. To date, two patient cases have reported with impressive results on the use of PCSK9 inhibitors through improvement in carotid-femoral pulse wave velocity[96]. Two-month use of alirocumab has improved endothelial function as assessed by brachial artery vasoreactivity test[97].

Prior to the major clinical outcome trials, FOURIER[98] and ODYSSEY OUTCOMES[99], findings from the published evidence gave an important signal that the reduction of LDL-C using PCSK9 inhibitors lowered the adverse CV events. In the OSLER[100] study ($n = 4465$), evolocumab as compared to the control group reduced LDL-C by 61% ($p < .001$) and adverse CV events rate by 53% (HR, 0.47, 95% CI $0.28 - 0.78$; $p = .003$) after one year of treatment. Alirocumab in the ODYSSEY LONG TERM[63] trial ($n = 2341$) over a period of 78 weeks, significantly reduced LDL-C by 62% ($p < .001$) and in a post hoc analysis of it, there was an evidence of a reduction in the rate of MACE (HR, 0.52, 95% CI $0.31 - 0.90$; nominal $p = .02$). A *post hoc* analysis[101] from ten ODYSSEY trials ($n = 4974$), showed that the incidence of MACE was reduced by 24% for every 39 mg/dL reduction in LDL-C (adjusted HR, 0.76, 95% CI $0.63 - 0.91$; $p = .0025$) and by 29% for every additional 50% reduction in LDL-C from baseline (HR, 0.71, 95% CI $0.57 - 0.89$; $p = .003$). A meta-analysis[102] of 24 randomized control trials (RCTs) ($n = 10,159$) showed that the

use of PCSK9 inhibitors was associated with reductions in LDL-C by 47.49% ($p < .001$), all-cause mortality (odds ratio (OR), 0.45, 95% CI 95% $0.23 - 0.86$; $p = .015$; heterogeneity $p = .63$; $I^2 = 0\%$), MI (OR, 0.49, 95% CI, $0.26 - 0.93$; $p = .03$; heterogeneity $p = .45$; $I^2 = 0\%$), and CV mortality (OR, 0.50, 95% CI, $0.23 - 1.10$; $p = .084$; heterogeneity $p = .78$; $I^2 = 0\%$) compared with no PCSK9 inhibitors treatment. A study[103] predicted the individual lifetime benefit of PCSK9 inhibition, expressed in terms of gain in life expectancy free of (recurrent) stroke or MI, in statin-treated patients with stable CAD based on competing two risk models developed in data from the Treating to New Targets (TNT) trial. The individual lifetime benefit varied substantially, ranging from < 6 months free of stroke or MI in 61% of patients to ≥ 12 months in 10% of patients. The expected benefit was the highest in younger patients (aged $40 - 60$ years) with risk factors, especially if LDL-C level is > 1.8 mmol/L (70 mg/dL).

