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PCSK9 Inhibitors: Mechanisms of Action, Metabolic Effects, and Clinical Outcomes

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Abstract

Atherosclerotic cardiovascular disease (ASCVD) is associated with significant morbidity and mortality worldwide. Increased serum levels of low-density lipoprotein cholesterol (LDL-C) are an independent risk factor for ASCVD, and clinical trial data have shown that lowering LDL-C generally reduces cardiovascular risk. Until recently, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) have been the main therapy for lowering LDL-C. However, some statin-treated patients have persistently elevated residual cardiovascular risk due to inadequate lowering of LDL-C levels or non-LDL-related dyslipidemia. In addition, adverse effects of statins may limit their tolerability and therefore the ability to attain effective doses in some patients. A new class of drugs that inhibit proprotein convertase subtilisin-kexin type 9 (PCSK9) has been developed to treat hyperlipidemia. This review discusses the history and mechanism of action of PCSK9 inhibitors, their metabolic effects, and clinical outcomes associated with these medications, highlighting recent large cardiovascular outcome trials investigating these therapies.

INTRODUCTION

Cardiovascular (CV) disease is the leading cause of mortality worldwide, accounting for an estimated 31.5% of all global deaths in 2013 (1). In particular, there is a high burden of atherosclerotic CV disease (ASCVD), which affects multiple vascular beds and can manifest as coronary heart disease (CHD), cerebrovascular disease, and peripheral artery disease (2). An increased serum level of low-density lipoprotein cholesterol (LDL-C) is an independent risk factor for ASCVD, and clinical trial data have demonstrated a relationship between lowering LDL-C and reductions in CV risk (3). Consequently, reducing LDL-C is a key strategy for primary and secondary prevention of ASCVD (2).

The cornerstone therapy for LDL-C lowering has been statins, which inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. Large-scale randomized trials have proven the efficacy of statins in reducing the risk of major vascular events by ~25% for each mmol/L reduction in LDL-C per year of statin use, with greater absolute benefit of statin therapy for higher-risk patients (4). In contrast, nonstatin lipid-lowering therapies, such as niacin and cholesteryl ester transfer protein inhibitors, have shown no CV benefit or have even increased the risk of CV events and mortality (5–7). Combination treatment with statin and ezetimibe to lower LDL-C modestly improve CV outcomes in patients with acute coronary syndrome and also suggest additional clinical benefit for reduction of LDL-C to levels below the prior practice guideline target of 70 mg/dl (8).

Despite the proven efficacy of statins to reduce LDL-C levels and CV events, additional therapies are needed. Even with statin treatment, some patients have high residual CV risk due to inadequate lowering of LDL-C levels or persistent non-LDL-C-related dyslipidemia (9–11). Furthermore, adverse effects, including myopathy (ranging from mild myalgias to severe rhabdomyolysis), new-onset or worsening diabetes, and possibly hemorrhagic stroke, may limit statin use or the ability to attain goal-effective statin doses in certain patients (4). Recently, another class of drugs inhibiting proprotein convertase subtilisin-kexin type 9 (PCSK9) has been developed for the treatment of hyperlipidemia. This review discusses the history, mechanism of action, metabolic effects, and clinical outcomes of PCSK9 inhibitors.

IDENTIFICATION OF PCSK9

In 2001, PCSK9 was first identified when elevated protein levels were found in studies of cerebellar neuron apoptosis (12). The protein was initially named neural apoptosis-regulated convertase 1, and the gene was characterized in 2003 (12, 13). Concurrent studies in patients with familial hypercholesterolemia provided insight into the clinical importance of PCSK9, with gain-of-function mutations causing hypercholesterolemia (13–16). Murine models overexpressing PCSK9 demonstrated increases in levels of total cholesterol and non–high-density lipoprotein cholesterol (non-HDL-C) and reduced levels of the hepatic LDL receptor (LDL-R), confirming a causal role for gain-of-function PCSK9 mutations in humans exhibiting the hypercholesterolemic phenotype (16–18). Later, it was shown that patients with loss-of-function PCSK9 mutations and associated hypocholesterolemia had a lower risk of CV disease (13, 19, 20).

