

Review

A short review of proprotein convertase subtilisin/kexin type 9 inhibitors

Rudaynah A. Alali

Department of Internal Medicine, King Fahd Hospital of the University, Alkhobar, College of Medicine, Imam Abdulrahman bin Faisal University 31441, Dammam, Saudi Arabia

*Correspondence: rudaynahalali@hotmail.com (Rudaynah A. Alali)

DOI: 10.31083/j.rcm.2019.01.31812

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Cardiovascular disease is the leading cause of morbidity and mortality globally, as estimated by the World Health Organization, where in 2016, 15.2 million deaths were attributed to ischemic heart disease and stroke. It is therefore essential to try to reduce the incidence of Cardiovascular disease by controlling modifiable risk factors. One such major modifiable risk factor is cholesterol, which influences the pathogenesis and progression of atherosclerosis. Statins are often prescribed to lower blood levels of low density lipoprotein cholesterol, thereby reducing the risk of Cardiovascular disease by approximately 25-35%. However, there is an increasing number of patients (in particular those with intolerance to statin therapy and those with familial hypercholesterolemia) for whom statin therapy alone is not enough to control low density lipoprotein cholesterol. In this review, the regulation of cholesterol metabolism will be discussed with an emphasis on novel cholesterol lowering drugs used in clinical trials. These second-generation drugs, monoclonal antibodies against the low density lipoprotein receptor gene known as proprotein convertase subtilisin/kexin type 9 inhibitors, are expected to be prescribed to patients who are intolerant to statins, as well as in conjunction with statins. Future perspectives of the clinical use of these drugs is also discussed.

Keywords

Cardiovascular disease; statin; hypercholesterolemia; proprotein convertase subtilisin/kexin type 9 inhibitors

1. Introduction

1.1 Historical Overview

In 1758, French doctor and chemist François Poulletier de la Salle was the first to isolate cholesterol in solid form in gallstones. The compound was named “cholesterine” in 1815 by Michel Eugène Chevreul, French chemist and pioneer (living to the age of 102). Yet it was not until 1927 that the structure of cholesterol was defined by Heinrich Wieland, the German Nobel Prize winner in Chemistry (Olson, 1998).

The structure of cholesterol is based on a sterol ring system. It has an amphipathic character: its hydrocarbon ring system is

hydrophobic, while the hydroxyl group is hydrophilic. Hence, cholesterol is sparingly soluble in water.

Cholesterol is essential for animal life, biosynthesized de novo by all animal cells, especially liver and intestinal cells. A complex 37-step process is required for its synthesis, with the step catalyzed by 3-hydroxy-3-methylglutaryl CoA (HMG CoA) reductase being the rate limiting and irreversible step. Cholesterol is incorporated into the cell membrane and it plays a major role in membrane fluidity. It is also a precursor for a number of biologically important compounds, including steroid hormones, bile acids, and vitamin D. Due to its poor solubility cholesterol cannot be transported freely in the blood, instead being carried via the formation of lipoprotein complexes. Cholesterol in the blood is mainly found within low- and high-density lipoproteins (LDL and HDL, respectively). LDL transports cholesterol to peripheral tissues, and HDL returns excess cholesterol to the liver. Therefore, a high level of LDL cholesterol (LDL-C) increases the risk of cardiovascular disease (CVD), while a high level of HDL cholesterol decreases this risk (Gordon et al., 1977; Correia et al., 2009; Androulakis et al., 2017; Packard, 2018).

1.2 Cardiovascular Disease

The World Health Organization (WHO) defines CVD as a group of disorders of the heart and blood vessels, including coronary heart disease, cerebrovascular disease, peripheral arterial disease (PAD), rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism (Collaborators., 2016; Feigin et al., 2018). According to the WHO, ischemic heart disease and stroke are the leading cause of mortality globally (Collaborators., 2016). Of the 56.9 million deaths worldwide in 2016, 15.2 million deaths were due to ischemic heart disease and stroke (Fig. 1) (Collaborators., 2016).

