

Safety and Tolerability of PCSK9 Inhibitors: Current Insights

This article was published in the following Dove Press journal:
Clinical Pharmacology: Advances and Applications

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Abstract: The current era of preventive cardiology continues to emphasize on low-density lipoprotein cholesterol (LDL-C) reduction to alleviate the burden of atherosclerotic cardiovascular disease (ASCVD). In this regard, the pharmacological inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) enzyme via monoclonal antibodies has emerged as a novel lipid-lowering therapy, leading to a marked reduction in circulating LDL-C levels and subsequent improvement of cardiovascular outcomes. As these agents are increasingly used in current clinical practice, mounting scientific and clinical evidence supports that PCSK9 inhibitors offer an excellent safety and tolerability profile with a low incidence of adverse events. Notably, the most frequently reported side effects are injection-site reactions. In contrast to statins, PCSK9 inhibitors do not appear to exert a detrimental effect on glycemic control or to increase the incidence of new-onset diabetes mellitus. Accumulating evidence also indicates that PCSK9 inhibitors are a safe, well-tolerated and effective therapeutic strategy for patients with statin intolerance. On the other hand, as PCSK9 inhibitors reduce LDL-C to unprecedented low levels, a large body of current research has examined the effects of their long-term administration on neurocognition and on levels of vitamin E and other fat-soluble vitamins, providing encouraging results. This review aims to present and discuss the current clinical and scientific evidence pertaining to the safety and tolerability of PCSK9 inhibitors.

Keywords: hypercholesterolemia, cardiovascular disease, CVD, PCSK9 inhibitors, safety, tolerability

Introduction

Cardiovascular disease (CVD) has consistently been the leading cause of mortality worldwide, accounting for 17.8 million deaths in 2017.¹ Hypercholesterolemia represents a major risk factor for CVD. The major sites for cholesterol synthesis are in hepatocytes and enterocytes. The intestinal cholesterol pool size is influenced mostly by endogenous sources, as the diet contributes only 25–30% of cholesterol per day. The reaction that represents the key point of regulation in cholesterol synthesis is the reduction of HMG-CoA to mevalonate and is catalyzed by the enzyme HMG-CoA reductase, which is inhibited by statins. The LDL receptors (LDLR), located on the cell membranes of hepatocytes and other cells, are responsible for cholesterol uptake. Reverse cholesterol transport (RCT) is the major pathway for cholesterol removal and is an essential mechanism to maintain cellular cholesterol homeostasis. Cholesterol efflux from macrophages can occur through a unidirectional ATP-dependent pathway mediated by ATP-binding cassette transporter A1 (ABCA1) and/or ATP-binding cassette transporter G1 (ABCG1), as well

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as by scavenger receptor class B type 1 (SR-BI), in a bidirectional ATP-independent pathway. The efflux of cholesterol can also occur through a receptor-independent diffusion of cholesterol in a gradient dependent process, which contributes to 30% of total cholesterol efflux.²

It has been unequivocally proven that increased levels of low-density lipoprotein cholesterol (LDL-C) are a causative modifiable risk factor for developing CVD, as LDL-C plays an undeniably pivotal role in the pathogenesis and progression of the atherosclerotic process.³ The use of lipid-modifying therapies has elicited a substantial decrease in the occurrence of major adverse CV events, thus being a fundamental pillar in current preventive cardiology practice.⁴

The recent development of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which was driven by novel genetic and mechanistic insights, was a remarkable achievement that addressed several unmet needs in the management of hyperlipidemia. Regulation of PCSK9 expression is dependent upon genetic factors, as well as upon factors associated to a complex transcriptional system, mainly controlled by sterol regulatory element binding proteins. In addition, PCSK9 is further regulated by lipid-lowering drugs, particularly by statins, which increase PCSK9 secretion but decrease its stimulatory phosphorylated form.⁵ The physiological role of PCSK9 is the enhancement of the endosomal and lysosomal degradation of hepatic LDL-R, resulting in increased circulating LDL-C levels.⁶ Thus, the use of PCSK9 inhibitors, which are human monoclonal antibodies that target and inhibit the PCSK9 enzyme, leads to the upregulated recycling and expression of LDL-R at the cell surface and, ultimately, to more rapid clearance of LDL-C from the bloodstream. Indeed, many clinical studies have proven that PCSK9 inhibitors, either as a monotherapy or in combination with statins, produce a potent and robust reduction in circulating LDL-C values. Notably, a meta-analysis of 71 randomized, placebo-controlled clinical trials demonstrated that PCSK9 inhibitors provide a marked decrease of 50.7% in LDL-C serum concentrations, as compared to placebo.⁷ Thus, the use of PCSK9 inhibitors has been approved in both US and Europe for patients with clinical ASCVD or FH who require further LDL-C-lowering in combination with other lipid-lowering treatments, although eligibility for PCSK9 inhibitor treatment differs based on the 2018 American College of Cardiology (ACC)/American Heart Association (AHA) and 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) recommendations. More