PCSK9 STRUCTURE AND FUNCTION

The gene for *PCSK9* is located on chromosome 1p32 and codes for a 692-amino-acid serine protease (16). PCSK9 is primarily expressed in the liver, but lower levels of protein expression have also been found in the intestine, kidney, and central nervous system. Transcription of PCSK9 is

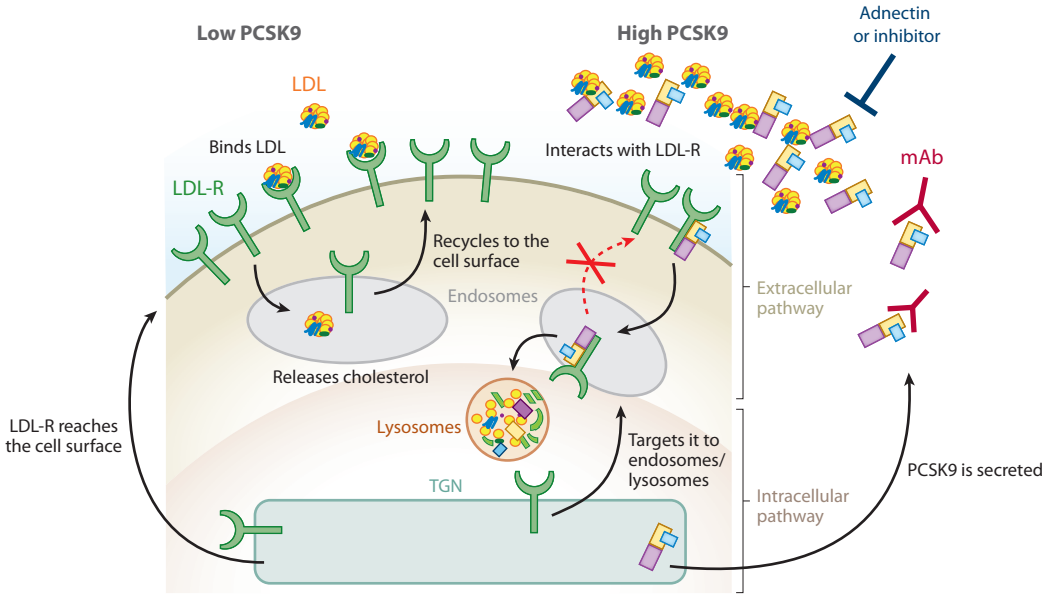

Figure 1

The role of PCSK9 in LDL-R metabolism. When PCSK9 levels are high, the degradation of the LDL-R through extracellular and intracellular pathways is enhanced, resulting in increased degradation of the PCSK9–LDL-R complex in lysosomes. Low surface LDL-R levels lead to greater levels of circulating LDL-C. Conversely, if PCSK9 levels are low, then cell surface LDL-R levels are high, and LDL-R can be recycled to the cell surface after delivery of LDL-C particles to endosomes, resulting in lower circulating LDL-C levels. PCSK9 activity via the extracellular pathway can be inhibited by monoclonal antibodies (mAb) or adnectins. Adapted with permission from Reference 22. Abbreviations: LDL-R, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin-kexin type 9; TGN, trans–Golgi network.

primarily regulated by sterol regulatory element-binding protein-2. In the hepatocyte, PCSK9 is synthesized as a zymogen, requiring activation by another enzyme; it is composed of a signal peptide, a prosegment, a catalytic domain, and a C-terminal domain (21). In the endoplasmic reticulum, PCSK9 undergoes cleavage of its signal peptide and undergoes cotranslational autocatalytic cleavage into a prosegment and a mature protein, the latter of which is required for secretion from the endoplasmic reticulum to the Golgi body. Unique to PCSK9, the prosegment remains associated with the mature protein, facilitating protein folding, preventing enzyme activity by blocking access to the catalytic site, and chaperoning PCSK9 through the secretory pathway.

