MEDS Clinical Medicine (2025)
Clausius Scientific Press, Canada

DOI: 10.23977/medsc.2025.060201
ISSN 2616-1907 Vol. 6 Num. 2

# *Multidimensional Modulation of PCSK9 Inhibitors in the Therapeutic Management of Ischemic Stroke*

**Xinyi Cui[1,a], Hai Lin[2,b,*]**

*[1]Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, China*
*[2]The Affiliated Hospital of Shaanxi University of Chinese Medicine, Xi'an, Shaanxi, China*
*[a]2531402872@qq.com, [b]Linhai626@163.com*
*[*]Corresponding author*

***Keyword:*** PCSK9 Inhibitors; Ischemic Stroke; Lipid Metabolism; Inflammation; Thrombosis; Plaque Stabilization

***Abstract:*** Proprotein convertase subtilisin/kexin type 9 (PCSK9), a key regulator of lipid metabolism, exacerbates ischemic stroke pathogenesis by promoting Low-Density Lipoprotein (LDL) receptor degradation, elevating Low-Density Lipoprotein Cholesterol (LDL-C) levels, and amplifying vascular inflammation and platelet activation. PCSK9 inhibitors counteract these effects through multifaceted mechanisms: reducing LDL-C, suppressing endothelial inflammation, inhibiting thrombus formation, and stabilizing atherosclerotic plaques. Clinical studies underscore their efficacy in lowering cardiovascular and ischemic stroke risks, with agents like Alirocumab and Evolocumab demonstrating robust plaque-modifying properties. While the efficacy of PCSK9 inhibitors, particularly when combined with statins, has been robustly validated across clinical studies, their safety profile reveals nuanced challenges. Adverse events such as muscle-related toxicity and new-onset diabetes demonstrate no statistically significant risks in most trials; however, neurocognitive implications remain contentious, with conflicting evidence requiring mechanistic clarification. Future research must bridge molecular insights with clinical translation, emphasizing the role of PCSK9 in neurovascular crosstalk and systemic inflammation. Advancing beyond lipid-centric strategies to holistic neurovascular network modulation could redefine therapeutic paradigms, necessitating interdisciplinary efforts to optimize precision therapies for ischemic stroke.

## 1. Introduction

Ischemic stroke (IS) refers to the ischemic necrosis or softening of localized brain tissue caused by ischemia and hypoxia in the brain, and the corresponding nervous system function defect. The pathological mechanism is closely related to atherothrombosis and lipid metabolism disorder. Proprotein convertase subtilisin/kexin type 9 (PCSK9) degrades Low-Density Lipoprotein Cholesterol (LDL-C) receptors (LDL-R) to elevate Low-Density Lipoprotein Cholesterol (LDL-C) levels. Simultaneously, it activates the nuclear factor Nuclear Factor kappa-B (NF-κB) inflammatory pathway and upregulates platelet Cluster of Differentiation 36 (CD36) molecule (thrombospondin receptor), establishing a vicious "lipid dysfunction-endothelial

damage-thrombosis" cycle that increases plaque vulnerability.Clinical studies demonstrate their ability to reduce LDL-C while remodeling plaque structure, inhibiting endothelial apoptosis, and modulating macrophage polarization to mitigate neuroinflammation, is shown in Figure 1. However, critical knowledge gaps persist regarding their acute-phase neuroprotective effects on blood-brain barrier repair, potential bleeding risks from platelet overactivation, and the absence of biomarkers for individualized therapy. This study aims to systematically analyze the pleiotropic mechanism of PCSK9 inhibitors in ischemic stroke and provide a theoretical basis for promoting stroke prevention and treatment.