specifically, the 2019 ESC/EAS guidelines rendered 51% of all post-acute coronary syndrome (ACS) patients potentially eligible for PCSK9 inhibitor treatment, as compared to a 14% eligibility rate based on the 2018 ACC/AHA guidelines.⁸ On the other hand, apart from their beneficial effect in LDL-C lowering, PCSK9 inhibitors represent also an emerging therapeutic strategy for the treatment of hyperlipoproteinemia (a).⁹ In addition, aside from plain lipid-lowering, PCSK9 inhibition may also exert additional beneficial effects. More specifically, there are data indicating that reduced PCSK9 function increases LDLR-mediated pathogen lipid clearance and thus reduces the inflammatory response and improves outcomes in sepsis in both mice and humans.^{10,11}

Despite a dramatic reduction in LDL-C, PCSK9 inhibitors, in contrast to statins and the recently approved LDL-C-lowering agent, bempedoic acid, do not reduce high-sensitivity C-reactive protein (hs-CRP), a major biomarker of inflammation and associated risk in CVD.^{12,13} This may fuel skepticism regarding the effects of PCSK9 inhibitor therapy on cardiovascular (CV) outcomes. However, long-term outcome studies have unequivocally demonstrated that the LDL-C lowering effect of PCSK9 inhibitors also translates into substantial clinical benefit with significant improvement in CV outcomes.^{14,15} Notably, the higher risk patients, such as those with a more recent coronary event, those with higher baseline LDL-C levels, those with diabetes mellitus (DM) and prior revascularization, as well as those with ASCVD and peripheral arterial disease, appear to benefit the most.¹⁶ Given the above, PCSK9 inhibitors have ushered in the current era of lipid-lowering therapy, emerging as a valuable therapeutic approach for the optimal management of hyperlipidemia.¹⁷

Adding to their effectiveness in LDL-C lowering, PCSK9 inhibitors also possess a favorable safety and tolerability profile with a low incidence of adverse events and high therapeutic compliance among patients in clinical trials, in which the cost of therapy is not an impediment. Notably, the most frequently reported side effects are mild injection-site reactions. Moreover, PCSK9 inhibitors have been thoroughly assessed in patients with DM and statin intolerance, and they do not appear to exert a detrimental effect on glucose homeostasis or cause muscle-related symptoms. Notwithstanding, mainly due to the long-term use and the unprecedented low levels of LDL-C achieved by PCSK9 inhibition, concerns regarding potential adverse effects on neurocognition and fat-soluble vitamin (especially vitamin E) levels associated with the use of PCSK9

inhibitors have been raised. However, clinical trials have provided considerable evidence that no such association exists. This review aims to present and discuss the current clinical and scientific evidence pertaining to the safety and tolerability of PCSK9 inhibitors.

Adverse Events of PCSK9 Inhibitors

Many genetic and clinical studies have provided mounting evidence that the causal effect of LDL-C on the risk of CV disease is determined by both the absolute circulating levels and the cumulative duration of exposure of the vasculature to LDL-C.³ Therefore, as prompt initiation and long-term continuation of lipid-modifying therapies are supported nowadays, long-term safety and tolerability of these interventions are of utmost importance to determine therapeutic compliance, which would be a critical factor for the successful prevention of CVD and its associated mortality.¹⁸ As alluded earlier, accumulating evidence suggests that PCSK9 inhibitors have a favorable safety and tolerability profile. Common side effects of PCSK9 inhibitors are generally mild and include nasopharyngitis, injection-site reactions, and upper respiratory tract infections.¹⁷

Several clinical trials have evaluated the safety profile of PCSK9 inhibitors up to date. In the ODYSSEY LONG TERM trial, which studied 2341 patients on maximum tolerated statin therapy over a follow-up period of 78 weeks, adverse events that occurred more frequently with alirocumab, as compared with placebo, included injection-site reactions, myalgia, neurocognitive events, and ophthalmologic events. In addition, more patients in the alirocumab group, as compared with placebo, had vitamin E or vitamin K levels below the lower limit of the normal range; however, no clinically meaningful changes were demonstrated.¹⁹ Furthermore, in the OSLER-1 and OSLER-2 studies, which consisted of 4465 patients in total, the incidence of adverse events was in general similar in the evolocumab and the standard-therapy groups during 11.1 months of follow-up, although adverse neurocognitive events were reported more frequently in patients receiving evolocumab. Notably, such events were rare (<1% of patients) and were not correlated with the LDL-C levels during treatment.²⁰ Unsurprisingly, the reported increased rate of neurocognitive events associated with PCSK9 inhibitor treatment had fueled skepticism regarding the safety profile of PCSK9 inhibition.