PCSK9 plays an important role in LDL-C metabolism (**Figure 1**) (16, 21). LDL-C bound to the LDL-R is internalized into hepatocytes through clathrin-coated vesicles, after which the acidic environment of the endosome causes dissociation of LDL-C from its receptor. Recycling vesicles return the LDL-R to the cell surface, while endosomes containing the LDL-C particles fuse with lysosomes, resulting in degradation of LDL-C, hydrolysis of cholesterol esters, and distribution of free cholesterol to the rest of the cell. At the hepatocyte plasma membrane, the catalytic domain of secreted PCSK9 associates with the LDL-R and is internalized, entering the endosomal pathway. The low pH of the endosome enhances the affinity of PCSK9 for the LDL-R, preventing the receptor from being recycled to the cell surface. Instead, the complex is directed to the lysosome, where both components are degraded. In addition, PCSK9 appears to enhance intracellular LDL-R degradation prior to secretion, as PCSK9 can complex with the LDL-R within the Golgi and direct the receptor to the lysosome for degradation instead of transport to the plasma membrane.

Although the LDL-R is the best-studied PCSK9 target, PCSK9 has putative roles in other organ systems (21). In the small intestine, PCSK9 may regulate triglyceride-rich apolipoprotein B production, as treatment of enterocytes with PCSK9 increases secretion of apoB48 and apoB100 (23). Recent data suggest PCSK9 may also modulate transintestinal fecal cholesterol excretion, as well as expression of very-low-density lipoprotein receptors (VLDL-R) in adipose tissue and the apoE receptor 2 in the brain. Similar to the LDL-R, VLDL-R and apoE receptor 2 are degraded in the lysosome after binding to PCSK9. Finally, PCSK9 is also expressed in pancreatic islet cells. These extrahepatic sites for PCSK9 expression form the basis for concerns regarding potentially negative effects of PCSK9 inhibition, including neurocognitive injury and impaired glucose homeostasis.

PCSK9 INHIBITORS

Multiple strategies of PCSK9 inhibition are currently under investigation (16). The first approach prevents binding of PCSK9 to the LDL-R. Examples of this approach include monoclonal antibodies or adnectins, also termed monobodies (**Figure 1**). Monoclonal antibody therapeutic agents include evolocumab, alirocumab, and bococizumab. These bind the catalytic domain and prodomain of PCSK9, blocking interaction with the LDL-R and neutralizing PCSK9 activity. Studies have shown maximal suppression of circulating unbound PCSK9 within 4–8 h after administration of the monoclonal antibody (24), with reductions in LDL-C of ~65% in healthy subjects and ~60–80% in patients with hypercholesterolemia (25, 26). Like monoclonal antibodies, adnectins also have high specificity for targets, with low toxicity. Currently, the adnectin BMS-962476, which has high binding affinity to human PCSK9, has been tested in a phase I clinical trial showing a 90% reduction in free PCSK9 and 48% lowering of LDL-C (27).

The second major strategy for PCSK9 inhibition is directed toward PCSK9 synthesis and processing. Small interfering RNAs (siRNAs) are molecules that can be used to target PCSK9 mRNA and arrest translation, leading to mRNA degradation. In a phase I clinical trial, the anti-PCSK9 siRNA ALN-PCS reduced free PCSK9 levels by 70% and LDL-C levels by 40% (28). Another approach to silence mRNA is the use of antisense oligonucleotides, which are short nucleic acid sequences that bind to mRNA. After data from animal studies demonstrated reductions in circulating PCSK9 and LDL-C levels, two PCSK9-directed antisense oligonucleotides, SPC5001 and BMS-844421, were tested in phase I clinical trials. Development was terminated for undisclosed reasons (16).

LIPID EFFECTS OF PCSK9 INHIBITORS

PCSK9 inhibition can significantly lower LDL-C concentrations in humans, even on a background of statin therapy. Patient populations studied in clinical trials range from those at low CV risk to the very-high-CV-risk population of individuals homozygous for familial hypercholesterolemia (HoFH). Data on lipid-lowering effects of the two clinically available PCSK9 inhibitors, evolocumab and alirocumab, as well as a brief discussion of bococizumab, are presented in this section.