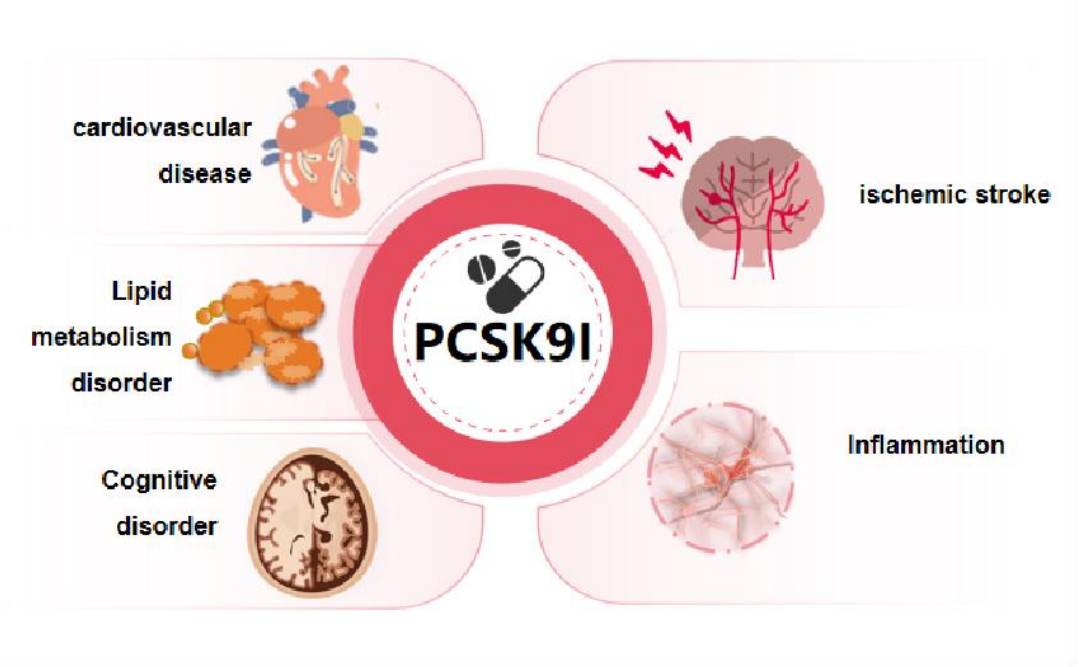


Figure 1. Mechanism of action of the Inclisiran

## 2. Effects of PCSK 9 on lipids

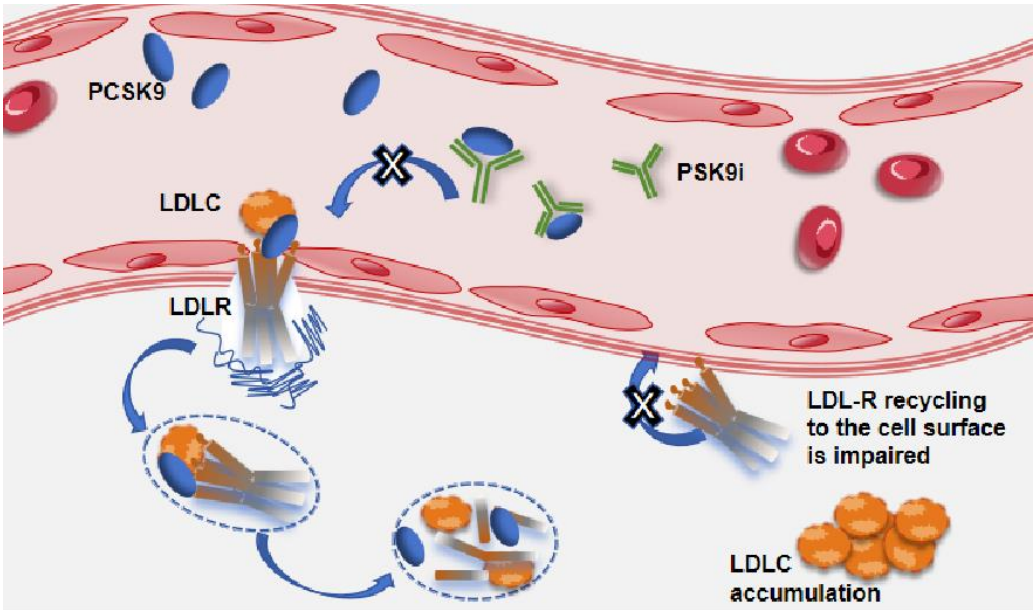


Figure 2 Effects of PCSK9 on Lipids

Hyperlipidemia is a significant risk factor for stroke, with atherosclerosis driven by elevated lipid levels serving as a primary etiology of ischemic stroke. The current major lipid-lowering regimen is oral statins, namely inhibitors of hydroxymethylglutaryl-CoA reductase. PCSK9, a serine protease synthesized in the liver, intestine, and kidneys, binds to the epidermal growth factor precursor homology domain A (EGF-A) of LDL-R. This interaction facilitates LDL-R-LDL-C complex internalization into endosomes, where acidic conditions dissociate LDL-R from LDL-C. While LDL-C undergoes lysosomal degradation, LDL-R recycling to the cell surface is impaired, reducing hepatic LDL-C uptake, is shown in Figure 2. While the main effect of PCSK-9 inhibitors is to block the effect of PCSK-9 protein, promote LDL-R recycling and LDL-C reduction[1]. Additionally, PCSK9 inhibitors enhance Lipoprotein(a) (Lp (a)) clearance via receptors (e.g., LDL-R, LRP, CD36) and reduce Lp (a) production.