Fortunately, subsequent studies did not confirm the above findings. The FOURIER and ODYSSEY OUTCOMES

clinical trials demonstrated that there was no significant difference in the incidence of adverse events, including neurocognitive events and new-onset diabetes mellitus, between patients receiving a PCSK9 inhibitor versus placebo. Notably, the incidence of injection-site reactions was more frequent in patients receiving PCSK9 inhibitors; however, this finding did not raise any concern, as the large majority of these reactions were mild.^{14,15} On the other hand, a prespecified secondary analysis of the FOURIER trial provided insights into the effect of extremely low LDL-C concentrations induced by PCSK9 inhibition, demonstrating that neither serious adverse events nor adverse events leading to drug discontinuation occurred more frequently in patients with plasma LDL-C values <15 mg/dl. This marked reduction in circulating LDL-C levels actually led to further improvement of CV outcomes, thus indicating that the approach of “the lower, the better” regarding circulating LDL-C levels may be feasible and convincing.²¹

Several subsequent studies provided similar results and a meta-analysis of 32 randomized, placebo-controlled clinical trials, including 57,090 patients in total, demonstrated that anti-PCSK9 monoclonal antibodies were in general safe, but for the increased risk of injection site reactions [Relative Risk (RR): 1.54; $P < 0.001$].²² Furthermore, in the OSLER-1 study, PCSK9 inhibitor therapy demonstrated durable efficacy and a consistent safety profile during exposure of up to 5 years. Adverse events did not increase over time and were comparable to those of the standard-therapy group.²³ Thus, there is optimism that the long-term administration of PCSK9 inhibitors is safe, tolerable, and efficacious, although further clinical studies are warranted to corroborate these findings.

Finally, another issue that may raise concerns with the use of monoclonal antibodies is their immunogenicity, ie, an immune response that leads to the production of anti-drug antibodies and neutralizing antibodies, which could impact on the safety and efficacy of the drugs. However, very low rates of immunogenicity were observed in clinical trials of evolocumab and alirocumab (the two approved PCSK9 inhibitors).^{20,24} In a study, which analyzed data from 10 trials involving 4747 patients, 5.1% of patients being treated with alirocumab developed anti-drug antibodies. However, even in those patients, the LDL-C-lowering effect of alirocumab was not adversely affected.^{24,25}

Below, we will address more specifically the effects of PCSK9 inhibitors on the risk of DM, on the incidence of myalgias, especially in statin-intolerant patients, on

neurocognition, as well as on serum soluble vitamin (especially vitamin E) levels. In addition, we will briefly discuss the cost-effectiveness of PCSK9 inhibitor therapy.

PCSK9 Inhibitors and Diabetes Mellitus

Diabetes mellitus (DM) is a chronic, multisystem metabolic disorder that constitutes a growing public health problem throughout the world. DM is a well-established CV risk factor that leads to accelerated atherosclerosis, microvascular and macrovascular disease. As dyslipidemia is very common in patients with DM, with a prevalence of 72%-85%, individuals with DM constitute an important group of patients in need of lipid-modifying therapy.²⁶ Although statin therapy remains the cornerstone of dyslipidemia management in current clinical practice, overwhelming evidence suggests that statins adversely affect glycemic control and increase the risk of new-onset DM by 9% to 44% in different studies.²⁷ Thus, after the development of PCSK9 inhibitors, a critical question that emerged was whether the use of this new class of lipid lowering agents could be safe, tolerable and beneficial for patients with DM.

A large body of recent research investigated the effect of several alleles at the PCSK9 locus on the incidence of DM. In a meta-analysis of genetic association studies, for certain PCSK9 genetic variants there was a 19% increase in the incidence of type 2 DM per 1 mmol/L (38.67 mg/dl) genetically predicted reduction in LDL-C ($P=0.03$).²⁸ Furthermore, in a mendelian randomization analysis, after adjustment for a standard decrement of 10 mg/dl in the LDL-C level, PCSK9 variants were associated with an 11.2% increase in the risk of DM.²⁹ In addition, a large-scale mendelian randomization study demonstrated that certain genetic PCSK9 variants, scaled to 1 mmol/L lower LDL-C, were associated with a 29% increase in the risk of type 2 DM. Moreover, these specific PCSK9 variants were associated with adverse metabolic consequences, including increased fasting glucose, bodyweight, and waist-to-hip ratio.³⁰ Undoubtedly, these genetic studies have fueled skepticism that the long-term exposure to decreased PCSK9 and LDL-C levels, induced either by genetic variations or pharmacotherapy, may lead to impaired glucose homeostasis and DM. On the other hand, in an interesting recent study, it was shown that depression was associated also with the homeostatic model assessment index of

insulin resistance (HOMA-IR), 11% of this effect operating indirectly via PCSK9.³¹

