# Lipid-Lowering Therapy and PCSK9 Inhibitors: The Function of PCSK9 inhibitors in Controlling High Cholesterol Level and Lowering the Possibility of Stroke

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**Abstract**

*Ischemic strokes account for the majority of stroke cases. A stroke happens when the blood supply to the brain is abruptly interrupted. The insufficient blood flow can lead to brain damage and a range of physical and cognitive impairments. High cholesterol in the body is a significant risk factor for stroke. Reducing high cholesterol levels through lifestyle changes and medications can help lower the risk of stroke. PCSK9 inhibitors belong to a group of drugs employed for managing elevated cholesterol levels, particularly low-density lipoprotein cholesterol (LDL-C). These medications function by focusing on a specific protein within the body, known as PCSK9, which is responsible to control LDL receptor levels. Through the inhibition of PCSK9, these medications can efficiently reduce LDL cholesterol levels in the bloodstream. This review study was conducted to describe or evaluate the function of PCSK9 inhibitors in controlling high cholesterol level and lowering the possibility of stroke.*

**Objectives:**

**Key words:** *Hyperlipidemia; High Cholesterol Level; Statins; Proprotein convertase subtilsin-kexin type 9, Stroke*

## INTRODUCTION:

The quantity of low-density lipoprotein (LDL) receptors on cell surfaces is regulated by a protein in the body called PCSK9.[(1)] They work by targeting a specific protein in the body, PCSK9, which plays a crucial role in regulating cholesterol levels in the bloodstream. PCSK9 inhibitors are medications designed to interfere with the action of PCSK9. Because these medications inhibit PCSK9, more LDL receptors are present on the surface of liver cells. This improves the elimination of LDL cholesterol from the blood, lowering LDL cholesterol levels and lowering the risk of cardiovascular events like heart attacks and strokes in people with high cholesterol. The removal of LDL-C from the circulation is accomplished by these receptors.[(2)] PCSK9 inhibitors work by interfering with this process, preventing PCSK9 from binding to LDL receptors and targeting them for degradation. High blood lipid levels brought on by an excessive intake of a high-cholesterol diet are the cause of hyperlipidemia. It's significant to note that up to 60% of reported patients in registries and clinical trials had high levels of blood lipids, particularly cholesterol.[(3)] Some of the common types and conditions within the spectrum of CVD include: CHD, stroke, heart failure, hypertension and arrhythmias [(4)] According to Leppälä et al. (1999), people with elevated cholesterol levels (>7.0 mmol/L) had a higher chance of having a stroke.[(5)] Hyperlipidemia, which is characterized by high levels of lipids (fats) in the blood, is a significant risk factor for the development of atherosclerosis, not only in extracranial (outside the head) arteries but also in the cervical (neck) and coronary (heart) arteries. This increased risk of atherosclerosis in multiple arterial beds can have serious consequences, particularly when it comes to the risk of stroke[(6).] CVD development is known to be influenced by hyperlipidemia [(7).] A class of drugs known as statins functions by blocking an enzyme that the liver uses to produce cholesterol. By reducing LDL-C levels, which are often referred to as "bad" cholesterol, statins can help lower the risk of atherosclerosis and CVD, including heart attacks and strokes. Statin therapy is typically suggested for individuals with CVD, such as heart attacks or strokes, as well as for those with specific risk factors for CVD, including high LDL-C levels, diabetes, or hypertension. This is supported by numerous double-blind placebo-controlled trials and a substantial body of research. [(8, 9).] Nevertheless, despite getting maximally tolerated therapy, some individuals taking statins still experience CVD events. PCSK9 inhibitors play a critical role in managing elevated cholesterol levels. They function by obstructing the activity of PCSK9, leading to an enhanced quantity of active LDL receptors on liver cells and facilitating the elimination of LDL-C from the bloodstream. Consequently, this leads to a substantial decrease in LDL-C levels and reduces the likelihood of cardiovascular events in individuals with high cholesterol. Nevertheless, these medications are typically prescribed for individuals who fail to reach their cholesterol targets with alternative treatments or for those with a heightened cardiovascular risk.

