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REVIEW ARTICLE

PCSK9 inhibition as an emerging lipid lowering therapy: Unanswered questions

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Abstract Although statins have been used for the treatment of hypercholesterolemia for more than two decades, cardiovascular disease (CVD), which is related at least in part to high levels of low-density lipoprotein cholesterol (LDL-C), is the number one cause of death in Europe and the USA. Several studies have shown that the reduction in cardiovascular (CV) events is proportional to the absolute LDL-C lowering achieved with statins. In the quest for further reduction in LDL-C and CV events, new drugs that mainly support statin action have emerged. Since 2003, with the discovery of proprotein convertase subtilisin/kexin type 9 (PCSK9), which is a key factor in the LDL clearance pathway, new modalities, mainly in the form of monoclonal antibodies that block this protein (PCSK9 inhibitors), have reached phase III of clinical development with very promising efficacy and safety data. With a mean further reduction of LDL-C levels of ~60% beyond that achieved with statins, the PCSK9 inhibitors set the bar even lower in terms of LDL-C levels. This review manuscript addresses important questions about the efficacy, safety and clinical use of PCSK9 inhibitors to evaluate the role of these agents in reducing CV risk.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death in Europe and the USA.[1,2] Over the past few years, studies have shown a very strong correlation between low-density lipoprotein cholesterol (LDL-C) levels and the development of CVD, mainly due to the key role of LDL-C in the atherosclerotic process.[3,4] The treatment of hypercholesterolemia has been primarily based on statin use. Indeed, statins have successfully served their purpose as a very effective lipid lowering medication class for 25 years since their introduction. However, a significant number of very high risk patients fail to achieve the LDL-C targets despite statin treatment necessitating the development of new agents for additional LDL-C lowering.[5]

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Following the discovery of the LDL receptor (LDLR) by Goldstein and Brown,[6] a new part of the puzzle of LDL clearance and homeostasis was elucidated by Abifadel and her coworkers in 2003.[7] The discovery of proprotein convertase subtilisin/kexin type 9 (PCSK9) by this group not only identified a new important and unknown element of the LDL clearance mechanism but also explained the limitations of statin therapy. PCSK9 is the last identified member of the proprotein convertase family. It is produced mainly in hepatocytes, and after an auto-processing cleavage reaction, it is secreted in the plasma where it binds with the LDLR. This does not interfere with the LDLR's ability to bind with LDL, but it incapacitates the LDLR's ability to return to the surface of the hepatocyte and bind to a new LDL molecule (Fig. 1). In particular, the direct interaction between PCSK9 and LDLR leads to the destruction of the receptors, a decrease in their concentration at the surface of the hepatocytes and a reduction in LDL clearance from the plasma. An important aspect of this process is that at the transcriptional level, PCSK9 production is upregulated by the activity of sterol regulatory element binding protein-2 (SREBP-2). SREBP-2 activity is increased in very low levels of intracellular cholesterol in the hepatocytes, and its main role is to promote the transcription of LDLR and PCSK9. As statins diminish intracellular cholesterol synthesis, they indirectly promote both LDLR and PCSK9 production through SREBP-2. This explains the statin treatment plateau that is achieved even at maximal doses.[8] Although PCSK9 was initially discovered through the analysis of familial hypercholesterolemia (FH) patients with a gain of function (GOF) mutation of the *PCSK9* gene, further studies have revealed naturally occurring loss of function (LOF) mutations. Homozygotes or compound heterozygotes for two LOF mutations in the *PCSK9* gene have minimal or even no PCSK9 production; their LDL-C levels are $\leq$20 mg/dL, and they are healthy.[9] These findings, in conjunction with the extracellular PCSK9 mode of action and the identification of its crystal structure and its active binding site with the LDLR,[10,11] have led to the development of pharmaceutical agents aimed at PCSK9 inhibition. To date, one of these modalities has been extensively tested and reached phase III of clinical development with great success. The use of monoclonal antibodies (mAbs) as a means of inhibiting PCSK9 action has shown consistent efficacy regarding the reduction of LDL-C levels (~60%) and a good safety profile with short-term administration.

To date, two of these fully human mAbs (evolocumab developed by Amgen and alirocumab developed by Sanofi/Regeneron) have completed most of their phase III programs, whereas a third PCSK9 inhibitor, bococizumab developed by PFIZER, is currently in phase III trials. On July 21st, 2015 and August 27th, 2015, the European Commission (EC) and the US Food and Drug Administration (FDA), respectively, announced the approval of evolocumab (Repatha) as an adjunct to diet and maximally tolerated statin therapy in adult patients with FH who failed to achieve LDL-C treatment goals, adult patients who were unable to tolerate statin therapy, and in homozygous FH adults and adolescents ($\geq$12 years old). On July 25th, 2015, the FDA, and one month later the EC, approved alirocumab (Praluent) as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous FH or CVD, who require additional lowering of LDL-C and in patients who cannot tolerate statins.

Recently, a reduction of cardiovascular (CV) events with the administration of PCSK9 inhibitors was reported. In the ODYSSEY LONG TERM trial, 2341 high-risk patients with LDL-C levels $\geq$70 mg/dL while on a maximally tolerated statin dose were randomized in a 2:1 ratio to 150 mg alirocumab every two weeks subcutaneously or placebo over a period of 78 weeks. Alirocumab reduced LDL-C levels by an additional 62%, and post hoc analysis showed that this was associated with a 48% relative risk reduction of CV events (1.7% in the alirocumab group vs. 3.3% in the placebo group, $p = 0.02$).[12]

In addition, the OSLER (Open-Label Study of Long-Term Evaluation against LDL Cholesterol)-1 and OSLER-2 trials reported similar results. The participants of the OSLER-1 trial had already completed one of the five phase 2 parent evolocumab studies, whereas the OSLER-2 participants had participated in at least one of the seven phase III evolocumab studies.[13] Patients (n = 4465) were randomly assigned in a 2:1 ratio to receive either subcutaneous evolocumab 140 mg every two weeks or 420 mg monthly in addition to their standard therapy or standard therapy alone. The use of evolocumab plus standard therapy reduced the levels of LDL-C by 61% compared to standard

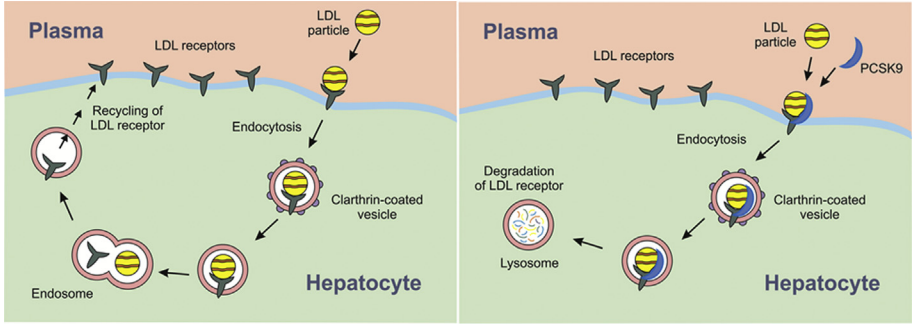

Figure 1 **Left panel**: LDL receptors carry LDL particles into hepatocytes via clathrin-coated vesicles that fuse with endosomes allowing the recycling of LDL receptors to the cell membrane up to 150 times. **Right panel**: Proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to LDL receptors, and the complex LDL receptor-PCSK9 is degraded in the lysosomes. Therefore, increased plasma concentrations of PCSK9 result in low levels of LDL receptors at the cell surface and increased levels of circulating LDL cholesterol.