Evolocumab

Evolocumab has been tested in multiple randomized controlled trials, including several 12-week trials involving >3,000 patients, one 52-week trial involving 901 patients (29), and the recently published Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with

Elevated Risk (FOURIER) trial (30). The lipid-lowering effects of evolocumab were consistent in these trials except for lesser LDL-C reductions in the HoFH population than expected, given its mechanism of action requiring the presence of LDL receptors.

Evolocumab was initially studied in the following clinical conditions: as monotherapy in patients at low CV risk (31), for hypercholesterolemia in patients on statin therapy (32), in "statin-intolerant" patients with LDL-C above the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) goals (33), in patients with heterozygous familial hypercholesterolemia (HeFH) and LDL ≥100 mg/dl (34, 35), and in HoFH patients (36, 37). The range of LDL-C lowering in these trials was −48% to −66.1%, with an absolute reduction in LDL-C of up to −90.8 mg/dl from baseline. The longest of these trials was the Durable Effect of PCSK9 Antibody Compared with Placebo Study (DESCARTES), a randomized double-blind placebo-controlled trial that compared the effect of evolocumab with placebo in patients with hyperlipidemia (29). Patients received the study drug for 52 weeks after a run-in period of 4–12 weeks of background lipid-lowering therapy which could consist of diet alone, atorvastatin 10 mg or 80 mg, or atorvastatin 80 mg with ezetimibe 10 mg daily. The mean LDL-C concentration at baseline was 104.2 mg/dl, and the mean [± standard error (SE)] LDL-C concentration at week 52 was 50.9 (±1.4) mg/dl, representing a mean reduction of 50.1% (±1.2). There was an increase in LDL-C in the placebo group by week 52, so the least-squares mean (±SE) percentage change from baseline in the LDL-C group versus placebo was −57% (±2.1).

Additional support for durable LDL-C lowering with evolocumab came from the Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER) Randomized Trial, which lasted 52 weeks (38). In OSLER, 1,359 initially randomized and dosed patients in the four evolocumab phase II parent studies were offered enrollment the open-label extension. A total of 1,104 (81%) patients agreed and were randomized 2:1 to receive open-label subcutaneous (SC) evolocumab 420 mg every four weeks with standard of care (SOC) (N = 736) or SOC alone (N = 368), regardless of treatment assignment in the parent study. Patients without prior evolocumab exposure had a mean reduction in LDL-C of 52.3% (SE 1.8%) at week 52 ($p < 0.0001$). Patients who received one of six dosing regimens of evolocumab in the parent studies and received evolocumab plus SOC in OSLER had a mean reduction in LDL-C of 50.4% (SE 0.8%) at the end of the parent study and a persistent reduction of 52.1% (SE 1.0%) at 52 weeks ($p = 0.31$). Patients who were on evolocumab when they entered OSLER and were randomized to SOC alone exhibited a return of LDL-C levels to near baseline levels.

Fifty patients with HoFH were evaluated in the Trial Evaluating PCSK9 Antibody in Subjects with LDL Receptor Abnormalities (TESLA) Part B, a randomized double-blind placebo-controlled phase III trial of evolocumab 420 mg SC every four weeks (37). The absolute change in LDL-C by ultracentrifugation at 12 weeks was −1.9 mmol/L, but because the placebo group increased by 0.5 mmol/L, the difference between treatment groups was −2.5 mmol/L [95% confidence interval (CI) −3.7 to −1.1 mmol/L, $p = 0.0004$]. In this trial, the lower efficacy of LDL-C lowering with evolocumab was not surprising, as patients with HoFH have varying degrees of LDL-R expression; in this population, greater reductions in LDL-C with evolocumab were observed in patients with more highly expressed LDL-R. This was further evaluated in a very small open-label single-arm multicenter pilot study in eight patients with receptor-negative or -defective HoFH on stable drug therapy (36). Patients were treated with evolocumab 420 mg SC every four weeks for ≥12 weeks, followed by 420 mg every two weeks for an additional 12 weeks. At 12 weeks, the mean change from baseline in LDL-C was −16.5% (range, 5.2% to −43.6%; $p = 0.0781$) and −13.9% (range, 39.9% to −43.3%; $p = 0.1484$) with four- and two-week dosing, respectively. No reduction was seen in the two receptor-negative patients. Over the treatment periods, the LDL-C reductions in the six LDL receptor-defective patients were 19.3 ± 16% and 26.3 ± 20% with

four- and two-week dosing, respectively ($p = 0.0313$ for both values), ranging from 4% to 48% with two-week dosing.