## FUNCTIONAL MECHANICS OF PCSK9:

The majority of PCSK9 is produced in hepatocytes; the intestines and kidneys are the other two locations.[10, 11] By fostering their metabolism and subsequent destruction, PCSK9 lowers the amount of LDLR in hepatocytes.[12]

Inhibiting PCSK9 can be a useful therapeutic strategy to lower LDL cholesterol and lower the risk of cardiovascular disease. When PCSK9 binds to LDLR, it triggers the degradation of LDLR, reducing its ability to clear LDL cholesterol from the blood, ultimately leading to higher LDL cholesterol levels. Dysregulation of this process can contribute to the development of CVD. In order to stop PCSK9 from attaching to LDL receptors on the hepatocytes, monoclonal antibodies that target PCSK9 attach to PCSK9 in the circulation. This interference results in more LDL receptors being available on the cell surface, which leads to enhanced clearance of blood LDL cholesterol. Lowering LDL cholesterol levels is an essential goal in managing the risk of heart disease and related cardiovascular events. PCSK9 has been demonstrated to function as both an exogenous factor that encourages LDLR internalisation from the hepatocellular surface as well as intracellularly (where it functions as a chaperone). Under normal conditions, endosomes endocytose the LDL/LDLR complex. Because of the endosome's acidic pH, the LDL receptor's extracellular domain changes structurally to take on a hairpin structure. This transformation aids in its recycling to the plasma membrane by reducing the LDL receptor's affinity for LDL. The LDLR is kept in an open conformation, which hinders recycling, and PCSK9 binding suppresses this change. The lysosomes are subsequently used to degrade the LDLR as shown in Figure 1.[13, 14] The bloodstream carries PCSK9 in its secretory form, which can be inactivated by proprotein convertase cleavage. The routine degradation of LDLR is supported by the release of the prodomain and catalytically inactive PCSK9. This implies that PCSK9 functions in a manner more akin to a chaperone protein rather than a conventional catalytic enzyme.[15, 16]

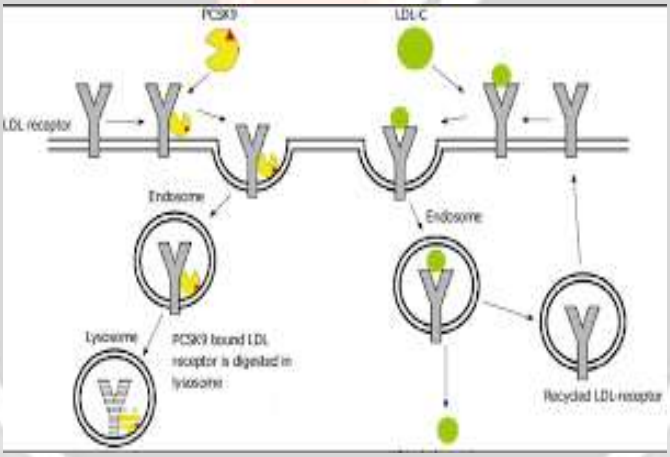


Figure 1: Mechanism and role of PCK9 in low-density lipoprotein-cholesterol metabolism.

## Lipids as vascular risk factor:

Lipids are important molecules in the body that play various roles, including energy storage, cell membrane structure, and the synthesis of hormones. However, elevated levels of certain lipids in the blood can be a significant vascular risk factor, contributing to the development of CVD.

The first three significant randomised trials that examined the effect of statin medication in lowering the incidence of cardiac events in patients with coronary artery disease and dyslipidemia identified the favourable effect of lowering cholesterol levels on the risk of stroke.[17-19] In the cholesterol and Recurrent Events (CARE) trial, the statin group's stroke incidence was 31% lower than that of the placebo group. According to the research conducted by Frank M. Sacks and colleagues [17], it was revealed that a significant number of individuals with coronary disease, despite having normal cholesterol levels, can still experience advantages from cholesterol-lowering medications. Over the course of the five-year median follow-up period in the Scandinavian Simvastatin Survival research (4S), research participants who were administered statin drugs saw a significant 35% drop in their LDL cholesterol levels. In a post-hoc analysis, individuals who were prescribed simvastatin experienced a 30% decrease in the relative risk (RR) of both fatal and nonfatal strokes when compared to those taking a placebo (p=0.024). [18] Furthermore, in another randomized study, the use of pravastatin reduced the risk of stroke by 19% in comparison to a control.[19]

In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, the investigation focused on the connection between the reduction in LDL-C induced by statin therapy and the prevention of secondary strokes.[20] In this study, 4,731 individuals who had recently suffered a stroke or a transient ischemic attack with an atherosclerotic cause were randomized to receive high dose atorvastatin versus a placebo. Following one month of randomization, the statin group exhibited an average LDL-C reduction of 53%, while the placebo group's LDL-C levels remained nearly unchanged ($p < 0.001$). During a median follow-up time of 4.9 years, 11.2% of patients in the atorvastatin group experienced a fatal or nonfatal stroke, with an adjusted hazard ratio (HR) of 0.84 and a 95% confidence interval (CI) ranging from 0.71 to 0.99, when compared to the placebo group. While there was an uptick in hemorrhagic strokes, this increase did not reach statistical significance.[20]

Investigations have also been done into the impact of combining a statin with a non-statin lipid-lowering drug to further lower LDL-C levels.