Alirocumab: The first FDA-approved PCSK9 inhibitor demonstrated. In the ODYSSEY OUTCOME trial a 59.5%–62.0% LDL-C reduction versus placebo, with 79% of patients achieving LDL-C <70 mg/Dl[2]. Another survey comparison of 18924 patients with acute coronary syndrome, the ODYSSEY trial examining the effectiveness of Alirocumab in reducing LDL-C levels, showed a 62% reduction in LDL-C at week 78 in the Alirocumab group compared to the placebo group[3].Evolocumab: This inhibitor reduces plasma Lp(a) by decreasing production and accelerating catabolism[4]. Ezetimibe targets Niemann-Pick C1-Like 1 (NPC1L1) at the apical membrane of enterocytes and hepatocytes to mediate cholesterol absorption and its hepatobiliary excretion in the intestine[5]. Inclisiran: Using the siRNA approach reduces PCSK-9 protein synthesis by blocking the intracellular translation of PCSK-9 mRNA, thus reducing the accumulation of PSCK-9[6], is shown in Figure 3. It was EMA approved in 2020 and received FDA approval in 2021.

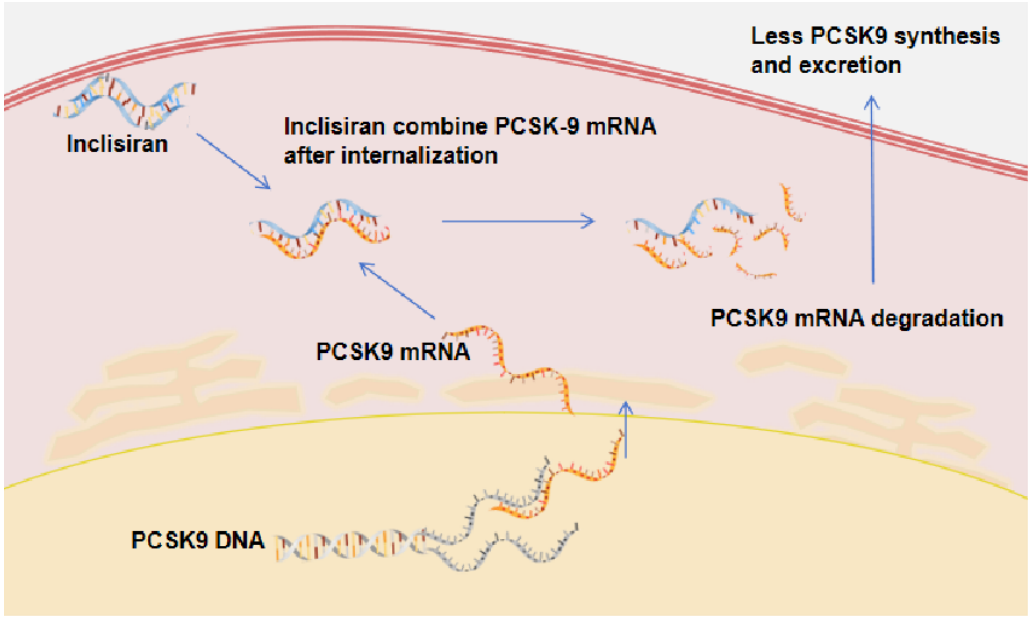


Figure 3. Mechanism of action of the Inclisiran

A pooled analysis of 7 RCTs (57,440 participants) showed PCSK9 inhibitors significantly reduced overall stroke risk (RR 0.77; 95% CI 0.67–0.88; P<0.001) and ischemic stroke risk (RR 0.76; 95% CI 0.66–0.89; P<0.001)[7]. Another meta-analysis of 41,979 patients (evolocumab: 17,244; bococizumab: 13,720; alirocumab: 11,015) revealed a 25% reduction in stroke incidence[8]. Across 16 RCTs (evolocumab: 6 trials, 33,450 patients; alirocumab: 10 trials, 5,654 patients), PCSK9 inhibitors consistently lowered ischemic stroke risk versus non-inhibitor therapies[9]. PCSK9 inhibitors offer robust LDL-C reduction and cardiovascular protection, particularly in

statin-resistant or high-risk populations. Their dual mechanisms—enhancing LDL-R recycling and modulating Lp (a) metabolism—position them as pivotal agents in stroke prevention strategies.