The recent FOURIER trial testing evolocumab was performed in >27,000 patients with a history of CV disease (13%) (30). Patients were on high-intensity or moderate-intensity background statin therapy, except for 0.3% who took low-intensity statin or for whom there was no information. Evolocumab decreased the median LDL-C level from 92 mg/dl at baseline to 30 mg/dl on treatment with no change in the placebo group. At 48 weeks, the least-squares mean percentage reduction in LDL-C was 59% (95% CI 58–60%, $p < 0.001$) in the evolocumab group with a mean absolute reduction of 56 mg/dl to a median LDL-C of 30 mg/dl (intraquartile range 19–46). A total of 87% of patients in the evolocumab group achieved an LDL-C level of ≤70 mg/dl, compared with 18% in the placebo group (evolocumab versus placebo, $p < 0.001$). The evolocumab group demonstrated a reduction in non-HDL-C of 51.2% and a reduction in apoB of 46%, while HDL-C increased by 8.4% ($p < 0.001$ for each versus placebo) at 48 weeks. Evolocumab therapy resulted in a median reduction in triglycerides of 16.2% and median reduction in lipoprotein(a) [Lp(a)] of 26.9% ($p < 0.001$ for each versus placebo).

Overall, available clinical trial results demonstrated that the potent lipid-lowering effects of evolocumab in non-HoFH patients were consistent across populations and were durable for up to 2.2 years. There was a lesser effect in HoFH patients depending on degree of LDL-R expression.

Alirocumab

Alirocumab was the first PCSK9 inhibitor approved by the US Food and Drug Administration (FDA), in July 2015, for use in addition to diet and maximally tolerated statin therapy in adult patients with HeFH or patients with clinical ASCVD who require additional lowering of LDL cholesterol (39). The Long-Term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY LONG TERM) trial was a large phase III randomized double-blind placebo-controlled parallel-group multinational study conducted at 320 sites in 27 countries throughout Africa, Europe, and North and South America (40). This trial enrolled 2,341 patients at high risk for CV events with LDL-C levels of at least 70 mg/dl while receiving treatment with statins at the maximum tolerated dose, with or without other lipid-lowering therapy. Patients were randomly assigned in a 2:1 ratio to receive alirocumab (150 mg) or placebo SC every two weeks for 78 weeks. The primary efficacy endpoint was the percentage change in calculated LDL-C from baseline to week 24. The baseline LDL-C was ~122 mg/dl in each group and decreased to 48.3 mg/dl in the alirocumab group and 118.9 mg/dl in the placebo group, representing a percentage change of −61% and 0.8%, respectively ($p < 0.001$). The least squares mean difference in percentage change of calculated LDL-C from baseline to week 24 in the alirocumab group versus placebo was -61.9 ± 1.3 with a 95% CI of −64.3 to −59.4 ($p < 0.001$). The least squares mean differences in other lipid elements also proved to be significant, including non-HDL-C (-52.3 ± 1.1), apoB (-54.0 ± 1.2), Lp(a) (-25.6 ± 1.3), fasting triglycerides (-17.3 ± 1.4), and HDL-C ($+4.6 \pm 0.7$), all $p < 0.001$ versus placebo control. At 78 weeks, there was some attenuation of the effect, with least squares mean calculated LDL-C increasing to 122.6 mg/dl in the placebo group and 57.9 mg/dl in the alirocumab group (least squares mean percentage change from baseline of +3.6% and −52.4%, respectively).

