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# Secondary Prevention of Coronary Heart Disease and PCSK9 Inhibitors

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**Editorial**

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## Introduction

Coronary heart disease (CHD) is the leading cause of death worldwide. According to the latest WHO data, more than 17 million people die from cardiovascular diseases (CVD) every year in the world [1]. For a long time, the main method of secondary prevention of hypercholesterolemia was a combination of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors and cholesterol absorption inhibitors, however, the target values of indicators were achieved in no more than 55% of patients, and therefore, for many years, the search for new types of drugs that reduce blood lipid levels continued. In 2003, the gene responsible for the amount of the PCSK9 protein was discovered, and in 2015. For the first time, drugs that are inhibitors of the PCSK9 protein were used in practical medicine, allowing achieving the target level of indicators in more than 90% of patients from the group of high and very high cardiovascular risk [2].

## Historical Background

For the first time, data on the PCSK9 protein were obtained in 2003 by Nabil G. Seidah. In 2007, the structure of the PCSK9 protein was shown for the first time, and in 2009, the results of the first studies were obtained proving a pronounced decrease in LDL-C levels in primates when the PCSK9 protein was inhibited by monoclonal antibodies. In 2015, PCSK9 inhibitors were approved for clinical use for the first time.

## Mechanism of Action of PCSK9 Inhibitors

Homeostasis of LDL-C in the body is as follows: LDL-C circulating in the blood is captured by hepatocytes with the help of LDL-C receptors (P-LDL). The resulting complex is delivered to the hepatocyte as part of the platinum vesicles, which merge with the endosomes, where the resulting complex is destroyed. After that, the P-LDL again returns to the surface of the hepatocyte, where new LDL-C is re-bound and delivered to the hepatocyte. It is proved that the protein convertase subtilisin / kexin type 9 regulates this process by binding to P-LDL, which is further destroyed in the lysosomes of the cell, which leads to an increase in the concentration of LDL cholesterol in the blood plasma [3].

## Summary of Major Clinical Trials of PCSK9 Inhibitors

Currently, two drugs that inhibit the PCSK9 protein are available-Alirocumab and Evolocumab. Evolocumab was studied in PROFICIO's extensive clinical trial program, which included more than 35,000 patients, and in 2015 became the first PCSK9 inhibitor approved for clinical use. The drug is available as a solution for subcutaneous administration at a dose of 140 mg / ml. Alirocumab was registered two years later in 2017 under the trade name Praluent. The drug is available as a solution for subcutaneous administration in doses of 75 and 150 mg / ml. The results of the main studies of these drugs will be discussed below.

The LAPLACE-2 study examined the efficacy of Evolocumab (140 mg, subcutaneously, every 2 weeks) when added to therapy with cholesterol synthesis inhibitors. Evolocumab has been shown to further reduce LDL-C by up to 75% compared to isolated statin therapy with intensive statin therapy. At the same time, 94% of patients treated with Evolocumab reached the target level of LDL-C [4]. In the GAUSS-2 study, Evolocumab (140 mg, subcutaneously, every 2 weeks) was used in patients with statin intolerance. It was shown that the use of Evolocumab led to a decrease in LDL cholesterol by 56%, and Ezetimibe-by 19% [5]. Evolocumab was also studied in patients with familial heterozygous hypercholesterolemia in the RUTHERFORD-2 study, where Evolocumab (140 mg, subcutaneously, every 2 weeks) and placebo were additionally prescribed against the background

of the maximum tolerated lipid-lowering therapy. The Evolocumab group was shown to have a 60% reduction in LDL cholesterol compared to placebo. In addition, 67% of the study participants treated with Evolocumab achieved the target value of LDL-C compared to 2% of patients treated with placebo [6]. The longest study of Evolocumab (more than 4 years) was called OSLER-1, the results of which were published in 2017. It was proved that after discontinuation of the drug, there is no "rebound effect", i.e., after 12 months, the level of LDL cholesterol reached the initial values and did not exceed them [7]. It was also shown that against the background of long-term use of Evolocumab, the level of LDL cholesterol was maintained at the same level: after 1 year, a decrease in LDL cholesterol by 61%, after 4 years by 57% from the initial indicators [8]. Thus, the clinical effectiveness of Evolocumab is maintained throughout the entire treatment period and does not depend on the individual characteristics of patients.