## The Improved Reduction of Outcomes:

The Vytorin Efficacy International Trial enrolled 18,144 patients who had experienced a recent acute coronary syndrome (ACS). They were randomised in to two groups to receive either simvastatin monotherapy or simvastatin with ezetimibe.[21] Initially, both groups had an average LDL-C level of 93.8 mg/dL. However, after one year of follow-up, the simvastatin-ezetimibe group exhibited a mean LDL-C of 53.2 mg/dL, while the monotherapy group had a mean LDL-C of 69.9 mg/dL, with a statistically significant difference ($p < 0.001$). Lower LDL-C levels were associated with a reduced risk of experiencing an ischemic stroke, as indicated by a hazard ratio (HR) of 0.79, with a 95% confidence interval (CI) ranging from 0.67 to 0.94.

**PCSK9 and the metabolism of lipids:** Lipoproteins play a crucial role in transporting lipids throughout the body, due to their insoluble nature, lipids must be transported via the bloodstream. Apolipoproteins and phospholipids make up the majority of the hydrophilic membrane that surrounds the hydrophobic core of lipoproteins, which is made of cholesteryl esters or triglycerides.[22] This unique structure of lipoproteins allows them to transport lipids in the bloodstream effectively. The hydrophilic membrane ensures that lipoproteins remain soluble in the aqueous environment of the blood, while the hydrophobic core carries the lipids. Different types of lipoproteins have variations in their composition, with varying amounts of triglycerides, cholesterol, phospholipids, and apolipoproteins, depending on their specific roles in lipid transport and metabolism in the body. LDL plays a significant role in atherogenesis and is a primary supply of cholesterol for peripheral tissues. Cholesterol is essential for many cellular functions, including the production of bile acids, steroid hormones, and plasma membranes.[23] Sterol regulatory element binding protein-2 (SREBP-2) responds to intracellular cholesterol levels to control the expression of LDLR on the cell membrane. It promotes the transcription of genes responsible for LDLR, subsequently enhancing the uptake of LDL-C, particularly as cellular cholesterol levels decrease.[24, 25] Additionally, SREBP-2 improves cholesterol production by promoting the expression of HMGCR, the rate-limiting enzyme in the synthesis of cholesterol.[26, 27] It is also present on the kidney and small intestine, the liver expresses PCSK9 protein most frequently. The complex invaginates inside an endosome as a result of mature PCSK9's competition with LDL and binding to the LDLR's epidermal growth factor [28] The acidic endosome environment dramatically increases PCSK9's affinity for LDLR.[29, 30] As a result, LDLR is unable to separate from the ligand and is lysosomally degraded rather than being recycled.[31] This results in the reduction of LDLR density on the surface of the cell which leads to an elevation in plasma LDL levels.

## Lipid metabolism and PCSK9 gene activity:

The PCSK9 gene are responsible for lipid metabolism. The primary role of the PCSK9 protein is to regulate the quantity of LDL receptors on the liver cells.

The PCSK9 gene is situated on chromosome 1, (1p32.3) which is known to be highly polymorphic, meaning it has a significant amount of genetic variation within the human population. Polymorphisms in the PCSK9 gene can lead to different functional variants of the PCSK9 protein, and these variants can have varying effects on cholesterol metabolism and, subsequently, cardiovascular health. Some individuals may carry genetic variants that result in the over activity of PCSK9, that causes high level of LDL cholesterol and cardiovascular diseases. On the other hand, some individuals may possess variations that lead to decreased PCSK9 activity, resulting in reduced LDL cholesterol levels and a lower susceptibility to cardiovascular diseases. Research has shown a significant decline in the risk of CHD in individuals with mutated PCSK9 gene. These genetic mutations are linked with low levels of LDL-C in the bloodstream.[32, 33]

**PCSK9 inhibitor usage recommendations for preventing stroke:**

The primary role of PCSK9 inhibitors was not specifically focused on preventing stroke, although there could be potential benefits related to stroke prevention due to their effects on reducing atherosclerosis and cardiovascular risk factors. Recommendations for PCSK9 inhibitor usage may vary depending on the specific guidelines and the patient's risk profile.