This degree of lipid-lowering efficacy was similar to what has been demonstrated in other trials, including a 52-week trial in 316 patients with established CHD or CHD risk equivalents and hypercholesterolemia (41), as well as a 24-week active comparator trial of alirocumab versus ezetimibe involving 103 patients (42). In the former 52-week trial, the primary endpoint was

percentage change in LDL-C from baseline to week 24. In the intent-to-treat analysis, the baseline LDL-C was 100.3 mg/dl in the alirocumab group and 106.0 mg/dl in the placebo group, with an estimated mean change at week 24 of −48.2 (95% CI −52.0 to −44.4) compared with −2.3 (95% CI −7.6 to 3.1) in the placebo group. In the latter trial, the baseline LDL-C was ∼140 mg/dl in both groups, and LDL-C decreased by 54.1% in the alirocumab group (who received alirocumab 75 or 150 mg SC every two weeks) compared with 17.2% in the ezetimibe group at week 24. Another trial demonstrated that as add-on therapy to atorvastatin 20 mg, alirocumab 75 mg SC every two weeks lowered LDL-C by 44.1%, and adding alirocumab to atorvastatin 40 mg resulted in 54% LDL-C lowering at week 24 (43). The magnitude of LDL-C lowering with addition of alirocumab to rosuvastatin therapy was not as high, resulting in a change of −36.3% at week 24 (44). These effects of alirocumab have been confirmed in other patient populations (45, 46). Alirocumab has also been studied in >800 patients with HeFH (47, 48), including those with very high LDL-C of 160 mg/dl or above (48), causing a least squares mean change in calculated LDL-C at week 24 ranging from −39.1% to −57.9% compared with placebo and an absolute change in LDL-C from baseline of up to −75.3 mg/dl compared with placebo.

In summary, a variety of clinical trials have found that alirocumab has lipid-lowering effects similar to that of evolocumab, but for the majority of these trials, the primary endpoint consisted of the change in LDL-C from baseline to week 24. However, the ODYSSEY LONG TERM trial demonstrated durability of the LDL-C-lowering effect of alirocumab at 78 weeks.

Bococizumab

Bococizumab is a humanized monoclonal antibody that retains ∼3% murine sequences. The murine component has been shown to stimulate the production of high titers of antidrug antibodies in some patients, which directly attenuates the LDL-C lowering response and duration (49).

Bococizumab has been studied in a 24-week dose-ranging study involving 354 patients with hypercholesterolemia on statin therapy (50), in six multinational trials (49), and in two large multinational randomized controlled trials (Studies of PCSK-9 Inhibition and the Reduction of Vascular Events, SPIRE-1 and SPIRE-2) with different LDL entry criteria involving 27,438 patients (51). Bococizumab in doses of 100 mg and 150 mg SC every 14 days resulted in mean LDL-C lowering of 44.9% (52.3 mg/dl) and 52% (54.2 mg/dl), respectively; 200 mg every 28 days resulted in mean LDL-C lowering of 19.5% (21.3 mg/dl), and 300 mg SC every 28 days resulted in mean LDL-C lowering of 33.3% (38.3 mg/dl) (50). The effects on non-HDL-C, triglycerides, and HDL-C were similar to those of evolocumab and alirocumab in this trial. For the large-scale SPIRE trials, the mean baseline LDL-C was 109.2 mg/dl, with a decrease in LDL-C of 46.8% (95% CI of −47.7 to −45.8) in the combined SPIRE trial population at 52 weeks (51).

The mechanism of the lack of durability of the LDL-C lowering was examined in an analysis of six parallel, multinational lipid-lowering trials that had enrolled 4,300 patients with hyperlipidemia followed for up to 12 months (49). The patients were stratified by presence or absence of antidrug antibodies detected during the treatment period. High titers of antidrug antibodies developed in a substantial proportion of patients on bococizumab therapy and markedly diminished the degree and durability of LDL-C reduction. Furthermore, the degree of LDL-C reduction varied widely among patients who did not develop antidrug antibodies. Consequently, the bococizumab development program was halted in November 2016 (52).

PCSK9 INHIBITORS AND INFLAMMATION

Although PCSK9 inhibitors clearly modify LDL-C metabolism and other key lipid fractions such as Lp(a), their effects on inflammation are less well documented. A meta-analysis of 16 randomized

controlled trials including 2,546 patients found no effect of a PCSK9 inhibitor on high-sensitivity C-reactive protein levels (hs-CRP) levels (53). Potential effects of these drugs on other markers of inflammation are unknown.