To reduce this high rate of mortality, it is essential to try to prevent CVD by controlling its risk factors. These can be divided into modifiable and non-modifiable risk factors (Hermans et al., 2014). Lifestyle, diet, body mass index (BMI), smoking, socioeconomic status and the presence of hypertension and diabetes mellitus are considered modifiable risk factors, whereas age, gender, family history of CVD and ethnicity are non-modifiable risk factors. Hypercholesterolemia is a major risk factor for the development of CVD through atherosclerosis and consequent plaque deposition

within blood vessels (Bentzon et al., 2014). The primary treatment for hypercholesterolemia is statin therapy, which reduces LDL-C levels. Hypercholesterolemia has no clinical symptoms as such, but can manifest itself in CVD. For the majority of patients' statin therapy with lifestyle modification is sufficient to control the level of LDL-C. But there is an increasing number of patients, specifically those with an intolerance to statin therapy and those with familial hypercholesterolemia, for whom statin therapy alone is not enough to control LDL-C levels (McKinney and Kostis, 2012; Mancini et al., 2013; Ott et al., 2015; Waters et al., 2016).

To overcome the issues with standard statin therapy, investigators have strived to understand the exact mechanism of cholesterol metabolism and associated genes, in order to identify novel therapeutic targets. One such novel drug that specifically targets the LDL-C receptor gene is the PCSK9 inhibitor.

2. The Role of PCSK9 in Cholesterol Metabolism

PCSK9 is an enzyme encoded by the PCSK9 gene located on chromosome 1. The PCSK9 gene was discovered in 2003 by Abifadel et al., (Abifadel et al., 2003; Bove et al., 2019). PCSK9 encodes neural apoptosis regulated convertase (NARC-1), a human subtilase that is expressed in high amounts in the liver and contributes to cholesterol metabolism. The product of the PCSK9 gene is involved in the breakdown of LDL receptors prior to incorporation in the cell membranes of liver cells (Melendez et al., 2017; Blanchard et al., 2019).

LDL-C in the peripheral blood attaches to LDL receptors on the surface of hepatocytes. Then, the LDL-C and receptor are taken up by hepatocytes by an endosomal mechanism. The LDL-C is then metabolized, and the LDL receptor is recycled back to the surface of hepatocytes to attach to further LDL molecules (Melendez et al., 2017). With the presence of the PCSK9 gene mutation, the PCSK9 binds to the LDL receptor on the surface of hepatocytes. It is then taken up into the hepatocytes by an endosomal mechanism.

The binding of the PCSK9 to the LDL receptor promotes lysosomal breakdown of the LDL receptor. As such, the LDL receptors are not recycled back to the surface of hepatocytes, decreasing the overall number of LDL receptors on hepatocyte surfaces as well as the amount of cholesterol taken up by hepatocytes from the peripheral blood. This leads to excess LDL-C in the peripheral blood increasing the risk of atherosclerotic plaque formation and CVD.

A number of studies have identified novel loss-of-function mutation in the PCSK9 gene in a human cohort with low plasma levels of LDL-C (Cohen et al., 2005, 2006; Kotowski et al., 2006; Fasano et al., 2007). Most of the mutations in the PCSK9 gene were nonsense mutations.

3. PCSK9 Inhibitors

The first anti-PCSK9 antibody was generated in 2009 (Chan et al., 2009), and has been studied in mice and non-human primates. The antibody binds to PCSK9 adjacent to its binding site with LDL receptors, thus decreasing LDL receptor degradation and ultimately increasing uptake of LDL-C and decreasing LDL-C levels in the blood. The effect of the anti-PCSK9 antibody was attenuated when combined with statin therapy (Lüscher, 2018).

Three PCSK9 monoclonal antibodies included in the present review are: alirocumab (Praluent), evolocumab (Repatha) and bococizumab. The latter was withdrawn from development in 2016 (Bove et al., 2019; Schwartz et al., 2018; Sabatine et al., 2017; Pitts and Eckel, 2014). It should be noted that in the publication by Pitts and Eckel, the PCSK9 inhibitor bococizumab was mistakenly referred to as bocolicumab (Pitts and Eckel, 2014).

Phase 1 and 2 clinical trials of PCSK9 monoclonal antibody inhibition was reported in 2012 (Stein et al., 2012a; McKenney et al., 2012; Stein et al., 2012b). The US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approved evolocumab and alirocumab for clinical use in 2015. This was followed by National Institute for Clinical Excellence (NICE) approval in 2016.