As per the present AHA/ASA guidelines, individuals below the age of 75 with clinical ASCVD should be prescribed either high-intensity statin treatment, characterized by a decrease in LDL-C levels exceeding 50%, or moderate-intensity statin therapy, which involves a reduction in LDL-C levels by 30% to 49%, in case side effects related to statin use become apparent.[34] The recommendations also take patients with clinical ASCVD who are at very high risk, have LDL-C levels below 70 mg/dL14, and are receiving maximally tolerable LDL-C lowering treatment into account when prescribing PCSK9 inhibitors. Likewise, even when employing the highest tolerated statin dosage, the 2018 AHA guidelines for blood cholesterol management recommend the incorporation of a nonstatin medication, such as a PCSK9 inhibitor, for individuals with a very high-risk of ASCVD, encompassing stroke, and LDL-C levels at or above 70 mg/dL or non-HDL-C levels at or above 100 mg/dL.[35]

The European Stroke Organization released a consensus statement in 2019, "PCSK9 inhibitors were authorized as an adjunctive therapy for individuals who do not reach their LDL-C target levels despite being treated with statins and ezetimibe".[36] According to the European Society of Cardiology and the European Atherosclerosis Society's 2019 guidelines for managing dyslipidemia, individuals with very high-risk circumstances for secondary prevention should strive for an LDL-C level below 55 mg/dL.[37] According to these recommendations, PCSK9 inhibitors may be used in very high risk individuals who fail to meet their LDL-C objectives while taking the highest dose of tolerable statins in conjunction with ezetimibe.

## Conclusions:

The discovery of PCSK9 and the subsequent development of PCSK9 inhibitors represent significant advancements in the field of lipid management and the treatment of hyperlipidemia. Its function in cholesterol metabolism marked a significant milestone decade ago. Researchers identified PCSK9 is a main player in regulating LDL cholesterol levels. It revolutionized the management of hyperlipidemia, offering new treatment options for individuals more likely to CVD. These medications have the potential to reduce LDL cholesterol to previously unattainable levels and minimize the risk of atherosclerotic events.

## References:

1. Ference BA, Cannon CP, Landmesser U, Lüscher TF, Catapano AL, Ray KK. Reduction of low density lipoprotein-cholesterol and cardiovascular events with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors and statins: an analysis of FOURIER, SPIRE, and the Cholesterol Treatment Trialists Collaboration. European heart journal. 2018;39(27):2540-5.
2. Bandyopadhyay D, Ashish K, Hajra A, Qureshi A, Ghosh RK. Cardiovascular outcomes of PCSK9 inhibitors: with special emphasis on its effect beyond LDL-cholesterol lowering. Journal of Lipids. 2018;2018.
3. ElAli A, Doeppner TR, Zechariah A, Hermann DM. Increased blood–brain barrier permeability and brain edema after focal cerebral ischemia induced by hyperlipidemia: role of lipid peroxidation and calpain-1/2, matrix metalloproteinase-2/9, and RhoA overactivation. Stroke. 2011;42(11):3238-44.
4. Karunathilake SP, Ganegoda GU. Secondary prevention of cardiovascular diseases and application of technology for early diagnosis. BioMed research international. 2018;2018.
5. Leppala JM, Virtamo J, Fogelholm R, Albanes D, Heinonen OP. Different risk factors for different stroke subtypes: association of blood pressure, cholesterol, and antioxidants. Stroke. 1999;30(12):2535-40.
6. Ayata C. Spreading depression and neurovascular coupling. Stroke. 2013;44(6_suppl_1):S87-S9.
7. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25_suppl_2):S1-S45.
8. Brugts J, Yetgin T, Hoeks S, Gotto A, Shepherd J, Westendorp R, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. Bmj. 2009;338.
9. Taylor F, Ward K, Moore TH, Burke M, Smith GD, Casas JP, et al. Statins for the primary prevention of cardiovascular disease. Cochrane database of systematic reviews. 2011(1).
10. Rashid S, Curtis DE, Garuti R, Anderson NN, Bashmakov Y, Ho Y, et al. Decreased plasma cholesterol and hypersensitivity to statins in mice lacking Pcsk9. Proceedings of the National Academy of Sciences. 2005;102(15):5374-9.