CLINICAL EFFECTS OF PCSK9 INHIBITORS

Although statins have a long history of providing clinical benefit, not all drugs that lower LDL-C using other mechanisms have shown similar results (54, 55). As illustrated above, the PCSK9 class of drugs has shown substantial evidence of providing a metabolic benefit on key lipid fractions in a variety of clinical settings, and further evidence supporting the mechanism of action of evolocumab was provided by a clinical study using intravascular ultrasound to measure percent atheroma volume (56). This study, conducted in 968 patients undergoing coronary angiography, almost all of whom were taking background statin therapy, showed that evolocumab decreased atheroma volume relative to placebo, and this benefit was related to the decrease in on-treatment LDL-C levels. Despite these intriguing data and the striking lipid effects of PCSK9 inhibitors, whether these results translate into consistent clinical benefit is not yet fully understood.

In June 2015, the Endocrinologic and Metabolic Drugs Advisory Committee of the FDA reviewed the metabolic effects and potential clinical benefits of alirocumab and evolocumab (55). Both of these drugs are fully humanized monoclonal antibodies to PCSK9, and both resulted in similar and substantial reductions in LDL-C levels. Based on the statin data, these lipid changes were anticipated to provide protection against CV events. However, at the time of the FDA review, none of the proposed CV outcome trials had been completed, although the trials available for review did allow assessment of adverse CV events. In ODYSSEY LONG TERM, alirocumab was studied in 2,341 high-risk individuals on maximally tolerated statin to assess the drug's effects on lipid parameters; importantly, CV events were adjudicated by an independent clinical events committee (40). The composite CV endpoint included death from CHD, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization. In a post hoc analysis, these events were reduced compared with placebo, with a hazard ratio (HR) of 0.52 (95% CI 0.31 to 0.90). The FDA advisory committee also reviewed evolocumab data derived from a variety of studies in which reduction of LDL-C was the primary endpoint (57). CV adverse events were independently adjudicated and included death, coronary events (myocardial infarction, unstable angina requiring hospitalization, or coronary revascularization), cerebrovascular events (stroke or transient ischemic attack), and heart failure requiring hospitalization. Evolocumab significantly reduced the composite of these CV events at one year (HR 0.47, 95% CI 0.28–0.78).

The overall number of patient-years of exposure for both drugs was insufficient to assess long-term safety issues. Alirocumab was not associated with general allergic reactions, but there was a trend for more local injection-site reactions. The number of myalgia reactions was significantly greater than on placebo, and there was a numeric trend for more neurocognitive disorders. Similar findings were seen for evolocumab, including numeric imbalances in injection-site reactions, neurocognitive events, and arthralgias. Based on the lipid-lowering effects of both drugs and the potential for clinical benefit from the preliminary CV adverse event data, a majority of committee members voted in favor of approving alirocumab and evolocumab for clinical use (54). However, concern was raised about the limited amount of safety information and the need to complete the CV outcome trials. A more complete picture regarding the safety and efficacy of alirocumab will emerge with the conclusion of the ODYSSEY OUTCOMES trial (NCT01663402), which is being conducted in patients with acute coronary syndrome and is expected to be completed at the end of 2017 (see **Table 1**).