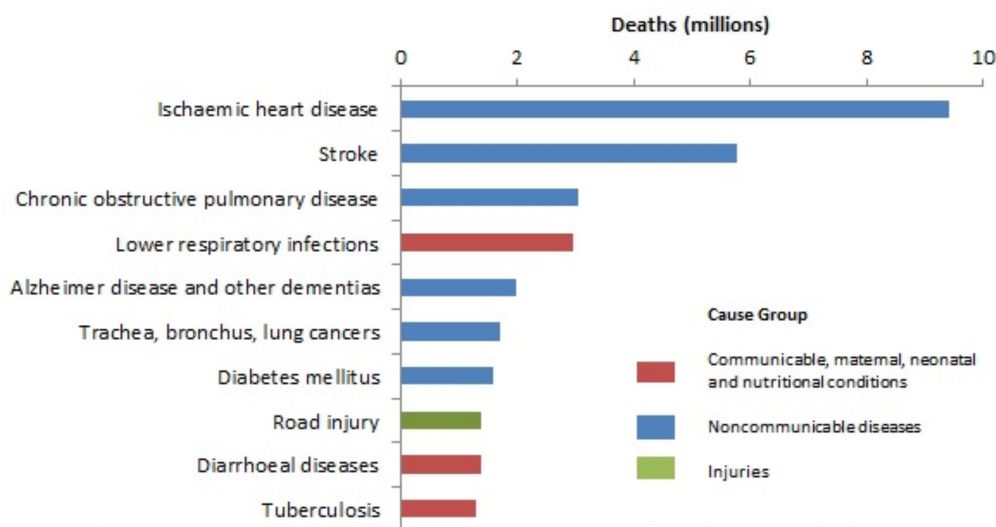


Figure 1. Mortality as a result of various diseases worldwide, led by ischaemic heart disease and stroke (Source: Global health estimates 2016: deaths by cause, age, sex, by country and by region, 2000-2016. Geneva, World Health Organization; 2018)

Table 1. Comparison of the three clinical trials of the PCSK9 inhibitors

	FOURIER	ODYSSEY OUTCOMES	SPIRE-1/SPIRE-2
Type of PCSK9 inhibitor	Evolocumab (Fully human monoclonal Ab)	Alirocumab (Fully human monoclonal Ab)	Bococizumab (Murine-derived Ab)
Timelines	Start: Jan. 2013; End: Feb. 2018	Start: Oct. 2012; End: March 2018	Start: Oct. 2013; End: Aug. 2017
Study design	Randomized, parallel, double-blind placebo	ACS within the last 4-52 weeks. History of clinically evident CVD disease at high risk for recurrent event	Subjects at high risk of a CVD event receiving background lipid lowering therapy
Patient type	History of clinically evident CVD disease at high risk for recurrent event	Median 2.8 years	-
Follow up	Median 2.2 years	18,000	-
Total patients	22,500 (including 9,000 ≥ 65 years)	LDL-C ≥70; Non-HDL-C ≥100 or Apo B ≥80	SPIRE-1: 12,000; SPIRE-2: 6,300
LDL-C (mg/dl) on background therapy	LDL-C ≥70 or Non-HDL-C ≥100	LDL-C ≥70; Non-HDL-C ≥100 or Apo B ≥80	SPIRE-1: LDL-C ≥70 & <100 or Non-HDL-C >100 & <130 SPIRE-2: LDL-C ≥100 or Non-HDL-C ≥130
Statin regimen	Atorvastatin 20-80 mg or an alternative statin. High dose 69%, Moderate dose 30%, Ezetimibe: 5.1%	Atorvastatin 20-80 mg or Rosuvastatin 20-40 mg. High-dose: 89%, Ezetimibe: 3%	Not specified
Inhibitor dose	140 mg Q2 weeks or 420 mg Q4 weeks	75 mg or 150 mg Q2 weeks	150 mg Q2 weeks
Mean age	63 years	58 years	-
% DM/HTN/Smoking	37% / 80% / 28.2%	29% / 63.3% / 23.9%	-
Stroke/PAD history	19.3% / 13.2%	2.9% / 3.7%	-
Exclusion criteria	•Myocardial infarction or stroke within 4 weeks •NYHA class III or IV CHF symptoms or LVEF <30% or uncontrolled VT •Planned revascularization within the next 3 months •Uncontrolled HTN or hemorrhagic stroke •CKD •Organ transplant or major active infection	•Recurrent ACS or coronary revascularization within 2 weeks •NYHA class III or IV CHF; LVEF <25% •Uncontrolled HTN or hemorrhagic stroke •Fasting TG >400 mg/dl or use of fibrates other than fenofibrate •Liver transaminases >3 x ULN; HBV, HCV infection, CK >3 x ULN •Estimated GFR<30 ml/min/1.73 m² •Positive pregnancy test	-
Primary endpoint	5-point MACE: CVS death, non-fatal MI, unstable angina, ischemic stroke & coronary revascularization	4-point MACE: CVS death, non-fatal MI, unstable angina & ischemic stroke	CVS death, non-fatal MI, unstable angina, ischemic stroke & coronary revascularization
Major findings/Outcomes	Lowered LDL-C by 59%; significantly reduced MACE by 9.8%, relative risk reduction of 15% over 2.2 years and absolute risk reduction of 1.5%	Lowered LDL-C by 63% with notable attenuation in reduction to 55% over the course of follow up due to the down titration of Alirocumab dose at low LDL-C levels; The reduction in MACE is also a challenge to interpret due this reason.	Lowers LDL-C by 55-60%; significantly reduced CV event rates in the higher-risk SPIRE-2 trial; Patients developed anti-drug antibodies