Three Phase III trials, FOURIER[98], ODYSSEY OUTCOMES[99], and SPIRE[104], investigated PCSK9 inhibitors in patients with a history of clinically evident CVD. The FOURIER trial ($n = 27,564$) randomized patients with stable ASCVD and fasting LDL-C level $\geq$ 1.8 mmol/L (70 mg/dL) or non-HDL ≥ 2.6 mmol/L (100 mg/dL) who were on statin therapy. At Week 48, evolocumab 140 mg Q2W or 420 mg QM, reduced LDL-C by 59% compared to placebo. The primary outcome of a composite of CV death, MI, stroke, hospitalization for unstable angina (UA), or coronary revascularization was significantly lower (HR, 0.85; 95% CI, $0.79 - 0.92$; $p < .001$) at a median duration of follow-up of 2.2 years[98] (Table 1). The reduction of the composite of CV events was greater in patients with high-risk features i.e. more recent MI (HR, 0.80, 95% CI, $0.71 - 0.9$), multiple prior MI (HR, 0.82; 95% CI, $0.72 - 0.93$), and residual multivessel CAD (HR, 0.79; 95% CI, $0.69 - 0.91$) with absolute risk reductions that exceeded 3% (3.4, 3.7, and 3.6%, respectively) versus around 1% in the low-risk groups (0.8, 1.3, and 1.2%)[105]. A Pre-specified secondary analysis[106] of the FOURIER trial evaluated the effect of evolocumab on total CV events. The total CV events were reduced by 18% (incidence rate ratio (RR), 0.82; 95% CI, 0.75-0.90; $p < .001$) which was driven by decreases in MI, stroke, and coronary revascularization. In another secondary ad hoc analysis[107] of the FOURIER trial, the reduction of adverse CV events was equally effective in patients with stable ASCVD regardless of the baseline LDL-C whether it was ≤ 1.8 mmol/L (70 mg/dL) or the background statins whether it was of a maximal or submaximal potency. Thirteen percent of patients in the FOURIER trial had PAD; evolocumab significantly lowered the primary end point in PAD patients (HR, 0.79; 95% CI $0.66 - 0.94$; $p = .0098$) and the risk of major adverse limb events in all patients (HR, 0.58; 95% CI, $0.38 - 0.88$; $p = .0093$). The reduction in LDL-C levels lowered the risk of major adverse limb events[108]. Evolocumab induced a relative reduction in venous thromboembolism (VTE) events by 29% (HR, 0.71; 95% CI, $0.50 - 1.00$; $p = .05$) in the first year and by 46% (HR, 0.54; 95% CI, 0.33–0.88; $p = .014$) thereafter, in a pre-specified analysis of the FOURIER trial[109]. Moreover, evolocumab in the FOURIER trial reduced adverse CV events across the strata of baseline high-sensitivity C-reactive

Table 1. Cardiovascular outcomes.

Study	MACE	CV death	MI	Stroke	UA	Revascularization
SPIRE 1&2[104] (combined)2017	0.88 (0.76–1.02) 0.08	1.00 (0.71–1.41)> 0.99	0.91 (0.75–1.11) 0.35	0.60 (0.41–0.86) 0.006	0.89 (0.64–1.24) 0.49	–
FOURIER[98]2017	0.85 (0.79–0.92) <0.001	1.05 (0.88–1.25) 0.62	0.73 (0.65–0.82) <0.001	0.79 (0.66–0.95) 0.01	0.99 (0.82–1.18) 0.89	0.78 (0.71–0.86) <0.001
ODYSSEY OUTCOMES[99] 2018	0.85 (0.78–0.93) <0.001	0.88 (0.74–1.05) NR*	0.86 (0.77–0.96) NR*	0.73 (0.57–0.93) NR*	0.61 (0.41–0.92) NR*	0.88 (0.79–0.97) NR*

[HR (95%CI) p value].
Abbreviations. CV, cardiovascular; HR, hazard ration; MACE, major adverse CV events; MI, myocardial infarction; NR, not reported; UA, unstable angina.
*Hierarchical analysis was stopped after the first nonsignificant p value was observed, in accordance with the hierarchical testing plan.