Table 1 Phase III cardiovascular outcome trials of PCSK9 inhibitors

Drug	Alirocumab	Evolocumab	Bococizumab	
Trial name	ODYSSEY OUTCOMES[a]	FOURIER (30)	SPIRE-1 (51)	SPIRE-2 (51)
Trial status	Ongoing	Completed	Discontinued early	
Patient population	Prior ACS within 12 months	History of MI, stroke, or PAD and additional risk	History of CV event or high risk primary prevention (diabetes, CKD, or PVD and additional risk factors)	
Sample size	18,000	27,564	16,817	10,621
Statin status of patients	Maximal tolerated statin dose	Atorvastatin ≥20 mg or equivalent	Statin therapy	Off statin allowed if intolerant
Baseline LDL-C	≥70 mg/dl	92 mg/dl	94 mg/dl	133 mg/dl
On-treatment LDL-C	Pending	−59% at 48 weeks	−57% week 14	−55% week 14
Primary endpoint	CHD death, MI, ischemic stroke, or UA hospitalization	CV death, MI, stroke, hospitalization for UA, or coronary revascularization	MI, stroke, CV death, or UA requiring urgent revascularization	
Results	Pending	HR 0.85, 95% CI 0.79–0.92	HR 0.99, 95% CI 0.80–1.22	HR 0.79, 95% CI 0.65–0.97

[a]ClinicalTrials.gov Identifier NCT01663402.

Abbreviations: ACS, acute coronary syndrome; CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; PAD, peripheral artery disease; PVD, peripheral vascular disease; UA, unstable angina.

Most recently, data from large CV outcome trials for evolocumab and bococizumab were presented at the 2017 conference of the American College of Cardiology (see **Table 1**). In the FOURIER trial of evolocumab, the primary endpoint of CV death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization had an HR of 0.85 (95% CI 0.79–0.92), and the key secondary endpoint of CV death, myocardial infarction, or stroke had an HR of 0.80 (95% CI 0.73–0.88)—both of which were highly statistically significant (30). This benefit was primarily driven by reductions in myocardial infarction, ischemic stroke, and coronary revascularization. CV death was not reduced (HR 1.05, 95% CI 0.88–1.25), and there was also no reduction in all-cause mortality. Adverse events, including serious adverse events, were well balanced between groups, except for injection-site reactions, which were more common with evolocumab. There was no signal for increased risk of diabetes or neurocognitive events. A separate long-term follow-up study of evolocumab reported persistence of LDL-C lowering effects with no emergence of neutralizing antibodies (58).

Bococizumab was studied in two similar multinational CV outcome trials enrolling >27,000 patients in total (51). Patients were enrolled with either established CV disease or high risk (~15%). A major distinction between the two trials was the LDL-C inclusion criterion, which required LDL-C levels of ≥70 mg/dl in SPIRE-1 and ≥100 mg/dl in SPIRE-2. Approximately 93% of subjects were on a statin at baseline, with the remainder considered statin intolerant or taking ezetimibe. The initial effect on lipid levels was substantial, as observed in other PCSK9 lipid trials, but owing to the formation of antidrug antibodies, the lipid effects were attenuated in proportion to the level of antidrug antibody. The primary outcome of nonfatal myocardial infarction, nonfatal stroke, CV death, or unstable angina requiring urgent revascularization was significantly reduced in SPIRE-2 (HR 0.79, 95% CI 0.65–0.97) but not SPIRE-1 (HR 0.99, 95% CI 0.80–1.22). There were numeric trends for lower CV and all-cause mortality in SPIRE-2. Unfortunately, these trials were stopped early because of the attenuation of lipid effect associated with antidrug antibodies.

CONCLUSIONS

PCSK9 drugs represent a novel approach to achieving substantial reductions in LDL-C concentrations in a variety of patient populations at high CV risk even on a background of maximally tolerated statin therapy. To date, the primary clinical benefit of evolocumab is a reduction in myocardial infarction, ischemic stroke, and coronary revascularization but not CV or all-cause mortality. The bococizumab trials (stopped early) showed a reduction in nonfatal myocardial infarction and a numeric trend for fewer CV deaths. The net clinical benefit of the class also appears favorable, without major safety signals regarding neurocognition or an increased risk of diabetes. An outstanding question is whether this drug class primarily reduces nonfatal ischemic events without any effect on mortality or whether the lack of a mortality benefit in a single trial was just a play of chance. The ongoing alirocumab trial should clarify our understanding of the overall CV benefit and risks of reducing LDL-C to very low levels with PCSK9 inhibition. Future trials may also help to determine whether the marked lowering of Lp(a) by PCSK9 inhibition is a clinically significant benefit, as published trials thus far have not been designed to answer this question.

DISCLOSURE STATEMENT

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