NYHA = New York heart association; LVEF = left ventricular ejection fraction; HTN = hypertension; CK = creatinine kinase; ULN = Upper limit of normal; HBV = hepatitis B virus; CVS = cardiovascular system; HCV = hepatitis C virus; GFR = glomerular filtration rate; Apo B = apolipoprotein B; CHF = congestive heart failure

4. Clinical Trials

Many phase III clinical trials for the PCSK9 inhibitors have been completed, and one is ongoing at the time of conducting this review. Four of the five clinical trials reviewed investigate PCSK9 antibody inhibition in patients with a history of clinically evident CVD: the FOURIER trial for evolocumab, the ODYSSEY OUTCOMES trial for alirocumab, the SPIRE-1 and SPIRE-2 trials for bococizumab, and the EVOPACS trial for evolocumab (Sabatine et al., 2017; Bays et al., 2015; Ridker et al., 2016; Koskinas et al., 2018). The fifth clinical trial, BERNON, investigates evolocumab in patients with diabetes mellitus and dyslipidemia (Lorenzatti et al., 2019). Because the EVOPACS trial is ongoing and the BERNON trial mainly relates to patients with diabetes mellitus, these will only be discussed briefly, while the other three clinical trials will be discussed in detail. (Table 1)

4.1 FOURIER

The FOURIER trial for evolocumab was conducted between January 2013 and February 2018 (Bohula et al., 2018). It was a randomized, parallel, double-blind, placebo study. It included 22,500 participants (including 9,000 ≥ 65 years) with a median follow up of 2.2 years. Participants had a history of clinically evident CVD (myocardial infarction (MI), stroke, symptomatic PAD), were at high risk of a recurrent event, and had LDL-C of ≥ 70 mg/dL or non-HDL cholesterol of ≥ 100 mg/dL. Patients' background statin therapy included atorvastatin 20-80 mg or an equivalent statin dose. From the study cohort, 69% were on a high dose, 30% were on a moderate dose and 5.1% were on ezetimibe. Patients were a mean age of 63 years, and 75% were male, with 37% having a diagnosis of diabetes mellitus, 80% hypertension 28.2% were active cigarette smokers, 19.3% had a history of stroke, and 13.2% had a history of PAD.

Exclusion criteria included MI or stroke four weeks prior to the study, New York Heart Association (NYHA) class III or IV heart failure (HF) symptoms or left ventricular ejection fraction (LVEF) $< 30\%$, hemorrhagic stroke, uncontrolled ventricular tachycardia (VT), planned revascularization within the next three months, uncontrolled hypertension, chronic kidney disease (CKD), organ transplant, or major active infection. The evolocumab dose was 140 mg every 2 weeks or 420 mg every 4 weeks. The primary endpoint was major adverse cardiovascular events (MACE), a composite of death, non-fatal MI, unstable angina, ischemic stroke, and coronary revascularization (Abifadel et al., 2003; Ott et al., 2015).