protein (hs-CRP) (<1, $1-3$, and >3 mg/dL) with more absolute risk reductions in the patients with higher-baseline hs-CRP[110]. A meta-analysis[111] found that PCSK9 inhibitors do not impact the circulating hs-CRP levels in contrast to statins[112] or bempedoic acid[17,113]. A recent *post hoc* analysis of the FOURIER trial found that after the first 12 months of evolocumab use, there was a 52% relative reduction (HR, 0.48; 95% CI, 0.25-0.93) in aortic stenosis (AS) events rates in evolocumab group, which was attributed to the reduction in Lp(a) levels[114]. A previous study have suggested that PCSK9 inhibitors may potentially have a role in reducing the risk of AS based on the finding that PCSK9 R46L loss-of-function mutation was associated with lower Lp(a) and LDL-C level as well as reduced risk of AS[115]. The ODYSSEY OUTCOMES[99] trial ($n = 18{,}924$) randomized patients on statin therapy with inadequate LDL-C control who had a recent ACS event rather than the more stable ones enrolled in the FOURIER trial. Alirocumab 75 mg or 150 mg Q2W over a median follow up of 2.8 years, significantly reduced the four-point composite of CV death, nonfatal MI, fatal or nonfatal ischemic stroke, or UA requiring hospitalization (HR, 0.85, 95% CI, $0.78-0.93$; $p < 0.001$) (Table 1). The absolute benefit was greater among patients who had a baseline LDL-C of ≥ 2.6 mmol/L (100 mg/dL) than among patients with lower baseline LDL-C level. In a pre-specified analysis[116], alirocumab prevented total (first and recurrent) non-fatal CV events (HR, 0.87, 95% CI, $0.82-0.93$) and all-cause mortality (HR, 0.83, 95% CI, $0.71-0.97$) in the presence of a strong association between nonfatal and fatal event risk. In another pre-specified analysis[117], alirocumab has also reduced the total (first and subsequent) hospitalizations (HR, 0.96 [95% CI, 0.92-1.00]; $p = 0.04$) and slightly increased days alive and out of hospital (RR, 1.003 [95% CI, 1.000-1.007]; $p = 0.05$) due to a decrease in days dead (RR, 0.847 [95% CI, 0.728-0.986]; $p = 0.03$), defined as the time from a patient's death to the study end date. A third pre-specified analysis[118] of the ODYSSEY OUTCOMES trial investigated the effect of alirocumab in ACS patients with a history of coronary artery bypass grafting. Alirocumab was associated with large absolute reductions in MACE and death. In a prespecified analysis of other vascular events in the ODYSSEY OUTCOMES trial, alirocumab lowered PAD events (HR, 0.69; 95% CI, 0.54–0.89; $p = .004$) significantly, but missed the statistical significance in reducing VTE events (HR, 0.67; 95% CI, 0.44–1.01; $p = .06$)[119]. When combined data from the FOURIER and ODYSSEY OUTCOMES trials ($n = 46{,}488$) were analyzed, it resulted in a 31% reduction in VTE events [HR, 0.69; 95% CI, 0.53–0.90; $p = .007$][109]. Evidence also suggests the association with Lp(a) levels

reduction[109,119]. The two parallel, SPIRE-1 and SPIRE-2, CV outcome trials ($n = 27{,}438$)[104] were conducted in 2013 to assess the efficacy and safety of bococizumab, at a dose of 150 mg Q2W, in patients at high CV risk. However, the trials were terminated early by the sponsor after a median follow up of 10 months. The sponsor opted to stop the development of bococizumab due to the high rates of the anti-drug antibodies (ADAs), as detected in the data from other studies in the SPIRE program that consisted of a total of eight studies (i.e. six lipid-lowering and two CV outcome trials). In a combined analysis of SPIRE-1 and SPIRE-2 trials, bococizumab showed no benefit in term of MACE[9,104] (Table 1).

Safety of PCSK9 monoclonal antibodies

In general, the safety profile of both evolocumab and alirocumab is excellent. Nasopharyngitis and mild injection-site reactions are considered the most common adverse reactions[5].

Adverse effects

In two meta-analyses[1,79] of RCTs, treatment with PCSK9 inhibitors was not associated with the adverse effects commonly described with statin therapy such as myalgia and elevations in serum aminotransferases or creatine kinase, with overall serious adverse events that were comparable to the control group. The aforementioned meta-analyses did not report the injection site reactions which are the most frequent adverse events with the PCSK9 inhibitors use[4]. The allergic local injection-site reactions (e.g. itching, redness, swelling) rates were 3.8% in alirocumab group versus 2.1% in placebo ($p < .001$)[99] and 5.9 versus 4.2% over a period of 78 weeks[63]. Injection-site reactions are usually mild and self-limited[99]. The reactions rates with evolocumab were 2.1% versus 1.6% in the placebo group[98], and there was no increase in hypersensitivity with longer treatment[120]. Bococizumab caused higher injection-site reactions as compared to placebo (10.4 versus 1.3%, $p < .001$)[104] and 12.7 per 100 person-years in six trials evaluating bococizumab. However, the rates did not increase with longer time[121].