Based on the above, several studies assessed the effects of PCSK9 inhibitors on the incidence of DM. A prespecified analysis of the FOURIER trial demonstrated that the risk of new-onset DM in patients without DM or prediabetes at baseline was not increased with evolocumab treatment during 2.2 years of follow-up. Furthermore, the levels of glycated hemoglobin (HbA1c) and fasting plasma glucose (FPG) were not significantly different between evolocumab and placebo groups in patients with DM, prediabetes, or normoglycemia. Importantly, PCSK9 inhibition with evolocumab significantly reduced CV risk in patients with and without DM.^{32,33} Subsequent studies also corroborated the results obtained from the FOURIER analysis. The OSLER-1 extension study, having a longer follow-up period, documented that the annualized incidence of new-onset DM was not increased by evolocumab during 4 years of treatment. More specifically, in the OSLER-1 extension study, the annualized incidence of new-onset DM was 4% in the standard of care (SOC) treatment alone group versus 2.8% in the evolocumab plus SOC treatment group after adjustment for the duration of evolocumab exposure.^{33,34} Moreover, a post-hoc analysis of the ODYSSEY LONG TERM trial, comprising 812 individuals with type 2 DM, reported that FPG and HbA1c levels remained constant over 78 weeks with alirocumab treatment, regardless of the presence or absence of mixed dyslipidemia.³⁵ In addition, the results of a large-scale meta-analysis of 38 randomized controlled trials were also in line with that of the aforementioned studies, as it was shown that treatment with PCSK9 inhibitors was effective, in terms of LDL-C lowering and reduction of adverse cardiovascular events, in patients with and without DM, while the risk of incident DM was not increased by PCSK9 inhibitor therapy.³⁶

Given the above, sufficient evidence indicates that PCSK9 inhibitors achieve substantial CV benefit without adversely affecting glucose metabolism or increasing the incidence of new-onset DM. Notwithstanding, further clinical trials with a longer follow-up period may be needed to definitely confirm these findings.

PCSK9 Inhibitors in Patients with Statin Intolerance/Myalgias

Over the past few decades, the mainstay of lipid-lowering treatment has been statin therapy, significantly decreasing

the incidence of major adverse CV events in both primary and secondary prevention.³⁷ However, intolerance to statins, mostly due to muscle-related symptoms and weakness, may occur in some patients. This constitutes an essential barrier to maintaining long-term medication adherence, which subsequently leads to inadequate LDL-C reduction and increased mortality.^{38,39} In this regard, two large-scale retrospective studies provided consistent results, demonstrating that the adherence rates to statin therapy were very low, as 53% of patients discontinued their therapy.^{40,41}

In view of the above, and as PCSK9 inhibitors represent a novel addition to the lipid-lowering armamentarium, clinical trials have sought to determine whether PCSK9 inhibitors can cause myalgia or myopathy, which would potentially prevent their administration in statin-intolerant patients. The DESCARTES study, a randomized, placebo-controlled, Phase 3 trial, which was conducted to evaluate the safety and efficacy of 52 weeks of treatment with evolocumab in 901 hyperlipidemic patients, provided encouraging results, as elevation of creatine kinase (CK) levels to more than five times the upper limit of the normal range or myalgia occurred only in 1.2% and 4% of evolocumab-treated patients, respectively. Furthermore, the occurrence of these adverse events was similar between patients receiving evolocumab or placebo.⁴² A subsequent meta-analysis of 35 randomized controlled trials, consisting of 45,539 patients in total, confirmed the above findings, as it demonstrated that compared with no treatment with a PCSK9 inhibitor, treatment with a PCSK9 inhibitor was associated with a trend of fewer increases in CK [Odds Ratio (OR): 0.84; $P=0.06$] and was not associated with a statistically significant change in the rates of myalgia (OR: 0.95; $P=0.65$).⁴³

In addition, in ODYSSEY ALTERNATIVE, a randomized, double-blind, double-dummy, active-controlled, parallel-group study, which compared alirocumab with ezetimibe in 314 patients at moderate to high CV risk with statin intolerance, and included by protocol a statin rechallenge arm, it was shown that musculoskeletal adverse events were less frequent with alirocumab vs atorvastatin [hazard ratio (HR): 0.61; $P=0.042$]. Importantly, alirocumab decreased mean LDL-C by 45.0% vs 14.6% with ezetimibe.⁴⁴

In the GAUSS-3 study, which included patients with statin intolerance due to muscle-related side effects, treatment with evolocumab compared with ezetimibe led to a significantly greater lowering of LDL-C levels after 24 weeks (52.8% vs 16.7%; $P<0.001$). Active study drug was discontinued owing

to muscle symptoms in 5 of 73 ezetimibe-treated patients (6.8%) and only 1 of 145 evolocumab-treated patients (0.7%).⁴⁵ These findings were corroborated by the results of a subset analysis of the OSLER open-label extension studies, which showed that evolocumab plus SOC therapy was consistently safe, tolerable, and efficacious for up to 2 years in statin-intolerant patients.⁴⁶

Indeed, statin-intolerance currently represents an essential reason for initiating treatment with PCSK9 inhibitors, as, according to a recent study, physician-reported reasons for switching from statins to PCSK9 inhibitor therapy included myalgia in 28.6% of cases and myopathy in 11.1% of cases.⁴⁷