The effect of Alirocumab on the incidence of major cardiovascular events was studied in the ODYSSEY OUTCOMES study in patients after acute coronary syndrome. In addition, the objectives of the study were to study the safety and tolerability of Alirocumab, as well as its effect on the levels of various lipoprotein fractions and antibody production. The study involved 18,924 patients over 40 years of age with a history of ACS during the last year, but at least one month before selection. By the time of the appointment of Alirocumab, patients had been receiving intensive statin therapy for a long time and had not reached the target values of LDL cholesterol. Mandatory criterion for inclusion in the study was compliance with at least one of the following criteria: LDL cholesterol ≥ 70 mg/DL (≥ of 1.81 mmol/l), or apolipoprotein B ≥ 80 mg/DL (≥ 0.8 g/l), or Lprip cholesterol ≥ 100 mg/DL (≥ of 2.59 mmol/l). Throughout the study, the patients received Aliakum or placebo every two weeks. The initial dose of Alirocumab was 75 mg. In the future, depending on the values of LDL cholesterol, the dose of Alirocumab was increased to 150 mg or the patient was transferred to a placebo. The duration of the study was 2 years and 8 months. 44% of the patients were followed up for more than three years. 14.2% of patients in the Alirocumab group and 15.8% in the placebo group stopped treatment prematurely. 7.7% of patients were transferred from Alirocumab to placebo, the criterion for which was a decrease in LDL cholesterol of less than 0.3 mmol/l. In comparison with the placebo group, the level of LDL cholesterol decreased by 62.7% after four months of the study, by 61.0% after 12 months, and by 54.7% after 2 years. Major cardiovascular events were reported in 9.5% of patients in the Alirocumab group and 11.1% in the placebo group. Overall mortality was lower in the Alirocumab group - 3.5% and 4.1% placebo. The most pronounced hypolipidemic effect was most pronounced in patients with LDL-C levels > 2.6 mmol/l. In this group, the reduction in cardiovascular risk was 24% lower than in the placebo group, and the risk of death from any cause was 29% lower than in the placebo group [9].

## Conclusion

Coronary heart disease and its complications are currently the leading cause of death in the world. The cause of CHD is atherosclerosis of the coronary arteries, which has been fought for many years. Despite all the available variety of medications, hypercholesterolemia is still an urgent medical problem. The use of maximum tolerable doses of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors and Ezetemib does not allow achieving the LDL-C targets in all patients from the group of high and very high cardiovascular risk. In 2015, new drugs that are inhibitors of the PCSK9 protein were introduced into the practical world medicine, allowing to achieve the target level of indicators in more than 90% of patients. In addition, there are still a number of unresolved questions, the answers to which can be obtained from subsequent studies.

## References

1. Who (2013) A global brief on Hypertension. Silent killer, global public health crisis: © World Health Organization.

2. Seidah NG, Benjannet S, Wickham L, Marcinkiewicz J, Jasmin SB, et al. (2003) The secretory proprotein convertase neural apoptosis-regulated convertase 1 (NARC-1): liver regeneration and neuronal differentiation. Proc Natl Acad Sci USA 100: 928-933.

3. Brown MS, Goldstein JL (2009) Cholesterol feedback: from Schoenheimer's bottle to Scap's MELADL. J Lipid Res 50(suppl P): S15-S27.

4. Robinson JG, Nedergaard BS, Rogers WJ (2014) Effect of evolocumab or ezetimibe added to moderate- or highintensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. JAMA 311(18): 1870-1882.

5. Stroes E., Colquhoun D, Sullivan D, Civeira F, Rosenson RS, et al. (2014) Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab. J Am Coll Cardiol 63(23): 2541-2548.

6. Raal FJ, Stein EA, Dufour R, Turner T, Civeira F, et al. (2015) PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet 385(9965): 331-340.

7. Koren MJ, Giugliano RP, Raal FJ, Sullivan D, Bolognese M, et al. (2014) Efficacy and safety of longer-term administration of evolocumab (AMG 145) in patients with hypercholesterolemia: 52-week results from the Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER) randomized trial. Circulation 129(2): 234-243.

8. Koren MJ, Sabatine MS, Giugliano RP, Langslet G, Wiviott SD, et al. (2017) Long-term Low-Density Lipoprotein Cholesterol-Lowering Efficacy, Persistence, and Safety of Evolocumab in Treatment of Hypercholesterolemia: Results Up to 4 Years from the OpenLabel OSLER-1 Extension Study. JAMA Cardiol 2(6): 598-607.

9. Schwartz GG, Steg PG, Szarek M (2018) Alirocumab and cardiovascular outcomes after acute coronary syndrome. Engl J Med 379(22): 2097-2107.