Anti-drug antibodies

Therapeutic molecules may have an immunogenicity potential that may generate ADAs. The ADAs can be generated in response to fully human (e.g. alirocumab and evolocumab)

or humanized (e.g. murine-derived bococizumab) monoclonal antibodies. High-titer ADAs have substantially developed in response to treatment with bococizumab (i.e. high degree of immunogenicity), while treatment with either alirocumab or evolocumab has not significantly been associated with ADAs generation[104,121]. This immunologic difference explains the higher injection-site reactions rate reported with bococizumab[104]. ADAs can be either neutralizing or binding[122]. Binding ADAs bind to therapeutic proteins without affecting the molecules' function[120], while neutralizing ADAs can directly impair their function[122]. In the ODYSSEY OUTCOMES[99] trial, neutralizing ADAs were observed in 0.5% of patients on alirocumab versus 0.1% of those on placebo. Roth et al.[123] reported data from 10 trials and found that ADAs against alirocumab were observed in 5.1% of patients as compared to 1.0% in the control group with persistent ADAs found in 1.4% versus 0.2% after 12 weeks or more, respectively. Neutralizing ADAs were reported in only 1.3% of the patients in alirocumab group. In the FOURIER[98] trial, evolocumab generated binding ADAs in 0.3% of the patients and no neutralizing ADAs have been detected. These findings were consistent over a period of four years as observed in the OSLER-1[120] study. In four RCTs that reported data regarding ADAs for evolocumab and alirocumab, the ADAs were transient and their titers decreased over time[79]. Almost half of the patients who received bococizumab in the SPIRE studies had high-titer ADAs with neutralizing antibodies developed in 29% of the patients[104]. Comparisons of ADAs incidence among the different PCSK9 inhibitors may be misleading because immunogenicity potential is dependent on various factors[123]. Cross-reactivity between PCSK9 inhibitors is unlikely to occur due to the specificity of the binding domains[121]. ADAs directed against PCSK9 inhibitors are one of the theoretical mechanisms for the PCSK9 inhibitors hyporesponsiveness (i.e. <15% reduction in LDL-C level) due to the physiological impairment of monoclonal antibodies once absorbed into the circulation[14]. The occurrence of ADAs with PCSK9 inhibitors has attracted widespread attention. Although autoantibodies were detected in some patients on alirocumab or evolocumab, reductions in LDL-C levels induced by either monoclonal antibody were not attenuated[79]. ADAs did not appear to significantly attenuate the lipid-lowering effect of alirocumab[99,123] or evolocumab[98], unlike that of bococizumab[121]. The high immunogenicity rates and the wide variation in LDL-C response among patients on bococizumab led to the discontinuation of further clinical development of bococizumab[9,121].

Neurocognitive events

Low LDL-C levels in the clinical trials of PCSK9 inhibitors have raised a concern about the association of their use with cognitive impairment[124]. Neurocognitive adverse events were reported as delirium, attention disorders, amnesia, dementia, disturbances in thinking and perception, or mental impairment disorders[4,5]. Neurocognitive adverse events reported in the clinical trials of alirocumab and evolocumab were not significantly different from those reported in the control

groups[63,98,99]. Furthermore, similar findings were found in two meta-analyses of RCTs[1,79] and in the EBBINGHAUS[124] study (n = 1204), a sub-study of the FOURIER trial, that evaluated the cognitive deficits. The findings of the latter study were supported by a Mendelian randomization study which found no causal relationship between inhibition of PCSK9 function and neurodegenerative diseases[125].