PCSK9 Inhibitors and Neurocognitive Events

The brain is the most cholesterol-rich organ in the body, composing almost 25% of the body's total cholesterol; however, its cholesterol synthesis and regulation is isolated from peripheral tissues. Neither cholesterol nor PCSK9 can cross the blood-brain barrier under normal conditions.⁴⁸ PCSK9-inhibitors cannot also cross the blood-brain barrier in humans.⁴⁹ Notwithstanding, as mentioned before, some earlier studies had reported a somewhat increased rate of adverse neurocognitive events associated with the use of PCSK9 inhibitors, as compared with placebo.^{19,20} However, subsequent studies did not confirm the above findings, as the FOURIER and ODYSSEY OUTCOMES clinical trials demonstrated that there was no significant difference in the rate of adverse neurocognitive events between patients receiving a PCSK9 inhibitor versus placebo.^{14,15} A potential explanation for this discrepancy may be the lack of standardized cognitive testing and reliance on patients' self-reporting of what constituted as a neurocognitive deficit in the earlier trials. This may have led to a reporting bias contributing to the increase in neurocognitive deficits noted in the earlier studies and especially in the OSLER studies which were an open-label trial.⁵⁰

Notwithstanding, in order to better clarify this issue, a randomized, double-blind, placebo-controlled, multicenter study (EBBINGHAUS study) was conducted, which involved a subgroup of patients from the FOURIER trial. The EBBINGHAUS study prospectively assessed the cognitive function in 1204 patients using the Cambridge Neuropsychological Test Automated Battery. The patients were followed for a median of 19 months. The mean

($\pm$ SD) change from baseline over time in the raw score for the spatial working memory strategy index of executive function (primary end point) was -0.21 ± 2.62 in the evolocumab group and -0.29 ± 2.81 in the placebo group ($P < 0.001$ for noninferiority; $P = 0.85$ for superiority). Furthermore, there were no significant differences between groups in the secondary end points of scores for working memory, episodic memory, or psychomotor speed. Importantly, in an exploratory analysis, there were no associations between LDL-C levels and cognitive changes. Thus, in this randomized trial, which involved patients who received either evolocumab or placebo in addition to statin treatment, there were no significant differences observed between groups in cognitive function over a median of 19 months.⁵¹

The findings of the EBBINGHAUS study were corroborated by the results of two more recent meta-analyses, which demonstrated that there was no difference in the risk of neurocognitive deficits between PCSK9 inhibitors and control groups.^{50,52} In addition, no association was found between neurocognitive treatment-emergent adverse events and LDL-C < 25 mg/dL.⁵⁰

Furthermore, in a very recent study, which evaluated patient-reported cognition in the entire FOURIER trial using a self-survey, it was shown that the addition of evolocumab to maximally tolerated statin therapy had no impact on patient-reported cognition after an average of 2.2 years of treatment, even among patients who achieved LDL-C levels < 20 mg/dL.⁵³

Based on the above, it appears reasonable to conclude that PCSK9 inhibitor therapy does not cause any major harmful cognitive effects. However, it is unclear if this expectation can be extrapolated to periods of therapy of > 3 years or to patients older than 75 years of age, those at very high ASCVD risk, or those with histories of ischemic or hemorrhagic stroke, since in these subgroups of patients there are not enough data to form a definitive conclusion. For that reason, studies with longer follow-up periods and more diverse trial populations are needed.⁵⁴

Effect of PCSK9 Inhibitor Therapy on Vitamin E and Other Fat-Soluble Vitamins

Vitamin E is an essential fat-soluble micronutrient that possesses several beneficial biological activities, mostly due to its potent antioxidant properties. Vitamin E deficiency, although rare in humans, can originate from

a broad spectrum of diseases and its primary clinical features include neuromuscular disorders, retinopathy, impairment of the immune response, and anemia.⁵⁵ Vitamin E is transported in plasma almost exclusively by lipoproteins and preferentially apolipoprotein B (ApoB)-containing lipoproteins, including LDL.⁵⁶ In this regard, abetalipoproteinemia and familial hypobetalipoproteinemia, which are genetic diseases characterized by absent or extremely low circulating LDL-C, triglycerides, and ApoB-containing lipoproteins, cause severe deficiency of fat-soluble vitamins, including vitamin E.⁵⁷ The elucidation of the underlying molecular mechanisms involved in these rare genetic diseases has established the robust association between vitamin E transport and LDL-C metabolism. Thus, the above evidence gave rise to a theoretical concern that markedly low LDL-C plasma concentrations induced by pharmacotherapy may cause vitamin E deficiency.⁵⁸ Therefore, clinical trials evaluated the effect of lipid-lowering therapeutic interventions, and particularly PCSK9 inhibitors that decrease LDL-C to previously unprecedented levels, on fat-soluble vitamins, especially vitamin E.