4.2 ODYSSEY OUTCOMES

The ODYSSEY OUTCOMES trial for alirocumab (a fully human monoclonal antibody) was conducted from October 2012 to March 2018 (Bays et al., 2015). It was a randomized, parallel, double-blind, placebo study. It included 18,000 patients with a median follow up of 2.8 years. Patients included in this study had a history of acute coronary syndrome (ACS) within the last 4-52 weeks, or a history of clinically evident CVD, and were at a high risk for a recurrent event. LDL-C on background therapy was required to be ≥ 70 mg/dl for LDL-C, ≥ 100 mg/dl for non-HDL cholesterol, or Apo B ≥ 80 mg/dl. Background statin therapy included atorvastatin 20-80 mg or rosuvastatin 20-40 mg. From the study cohort, 89% were on high dose and 3% were on ezetim-

ibe. Mean patient age was 58 years, with 75% of male gender, 29% with diabetes mellitus, 63.3% with hypertension, 23.9% active cigarette smokers, 2.9% with a history of stroke, and 3.7% with a history of PAD.

Exclusion criteria included uncontrolled hypertension, NYHA class III or IV HF, LVEF $< 25\%$ if measured, hemorrhagic stroke, fasting triglycerides of > 400 mg/dl, use of fibrates other than fenofibrate, recurrent ACS or coronary revascularization within the two weeks prior to randomization visit or planned after randomization, liver transaminases $> 3\times$ the upper limit of normal, concurrent hepatitis B or C viral infection, creatinine kinase $> 3\times$ the upper limit of normal, estimated glomerular filtration rate (GFR) < 30 ml/min/1.73 m² or a positive pregnancy test. The alirocumab dose was 75 mg or 150 mg every 2 weeks. The primary endpoint was MACE, a four-point composite including death, non-fatal MI, unstable angina and ischemic stroke.

4.3 SPIRE-1/SPIRE-2

The SPIRE-1 and SPIRE-2 trials for bococizumab (a murine derived humanized antibody) commenced in October 2013. Patients included in this study were at high risk of a cardiovascular event and had been receiving background lipid lowering therapy. No statin therapy regimen was specified. SPIRE-1 and SPIRE-2 included 12,000 and 6,300 patients, respectively. Bococizumab was given at 150 mg every 2 weeks. The primary endpoint included death, non-fatal MI, unstable angina, ischemic stroke and coronary revascularization. The trial was terminated early in August 2017 due to anti-drug antibody production, specifically an unanticipated attenuation of antibody production over time (Ridker et al., 2016, 2017). The drug's higher immunogenicity also explains the higher rates of injection site reaction in comparison to the other PCSK9 inhibitors, which are fully human monoclonal antibodies. Nonetheless, bococizumab was found to lower LDL-C by 55-60% when given in conjunction with statin therapy; in addition, it significantly reduced cardiovascular event rates in the higher risk SPIRE-2 trial, but not in the lower risk SPIRE-1 trial (Bove et al., 2019).

4.4 EVOPACS

The EVOPACS trial for evolocumab (fully human monoclonal antibody) commenced enrolment in January 2018. It is a randomized, double-blind, placebo-controlled multicenter study (Koskinas et al., 2018). The 308 patients included so far in this study have ACS, with a corresponding recent hospitalization. The inclusion criterion is LDL-C of ≥ 70 mg/dl or non-HDL-C ≥ 100 mg/dl, with a background treatment of high-intensity statin within ≥ 4 weeks prior to enrollment in the study. The exclusion criteria include uncontrolled cardiac arrhythmia, severe renal dysfunction, active liver disease, atorvastatin intolerance, active malignancy, pregnancy, as well as those patients who have previously received evolocumab, another PCSK9 inhibitor, cholesterol ester transfer protein inhibitors, or cyclosporine.

Enrolled patients were randomly assigned to receive either 420 mg of evolocumab subcutaneously every 4 weeks or placebo. The primary outcome is the percentage change of calculated LDL-C at the end of the first 8-week period. Secondary endpoints are adverse events and serious adverse events. The EVOPACS study is

ongoing and has an estimated completion date of September 2019.