Diabetes

It has been hypothesized that the significant LDL-C-lowering effect of the PCSK9 inhibitors may negatively affect the glycemic status, namely the new-onset diabetes, as suggested with statin therapy to be associated with an increase in diabetes incidence[104,126]. It has been postulated that the genetic variations in the targets of statins and PCSK9 inhibitors i.e. 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) and PCSK9 respectively, have been associated with desirable protective effect against atherosclerosis but on the other hand with adverse effects in term of diabetes[104]. The currently available evidence did not suggest significant increase in new-onset diabetes or worsening of preexisting diabetes on shorter or longer terms with either alirocumab[39,63,99,127] or evolocumab[56,57,98,120,128–130]. In the SPIRE[104] studies, although bococizumab use was not associated with significant increase in new-diabetes, the early termination of the trials precluded the ability to assess adverse effect on glycemic control. The results of three recent meta-analyses[1,79,126] are in line with the findings of the previous studies. However, one[126] of the aforementioned meta-analyses has elaborated that the imbalance in the background LLT of the control arms may have masked the effect of PCSK9 inhibitors on diabetes.

Fat-soluble vitamins and steroid hormones

Fat-soluble vitamins and steroid hormones levels were measured as part of prespecified safety analyses in trials with PCSK9 inhibitors such as ODYSSEY LONG TERM[63] and DESCARTES[131]. In the alirocumab group, although the levels of vitamin E or vitamin K were below the lower limit of the normal range, there were no clinically important changes. Moreover, there was no clinically meaningful effect with regards the changes in the levels of cortisol or other fat-soluble vitamins[63]. Similarly, vitamin E levels were lower in evolocumab-treated subjects but the results were not statistically significant after the adjustment of LDL-C level, and there were no adverse effects reported for steroid or gonadal hormones[131].

Cost-effectiveness of PCSK9 monoclonal antibodies

Evaluation of cost effectiveness of PCSK9 inhibitors has been of interest to several trials. In 2015, they were not proven to be cost effective as their use increased annual prescription spending by $125 billion over ezetimibe in patients with HeFH or ASCVD[132]. Another study[133] recommended price reduction ($14,000–15,000) by 70% as they possessed

Table 2. Phase III registered clinical trials.