The aforementioned DESCARTES study, a phase 3, double-blind, randomized, placebo-controlled clinical trial, also assessed the safety of evolocumab with regard to vitamin E and steroid hormone levels. The investigators measured vitamin E plasma levels in 738 patients, whereas in a study subset of 80 patients vitamin E values were also measured in serum, LDL, high-density lipoprotein (HDL), and red blood cell membranes (RCM) at baseline and at 52 weeks of treatment. In patients treated with evolocumab, absolute vitamin E levels were reduced by 16% but increased by 19% after normalization for cholesterol levels. In the substudy, in patients treated with evolocumab, serum and LDL vitamin E levels were reduced by 26% and 61%, respectively, while the HDL vitamin E level increased by 31%. These changes reflected the favorable lipid changes induced by the evolocumab treatment. Serum and lipoprotein vitamin E levels did not change significantly after normalization for cholesterol. In addition, vitamin E in RCM remained unchanged from baseline to week 52 (both absolute and normalized). Unsurprisingly, no significant change in vitamin E levels was observed among placebo-treated patients. Moreover, no evidence of impairment of steroid hormone synthesis was found. Thus, in DESCARTES study, it was shown that the marked LDL-C lowering observed in evolocumab-treated patients led to a reduction of absolute serum and

LDL vitamin E levels but increased vitamin E levels after normalization for cholesterol. Most importantly, treatment with evolocumab did not alter tissue vitamin E levels, as assessed by RCM vitamin E. No evidence of impairment of adrenal or gonadal steroid hormone synthesis was found, even in patients with extremely low levels of LDL-C (<15 mg/dl).⁵⁶

In the ODYSSEY LONG TERM trial, as mentioned above, more patients in the alirocumab group, as compared with placebo, had vitamin E or vitamin K levels below the lower limit of the normal range; however, no clinically meaningful changes were demonstrated. Furthermore, when normalized for LDL-C levels, no meaningful changes in vitamin E were observed. In addition, no clinically meaningful effect was observed with respect to changes in levels of other fat-soluble vitamins (vitamin A and vitamin D) or cortisol.¹⁹

In a small trial of 11 Japanese patients with heterozygous familial hypercholesterolemia (HeFH) who were switched from biweekly LDL-C apheresis to biweekly subcutaneous injection therapy with evolocumab, serum vitamin E levels were decreased by 20% after 4 weeks of treatment. However, the mean vitamin E levels remained within the normal range and no subjective or objective side effects were observed.⁵⁹

Furthermore, a very recent prespecified analysis of the BERNSON clinical trial (a double-blind, randomized, placebo-controlled, multicenter study, which evaluated the safety and efficacy of evolocumab in combination with statin therapy in diabetic subjects with hyperlipidemia or mixed dyslipidemia) assessed the effect of 12 weeks of treatment with evolocumab on vitamin E and steroid hormones in 981 patients with type 2 diabetes mellitus and dyslipidemia. The results of this study were consistent with those obtained from the DESCARTES study. Although absolute vitamin E serum levels were reduced by 23% in patients treated with evolocumab, vitamin E concentrations normalized for plasma lipid concentrations (LDL-C, ApoB, and non-HDL-C) did not decrease.⁶⁰

Finally, in a 24-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of evolocumab in pediatric patients with HeFH (HAUSER-RCT), evolocumab reduced LDL-C levels by 44.5%. The incidence of adverse events that occurred during the treatment period was similar in the evolocumab group and the placebo group. Furthermore, levels of steroid hormones, fat-soluble vitamins (vitamins A, D, E, and K), glucose, and HbA1c were similar in the two groups at week 24.⁶¹

Thus, the above evidence indicates that therapeutic PCSK9 inhibition does not seem to cause any clinically meaningful adverse effects with respect to changes in levels of fat-soluble vitamins. In addition, treatment with PCSK9 inhibitors does not adversely affect normalized and tissue vitamin E levels, nor does it affect steroid hormone synthesis.

A summary of the trials pertaining to the safety and tolerability of PCSK9 inhibitors is shown in [Table 1](#).

Cost-Effectiveness of PCSK9 Inhibitor Therapy

PCSK9 inhibitors offer simple, attractive, and convenient dosing regimens, requiring only biweekly or monthly subcutaneous administration, thus leading to enhanced therapeutic compliance and adherence to therapy. On the contrary, the high economic burden that limited cost-effectiveness posed an obstacle limiting the access to PCSK9 inhibitors in clinical practice. The cost of PCSK9 inhibitors was \$14,100 per annum in the US until October 2018, far exceeding the costs of other lipid-lowering interventions.⁶² At that price, use of PCSK9 inhibitors in patients with HeFH or ASCVD did not meet generally acceptable incremental cost-effectiveness thresholds and was estimated to increase US health care costs substantially.⁶³ An analysis of the collected data from the OSLER and ODYSSEY LONG TERM clinical trials demonstrated the overwhelming financial implications of the administration of PCSK9 inhibitors for preventing either a major adverse CV event or a CV death.⁶⁴ Another study showed that the precedent price point yielded an incremental cost of \$348,807 per quality-adjusted life years (QALY), well beyond the highest acceptable willingness-to-pay threshold of \$100,000 per QALY.⁶⁵ The above findings emphasize the adverse cost-effectiveness of PCSK9 inhibitors, indicating that their use could not be affordable for either most health-care systems or private insurance payers.