4.5 BERSON

The BERSON trial for evolocumab (a fully human monoclonal antibody) was conducted between April 2016 and December 2017. It is a randomized, double-blind, placebo-controlled multicenter study (Lorenzatti et al., 2018). In contrast to the studies described above, the 986 patients included in BERSON had diabetes mellitus and dyslipidemia. Enrollment did not depend on statin therapy; but once enrolled, patients who had not been receiving statin therapy were put on 20 mg atorvastatin for a 4-week lipid stabilization period.

Patients included in this study were receiving pharmacological therapy for diabetes mellitus and were on lipid lowering therapy for at least the 4-week period prior to participation in the study. Other inclusion criteria included a fasting LDL-C of ≥ 100 mg/dL for those on statin therapy at the time of screening, and a fasting LDL-C of ≥ 130 mg/dL for those not on statin therapy at the time of screening. Exclusion criteria included NYHA class III or IV HF, uncontrolled cardiac arrhythmia, hypertension, hypothyroidism or hyperthyroidism, type 1 diabetes, or poorly controlled diabetes mellitus. After inclusion in the study, patients were randomized and received either 140 mg of evolocumab every 2 weeks, 420 mg monthly, or placebo (Lorenzatti et al., 2019).

The primary outcome was the change in the percentage of LDL-C at the end of the first 12-week period and to the mean of weeks 10 and 12. Secondary outcomes included atherogenic lipids, fasting blood glucose and haemoglobin A_{1c} measures, and adverse events.

5. Discussion

While an estimated 31% of all global deaths are due to CVD, recent studies conducted on population groups in Finland, England and Wales, USA, and Iceland have shown that CVD burden can be reduced by 40-80% through changes in modifiable risk factors (Unal et al., 2004; Aspelund et al., 2010; Go et al., 2014; Jousilahti et al., 2016; Roth et al., 2018). These modifiable risk factors encompass behaviours including tobacco use, salt consumption, calorie intake, and physical activity. Furthermore, other risk factors can be modified by medication, and it is well documented that the reduction of blood LDL-C is a principal risk factor modifiable in this way. Statins are considered to be the mainstay in cholesterol lowering drugs prescribed to patients with a high cholesterol level. However, as not all patients respond to statin therapy, and some might even develop an adverse reaction to statins, there is an urgent clinical need for novel drugs that achieve a cholesterol lowering effect while being tolerable to such patients. PCSK9 inhibitors are advanced in their development; they can be used to either augment the effect of statins, or used alone, to lower blood cholesterol level (Bays et al., 2015; Ridker et al., 2016; Sabatine et al., 2017).

The results of the FOURIER trial found evolocumab to significantly reduce the composite endpoint of cardiovascular death, MI, stroke, or hospitalization for unstable angina or coronary revascularization (9.8% vs 11.3% with placebo). This yielded a relative risk reduction of 15% over 2.2 years and an absolute risk reduction of 1.5% (number needed to treat, ~ 67). There were no significant

differences in all-cause mortality and no significant safety concerns, except a small increased risk of injection site reaction. The results of ODYSSEY OUTCOMES confirmed the findings of the FOURIER trial regarding the clinical importance of PCSK9 inhibitors, with relative risk reduction similar across all subgroups of patients. The greatest absolute benefit was identified in patients with a baseline LDL-C of ≥ 100 mg/dl, with a 3.4% reduction in the primary composite endpoint and a 1.7% reduction in all-cause mortality.

ODYSSEY OUTCOMES differed from FOURIER in that ODYSSEY OUTCOMES included participants with recent ACS, rather than the more stable patients enrolled in FOURIER. Similar to FOURIER, only patients with inadequate lipid control were enrolled in ODYSSEY OUTCOMES. A notable difference of ODYSSEY OUTCOMES, however, was that alirocumab was titrated between 75-150 mg, in order to maintain LDL-C in the range of 25-50 mg/dl but not < 15 mg/dl. Over the course of follow up in ODYSSEY OUTCOMES, there was a notable attenuation in the reduction of LDL-C after 48 months (from 63 to 55%). In contrast, this attenuation was not demonstrated in FOURIER. The results of absolute benefit in the reduction of primary composite endpoint and all-cause mortality in ODYSSEY OUTCOMES is a challenge to interpret due the down-titration of the alirocumab dose at low LDL-C levels. This would have occurred more often in those with a baseline LDL-C < 100 mg/dl. In the FOURIER and ODYSSEY OUTCOMES trials, 3% and 5% of patients, respectively, were on ezetimibe (Bohula et al., 2018; Bays et al., 2015). It could be hypothesized that if more patients in both trials had been prescribed ezetimibe, many of them would have been ineligible for enrolment.