11. Zaid A, Roubtsova A, Essalmani R, Marcinkiewicz J, Chamberland A, Hamelin J, et al. Proprotein convertase subtilisin/kexin type 9 (PCSK9): hepatocyte-specific low-density lipoprotein receptor degradation and critical role in mouse liver regeneration. Hepatology. 2008;48(2):646-54.
12. Denis M, Marcinkiewicz J, Zaid A, Gauthier D, Poirier S, Lazure C, et al. Gene inactivation of proprotein convertase subtilisin/kexin type 9 reduces atherosclerosis in mice. Circulation. 2012;125(7):894-901.
13. Surdo PL, Bottomley MJ, Calzetta A, Settembre EC, Cirillo A, Pandit S, et al. Mechanistic implications for LDL receptor degradation from the PCSK9/LDLR structure at neutral pH. EMBO reports. 2011;12(12):1300-5.
14. Pessentheiner AR, Pelzmann HJ, Walenta E, Schweiger M, Groschner LN, Graier WF, et al. NAT8L (N-acetyltransferase 8-like) accelerates lipid turnover and increases energy expenditure in brown adipocytes. Journal of Biological Chemistry. 2013;288(50):36040-51.
15. Li J, Tumanut C, Gavigan J-A, Huang W-J, Hampton EN, Tumanut R, et al. Secreted PCSK9 promotes LDL receptor degradation independently of proteolytic activity. Biochemical Journal. 2007;406(2):203-7.
16. McNutt MC, Lagace TA, Horton JD. Catalytic activity is not required for secreted PCSK9 to reduce low density lipoprotein receptors in HepG2 cells. Journal of Biological Chemistry. 2007;282(29):20799-803.
17. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. New England Journal of Medicine. 1996;335(14):1001-9.
18. Group SSSS. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). The Lancet. 1994;344(8934):1383-9.
19. Group L-TIwPiIDS. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. New England Journal of Medicine. 1998;339(19):1349-57.
20. Investigators SPbARiCL. High-dose atorvastatin after stroke or transient ischemic attack. New England Journal of Medicine. 2006;355(6):549-59.
21. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. New England Journal of Medicine. 2015;372(25):2387-97.
22. Feingold KR. Lipid and lipoprotein metabolism. Endocrinology and Metabolism Clinics. 2022;51(3):437-58.
23. Goldstein JL, Brown MS. Regulation of low-density lipoprotein receptors: implications for pathogenesis and therapy of hypercholesterolemia and atherosclerosis. Circulation. 1987;76(3):504-7.
24. Go G-w, Mani A. Low-density lipoprotein receptor (LDLR) family orchestrates cholesterol homeostasis. The Yale journal of biology and medicine. 2012;85(1):19.
25. Bauer S, Wanninger J, Schmidhofer S, Weigert J, Neumeier M, Dorn C, et al. Sterol regulatory element-binding protein 2 (SREBP2) activation after excess triglyceride storage induces chemerin in hypertrophic adipocytes. Endocrinology. 2011;152(1):26-35.
26. Morton JD, Shimomura L. Sterol regulatory element-binding proteins: activators of cholesterol and fatty acid biosynthesis. Current opinion in lipidology. 1999;10(2):143-50.
27. Li Q, Zhang H, Zou J, Feng X, Feng D. Bisphenol A induces cholesterol biosynthesis in HepG2 cells via SREBP-2/HMGCR signaling pathway. The Journal of toxicological sciences. 2019;44(7):481-91.
28. Giunzioni I, Tavori H. New developments in atherosclerosis: clinical potential of PCSK9 inhibition. Vascular Health and Risk Management. 2015:493-501.
29. Fisher TS, Surdo PL, Pandit S, Mattu M, Santoro JC, Wisniewski D, et al. Effects of pH and low density lipoprotein (LDL) on PCSK9-dependent LDL receptor regulation. Journal of Biological Chemistry. 2007;282(28):20502-12.
30. Ben-Naim L, Khalaila I, Papo N. Modifying pH-sensitive PCSK9/LDLR interactions as a strategy to enhance hepatic cell uptake of low-density lipoprotein cholesterol (LDL-C). Protein Engineering, Design and Selection. 2022;35:gzab032.
31. Zhang D-W, Garuti R, Tang W-J, Cohen JC, Hobbs HH. Structural requirements for PCSK9-mediated degradation of the low-density lipoprotein receptor. Proceedings of the National Academy of Sciences. 2008;105(35):13045-50.
32. Cohen J, Pertsemlidis A, Kotowski IK, Graham R, Garcia CK, Hobbs HH. Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. Nature genetics. 2005;37(2):161-5.
33. Cohen JC, Boerwinkle E, Mosley Jr TH, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. New England Journal of Medicine. 2006;354(12):1264-72.
34. Goyal M, Ospel J. Challenges to stroke care 5 years after endovascular therapy became the standard. The Lancet Neurology. 2020;19(3):210-1.
35. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management

of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Journal of the American College of Cardiology. 2019;73(24):3168-209.
36. Ahmed N, Audebert H, Turc G, Cordonnier C, Christensen H, Sacco S, et al. Consensus statements and recommendations from the ESO-Karolinska stroke update conference, Stockholm 11–13 November 2018. European stroke journal. 2019;4(4):307-17.
37. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). European heart journal. 2020;41(1):111-88.