Indeed, a study demonstrated that among 3472 patients requesting access to a PCSK9 inhibitor in 2016, only 36% of them were approved by payers. Notably, the incidence of acute CV events was higher in patients who were denied access, compared to the incidence in the overall relatively high risk patient population requesting PCSK9 inhibitors.⁶⁶ Moreover, a retrospective cohort study, enrolling 13,151 patients, reported that a large proportion of patients discontinued PCSK9 inhibitor therapy at 30 and

Table 1 Summary of Trials Pertaining to the Safety and Tolerability of PCSK9 Inhibitors

Trial	Design	Participants	Intervention	Results
FOURIER ¹⁴ and a prespecified analysis of FOURIER investigating the efficacy and safety of evolocumab by diabetes status and the effect of evolocumab on glycaemia and risk of developing diabetes ³²	Double-blind, placebo-controlled, multinational, phase 3 RCT	27,564 patients with ASCVD and LDL-C $\geq$ 70mg/dl or non-HDL-C $\geq$ 100mg/dl on statin therapy	Evolocumab for a median duration of 2.2 years vs placebo	Increased injection-site reactions with evolocumab vs placebo (2.1% vs 1.6%). Evolocumab did not increase new-onset DM, HbA1c or FPG.
ODYSSEY OUTCOMES ¹⁵	Double-blind, placebo-controlled, multicenter, phase 3 RCT	18,924 patients with an ACS 1–12 months earlier; LDL-C $\geq$ 70mg/dl, non-HDL-C $\geq$ 100mg/dl, or ApoB $\geq$ 80mg/dl, on high-intensity or maximum tolerated statin therapy	Alirocumab for a median duration of 2.8 years vs placebo	Increased injection-site reactions with alirocumab vs placebo (3.8% vs 2.1%).
ODYSSEY LONG TERM ¹⁹ and a post-hoc analysis of ODYSSEY LONG TERM evaluating the efficacy and safety of alirocumab in individuals with type 2 diabetes mellitus ³⁵	Double-blind, placebo-controlled, parallel-group, multinational, phase 3 RCT	2341 patients with high CVD risk, LDL-C $\geq$ 70mg/dl, on high-intensity or maximum tolerated statin therapy	Alirocumab for 78 weeks vs placebo	In the alirocumab group, there were increased injection-site reactions (5.9% vs 4.2%), myalgia (5.4% vs 2.9%), neurocognitive events (1.2% vs 0.5%) and ophthalmologic events (2.9% vs 1.9%), higher drug-discontinuation rates (7.2% vs 5.8%). Mean FPG and HbA1c levels remained constant in patients with DM.
OSLER-I and OSLER-2 ²⁰	Open-label, phase 2 and phase 3 RCTs, respectively	4465 participants on SOC therapy	Evolocumab + SOC therapy vs SOC therapy alone for a median duration of 11.1 months	In the evolocumab group, there were increased neurocognitive events (0.9 vs 0.3%), 4.3% injection-site reactions, 2.4% drug-discontinuation rate.
OSLER-I Extension Study ³⁴	Open-label, phase 2 RCT	1324 participants on SOC therapy	Evolocumab + SOC therapy vs SOC therapy alone for up to 4 years	Evolocumab did not increase new-onset DM (2.8% vs 4%), neurocognitive events (0.4% vs 0%), or muscle-related events (4.7% vs 8.5%)
ODYSSEY ALTERNATIVE ⁴⁴	Double-blind, double-dummy, active-controlled, parallel-group, phase 3 RCT	314 patients at moderate or high CVD risk, with statin intolerance, confirmed by statin rechallenge arm	Alirocumab or ezetimibe or atorvastatin for 24 weeks	Decreased musculoskeletal events with alirocumab vs atorvastatin (HR:0.61; P=0.042)
GAUSS-3 ⁴⁵	Double-blind, multicenter, phase 3 RCT	218 patients with statin intolerance, confirmed by statin rechallenge procedure	Alirocumab or ezetimibe for 24 weeks	Decreased muscle symptoms (20.7% vs 28.8%) and drug-discontinuation rates (0.7% vs 6.8%) in the evolocumab group compared to the ezetimibe group.

(Continued)

Table 1 (Continued).