The SPIRE-1/SPIRE-2 trial for bococizumab, which commenced in 2013, was terminated early in August 2017. This was primarily due to anti-drug antibody production, specifically an unanticipated attenuation of antibody production over time, and higher rates of injection site reaction than other PCSK9 inhibitors.

The EVOPACS trial for evolocumab, which commenced in 2018, is ongoing with completion expected in September 2019. No preliminary results have been published to date, but given the similarity of its design with that of the FOURIER trial, cross-trial comparison will be of interest.

In contrast to the four above mentioned clinical trials, the BERSON trial for evolocumab was conducted in patients with diabetes mellitus and dyslipidemia. Preliminary results demonstrated that evolocumab significantly reduced LDL-C levels in addition to other atherogenic lipids. Furthermore, evolocumab was well tolerated by patients, but had no impact on fasting glucose level or haemoglobin A_{1c}.

6. Future Perspectives

It has been clinically established that the decrease of LDL-C below 70 mg/dl is of great importance in the reduction of the burden of CVD both in high risk populations and those at high risk of recurrent disease. Clinical investigations have shown that not all patients can tolerate statins, with undesirable side effects in patients with uncontrolled LDL with or without CVD as well as in conditions such as familial hypercholesterolemia. The role

of PCSK9 inhibitors is vital for such patients. In this review, we show that all completed clinical trials to date have found PCSK9 inhibitors to be effective in reducing LDL-C levels within certain patient populations. It has also been shown that PCSK9 inhibitors are effective in the treatment of dyslipidemia associated with other comorbidities such as diabetes mellitus. Investigations into the clinical effectiveness of PCSK9 inhibitors have only commenced in the last three to four years, so follow up is somewhat limited to date. While PCSK9 inhibitors show promise as augmenting drugs for CVD alongside statin therapy, longer follow up periods are necessary to determine whether there are any unfavorable side effects with their longer-term use.

There is ongoing debate on the cost effectiveness of the long-term use of PCSK9 inhibitors. A recent report by Ko et al. explored the current disparity between the health value resulting from the use of PCSK9 inhibitors and its disproportionate cost (Ko et al., 2018; Nasir, 2018).

Regarding estimated cost calculation, the authors assumed a cost of Canadian \$8,000 annual patient cost which is beyond the means of most healthcare systems. In their paper, the authors put forward a suggestion that PCSK9 inhibitors could be used selectively by health care systems for patients in the highest risk bracket. More recently, Amgen announced a 60% reduction in cost of evolocumab in an effort to reduce patient cost, thereby making it more accessible to a wider patient cohort. It is hoped that a further price reduction may follow to allow this innovative therapy to be available to all those in need.

7. Conclusion

PCSK9 inhibition alone or as an addition to standard lipid therapy is an important step towards better control of lipid levels, either as primary or secondary prevention of cardiovascular incidents. However, the high financial cost of PCSK9 inhibitors at present limits the possibilities of widespread adoption throughout healthcare systems worldwide. Recently, there has been a 60% reduction in the cost of evolocumab. Moreover, a rationale has been put forward which assumes that PCSK9 inhibitors should be initially prescribed to patients in the highest risk bracket of cardiovascular disease. In light of this, the rationale for prescribing PCSK9 inhibitors needs further development, according to individual healthcare systems' capacities, the financial cost and value derived from the PCSK9 inhibitor in question, and individual patients' resources and needs.

Acknowledgments

I would like to express my gratitude to all those who helped me during the writing of this manuscript. I would also like to extend my thanks to all the peer reviewers and editors for their opinions and constructive suggestions.

Conflict of interest statement

The author declares no conflicts of interests.

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