Trial ID*	Agent	Trial brief title (acronym)	Target size	Primary outcome (time frame)	Start date	Status
Hypercholesterolemia						
NCT02476006	Alirocumab	Safety, tolerability, and effect of alirocumab in high cardiovascular risk patients with severe hypercholesterolemia not adequately controlled with conventional lipid-modifying therapies (ODYSSEY APPRISE)	998	Proportion of patients with adverse events and percent change in lipid levels (30 months)	June 2015	Completed
NCT03433755	Evolocumab	Safety and efficacy of evolocumab in addition to optimal stable background statin therapy in chinese subjects with primary hypercholesterolemia and mixed dyslipidemia	450	Mean percent change in LDL-C from baseline (10 and 12 weeks)	May 2019	Recruiting
NCT03156621	Alirocumab	Study in participants HoFH (ODYSSEY HoFH)	69	Percent change in LDL-C from baseline (12 weeks)	October 2017	Active, not recruiting
Cardiovascular outcomes						
NCT03872401	Evolocumab	Effect of evolocumab in patients at high cardiovascular risk without prior MI or stroke (VESALIUS-CV)	13,000	Time to coronary heart disease death, MI, or ischemic stroke (4.5 years)	June 2019	Recruiting
NCT02867813	Evolocumab	Further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk open-label extension (FOURIER OLE)	5,037	Subject incidence of adverse events (5 years)	September 2016	Active, not recruiting
NCT03080935	Evolocumab	Fourier open-label extension study in subjects with clinically evident cardiovascular disease in selected European countries	1,600	Adverse event measurement (5 years)	March 2017	Active, not recruiting
NCT03570697	Evolocumab	Imaging of coronary plaques in subjects treated with evolocumab (HUYGENS)	164	Absolute change in minimum FCT (50 weeks)	November 2018	Active, not recruiting
NCT03689946	Evolocumab	Effect of evolocumab on coronary artery plaque volume and composition by CCTA and microcalcification by F18-NaF PET	55	Change in NCPV from baseline (18 months)	March 2019	Recruiting
NCT02729025	Evolocumab	Effects of proprotein convertase subtilisin/Kexin Type 9 (PCSK9) inhibition on arterial wall inflammation in patients with elevated Lp(a) (ANITSCHKOW)	129	Percent change in Lp(a) in target-to-background ratio of an index vessel by FDG-PET/CT (16 weeks)	April 2016	Completed
JPRN-jRCT1051180064	Alirocumab	Effect of alirocumab and rosuvastatin or rosuvastatin alone on lipid core plaques in coronary artery disease evaluated by near-infrared spectroscopy intravascular ultrasound (ANTARES)	30	Absolute change of maxLCBI (4 mm) from baseline (36 weeks)	April 2018	Recruiting
JPRN-jRCT1051180063	Alirocumab	Efficacy of Alirocumab for thin-cap fibroatheroma in patients with coronary artery disease estimated by optical coherence tomography trial (ALTAIR)	24	Change in minimum FCT between baseline (36 weeks)	September 2017	Completed
NCT03067844	Alirocumab	Vascular effects of alirocumab in acute MI-patients (PACMAN-AMI)	294	Change in PAV from baseline (52 weeks)	April 2017	Recruiting
Special patient populations						
NCT03510884 [pediatrics]	Alirocumab	An efficacy and safety study of alirocumab in children and adolescents with HeFH	150	Percent change in LDL-C from baseline (24 weeks)	May 2018	Recruiting
NCT03510715 [pediatrics]	Alirocumab	An efficacy and safety study of alirocumab in children and adolescents with HoFH	18	Percent change in LDL-C from baseline (12 weeks)	August 2018	Completed
NCT02392559 [pediatrics]	Evolocumab	Trial assessing efficacy, safety and tolerability of PCSK9 inhibition in pediatric subjects with genetic LDL disorders (HAUSER-RCT)	159	Percentage change LDL-C levels from baseline (24 weeks)	February 2016	Completed
NCT02624869 [pediatrics]	Evolocumab	Open label study to evaluate safety, tolerability and efficacy of evolocumab (AMG 145) in pediatric subjects (10–17 years of age) with HeFH or HoFH(HAUSER-OLE)	163	Number of participants with treatment-related Adverse Events as assessed by CTCAE V4.0 (80 weeks)	September 2016	Active, not recruiting

(continued)

Table 2. Continued.

Trial ID*	Agent	Trial brief title (acronym)	Target size	Primary outcome (time frame)	Start date	Status
NCT03207945 [HIV subjects]	Alirocumab	Effect of PCSK9 inhibition on cardiovascular risk in treated HIV infection (EPIC-HIV)	140	FDG PET/CT Endpoint. Change in Target-to-background ratio from baseline. The main arterial endpoint is the most diseased segment of the index vessel (52 weeks)	April 2018	Recruiting
NCT02833844 [HIV subjects]	Evolocumab	Safety, tolerability & efficacy on LDL-C of evolocumab in subjects with HIV & hyperlipidemia/mixed dyslipidemia (BEIJERINCK)	467	Percent change of LDL-C from baseline (24 weeks)	May 2017	Completed
NCT03734211 [Heart transplant recipients]	Evolocumab	Cholesterol lowering with evolocumab to prevent cardiac allograft vasculopathy in de-novo heart transplant recipients (EVOLVD)	130	Maximal intimal thickness measured by coronary IVUS; defined as the largest distance (in mm) from the intimal leading edge to the external elastic membrane (12 months)	June 2019	Recruiting
NCT03480568 [dialysis patients]	Alirocumab	Alirocumab in patients on a stable dialysis regimen	20	Change in LDL cholesterol levels from baseline (4 ,8, 12 weeks)	May 2018	Recruiting
NCT03344692 [diabetics]	Alirocumab	Effect of alirocumab on postprandial hyperlipemia in patients with type 2 diabetes (EUTERPE)	24	Total AUC of post-prandial TG concentration-time from meal-time until 8 h after standardized high fat meal (During 8 hours at week 10 after first injection)	February 2019	Recruiting