Trial	Design	Participants	Intervention	Results
EBBINGHAUS ⁵¹	Double-blind, placebo-controlled, multicenter, phase 3 RCT	1204 patients with ASCVD, LDL-C $\geq$ 70mg/dl or non-HDL-C $\geq$ 100mg/dl, on moderate-intensity or high-intensity statin therapy	Evolocumab vs placebo for a median of 19 months	No significant difference in cognitive function, including the spatial working memory strategy index of executive function, as well as working memory, episodic memory and psychomotor speed
DESCARTES ⁵⁶	Double-blind, placebo-controlled, multicenter, phase 3 RCT	818 patients with LDL-C $\geq$ 75mg/dl, fasting triglycerides $\leq$ 400mg/dl	Evolocumab for 52 weeks vs placebo	With evolocumab, vitamin E levels did not decrease after normalization for cholesterol, tissue vitamin E levels did not change, and steroid or gonadal hormone synthesis was not affected
Prespecified analysis of BERSON ⁶⁰	Double-blind, placebo-controlled, multicenter, phase 3 RCT	981 patients with DM and hyperlipidemia or mixed dyslipidemia, LDL-C $\geq$ 100 mg/dl, on statin therapy	Evolocumab for 12 weeks vs placebo	With evolocumab, vitamin E levels did not decrease after normalization for plasma lipid concentrations (LDL-C, ApoB, and non-HDL-C), and there was no change in steroid hormone or gonadotropin levels.

Abbreviations: RCT, randomized controlled trial; ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; DM, diabetes mellitus; HbA1c, glycated hemoglobin; FPG, fasting plasma glucose; ACS, acute coronary syndrome; ApoB, apolipoprotein B; CVD, cardiovascular disease; SOC, standard of care.

90 days, which are the time frames for which many health plans require recertification to continue access to PCSK9 inhibitors. Overall, 42.6% of patients discontinued their therapies during the follow-up period of 6 months.⁶⁷ Thus, it becomes evident that adherence to PCSK9 inhibitors is significantly lower in real-world settings than in clinical studies, in which the cost of therapy is not an impediment.

Ultimately, in October 2018 and February 2019, respectively, the main PCSK9 inhibitor manufacturing companies announced a 60% reduction in the cost of PCSK9 inhibitors, to \$5850 per annum, making these agents much easier to prescribe nowadays.

Conclusions and Future Directions

The development of PCSK9 inhibitors, which are monoclonal antibodies directed against PCSK9, led to a significant enhancement of the lipid-lowering armamentarium, as PCSK9 inhibitors result in a consistent and robust reduction in LDL-C serum concentrations, substantially improving CV outcomes. The scientific and clinical experience with PCSK9 inhibitors suggests that they are a safe and well-tolerated therapeutic option with no

evidence of severe medication-related adverse events. PCSK9 inhibitors have also proven to be safe and effective in patients with DM or statin intolerance.

However, there are still some aspects of the treatment with PCSK9 inhibitors that remain to be explored. The effects of PCSK9 inhibitors in patients with HIV, who are at increased risk for ASCVD and are prone to statin-related adverse events from drug-to-drug interactions with certain antiretroviral regimens, have not been clearly established. In the recent BEIJERINCK study, which sought to evaluate the efficacy and safety of evolocumab in dyslipidemic patients with HIV, evolocumab reduced LDL-C levels by 56.9% and also significantly decreased levels of non-HDL-C, ApoB, and lipoprotein(a) (all $p < 0.0001$). Evolocumab was well tolerated and the incidence of treatment-emergent adverse events was similar among evolocumab and placebo groups.⁶⁸ However, the study had a short duration of 24 weeks and thus the effect of evolocumab on cardiovascular outcomes could not be assessed.

Furthermore, the safety of the use of PCSK9 inhibitors in pregnancy has not been established as yet. Thus, PCSK9

inhibitors are not currently approved during pregnancy. To that effect, a multinational observational study to evaluate the safety of evolocumab in pregnant women with FH is ongoing [ClinicalTrials.gov Identifier: NCT02906124].⁶⁹ Given the fact that women with FH experience certain barriers to care, such as under-representation in research, under-appreciation of risk, and interrupted therapy during childbearing,⁷⁰ the results of this study may help to close the gaps in care that women experience.

Notwithstanding, when all the above are considered, it becomes apparent that PCSK9 inhibitors are generally a safe, well-tolerated, and effective therapeutic strategy with an established role in the current therapeutic management of hyperlipidemia. As our experience with PCSK9 inhibitors is rapidly increasing, subsequent trials are expected to shed further light on their long-term safety and tolerability. On the other hand, other potential therapeutic strategies targeting PCSK9 are in development, including inclisiran (a small interfering RNA [siRNA] molecule), other small molecule inhibitors that disrupt the processing of PCSK9, as well as adnectins, which block the binding of PCSK9 to the LDLR.^{71–73}

Disclosure

Dr. Kosmas and Dr. Guzman have served on the Dyslipidemia Speaker Bureau of Amgen, Inc. The authors report no other conflicts of interest in this work.

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