Abbreviations. AUC, area under curve; CTCAE, Common Terminology Criteria for Adverse Events; FCT, fibrous-cap thickness; FDG PET/CT, fluoro-deoxyglucose positron-emission tomography/computed tomography; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous FH; HIV, human immunodeficiency virus; IVUS, intravascular ultrasound; LDL-C, low-density lipoprotein cholesterol (LDL-C); Lp(a), Lp(a); maxLCBI, maximal lipid-core burden index; MI, myocardial infarction; NCPV, noncalcified coronary artery plaque volume; PAV, percent atheroma volume; PET, positron emission tomography (PET); TG, triglycerides.
*From http://clinicaltrials.gov/ and http://www.who.int/ictrp/network/en/

incremental cost of about $350,000 per quality adjusted life years (QALYs) when compared to statins. A treatment cost analysis[134] of evolocumab versus ezetimibe to prevent one MACE in T2DM using data from the FOURIER and IMPROVE-IT trials had similar conclusion. In all analyses performed, ezetimibe was consistently a cost-saving strategy compared with evolocumab except for the case where evolocumab price is significantly reduced and the branded ezetimibe is used. In a review[135] of 10 health economic evaluations from United States of America (USA) and Europe, cost effectiveness of PCSK9 inhibitors remained uncertain and price reduction was recommended. Following the CV outcome trials, a study showed that relevant costs saved per CV event annually remained very small in Apulia, Italy[136]. In response to 2018 price reductions, National Lipid Association issued a statement to highlight in which subgroups of patients PCSK9 monoclonal antibodies are currently considered a cost-effective reasonable option ($<$ USD 100,000/QALY). The subgroups included (a) extremely high–risk patients with ASCVD of $>$40% 10-year ASCVD risk and LDL-C $\geq$ 1.8 mmol/L (70 mg/dL), (b) very-high-risk patients with ASCVD of 30–39% 10-y ASCVD risk and LDL-C $\geq$ 2.6 mmol/L (100 mg/dL) and (c) high-risk patients with 20–29% 10-year ASCVD risk and LDL-C $\geq$ 3.36 mmol/L (130 mg/dL). All patients should receive a maximally tolerated statin therapy and ezetimibe prior starting PCSK9 monoclonal antibodies therapy[137].

Registered clinical trials

The documented significant benefit of the PCSK9 monoclonal antibodies in decreasing lipid parameters and adverse CV events encouraged further investigations on their efficacy and safety. Research is ongoing in patients with familial and non-familial hypercholesterolemia. New research is targeting special patient populations such as pediatrics and human immunodeficiency virus (HIV) subjects. Relevant ongoing Phase III trials are listed in Table 2.

Conclusions

The currently-available PCSK9 monoclonal antibodies, alirocumab and evolocumab, are safe and effective when used as an add-on or as monotherapy. They are effective in lowering LDL-C levels by more than 50% in pooled populations. The outcome studies have confirmed that the significant LDL-C-lowering capacity was translated into a reduction in CV events without causing excessive adverse effects. The benefit in CV outcomes was attributed to the ability of PCSK9 inhibitors to lower atherogenic lipid fractions such as LDL-C, non-HDL-C, apo-B, and Lp(a) levels and atheroma volume. The ability to lower Lp(a) levels could potentially reduce PAD, VTE, and AS events as well.

Transparency

Declaration of funding

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