## 3. PCSK9 and inflammation

The progression of neuroinflammation is a critical contributor to ischemic stroke pathology. Within minutes of ischemic injury, damaged and stressed cells in the ischemic core and penumbra release damage-associated molecular patterns (DAMPs), such as high-mobility group box 1 (HMGB1), heat shock proteins (HSPs), and peroxiredoxin family proteins (PRDXs). These DAMPs activate astrocytes and microglia, triggering the secretion of pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α, iNOS), which exacerbate blood-brain barrier (BBB) disruption, cerebral edema, and peripheral leukocyte infiltration, ultimately leading to secondary brain tissue damage. While neuroinflammation may initially aid in clearing cellular debris, excessive inflammation becomes detrimental due to neurotoxin production and edema amplification. Thus, anti-inflammatory therapies represent a promising strategy for mitigating ischemic brain injury.

In a cardiac ischemia-reperfusion (I/R) injury study, PCSK9i significantly reduced activated astrocyte and microglial populations, restored the proliferative and hypertrophic phenotypes of reactive glial cells post-injury, and suppressed p-NF-κB expression[10]. Furthermore, in lipopolysaccharide (LPS)-stimulated BV2 microglia and THP-1 monocytes, PCSK9i attenuated TNF-α and IL-6 secretion via interactions with LDL receptors (LDLR)[11]. In a transient middle cerebral artery occlusion (tMCAO) model using C57BL/6 mice, subcutaneous PCSK9i administration improved neurological function (assessed via mNSS scores) and reduced cerebral infarct volume (quantified by TTC staining). RNA-seq, Western blotting, and immunofluorescence analyses revealed that PCSK9i suppresses neuroinflammation by activating the GPNMB/CD44 signaling pathway, concurrently downregulating IL-6 and iNOS expression[12].

Chronic inflammation, characterized by macrophage infiltration and progressive accumulation of inflammatory mediators/oxidative stress in arterial walls, drives atherosclerosis. In hyperlipidemic mouse models with PCSK9 overexpression, increased monocyte infiltration into vascular walls was observed[13]. The AT04A anti-PCSK9 vaccine significantly reduced plasma inflammatory markers, including serum amyloid A (SAA), macrophage inflammatory protein-1β (MIP-1β), macrophage-derived chemokine (MDC), stem cell factor (SCF), and VEGF-A. By lowering M-CSF-1 and VEGF-A levels, the vaccine suppressed endothelial activation (reduced ICAM-1 expression), monocyte recruitment/adhesion[14]. Thus resulting in a reduced size of the formed atherosclerotic plaques, as well as an attenuation of the inflammatory response.

## 4. PCSK9 promotes thrombosis

Thromboembolism, a primary cause of ischemic stroke, relies on platelet adhesion, activation, and aggregation. The mechanisms underlying thrombosis driven by PCSK9 involve both lipid-dependent and lipid-independent pathways: ① Lipid-Dependent Pathway: Elevated PCSK9 levels suppress LDL receptor (LDLR)-mediated clearance, leading to circulating oxidized LDL (ox-LDL) accumulation. ox-LDL binds to lectin-like ox-LDL receptor-1 (LOX-1) on platelets and endothelial cells, triggering phosphorylation of extracellular signal-regulated kinase 5 (ERK5) within the MAPK pathway. ERK5 enhances platelet aggregation by regulating CD36 receptor downstream signaling (e.g., Src kinase activation, ROS generation), forming a self-amplifying loop: "lipid dysregulation → PCSK9 upregulation → ox-LDL/LOX-1 → ERK5/CD36", perpetuating thrombogenesis[15]. ② Lipid-Independent Pathway: PCSK9 directly binds to platelet surface receptors CD36 and LOX-1, independent of LDL metabolism, to amplify platelet activation.

In FeCl3-induced arterial injury models, PCSK9-CD36 interaction activates Src kinases and MAPK pathways (ERK 5 and JNK subtypes), driving: Increased ROS production; Activation of the CD36/p38MAPK/cPLA2/COX-1 axis; Thromboxane A2 (TXA2) synthesis via thromboxane synthase, which activates integrin αIIbβ3 via platelet agonist receptors.αIIbβ3 conformational changes promote fibrinogen crosslinking, culminating in platelet aggregation and thrombus formation. Additionally, CD36-ox-LDL binding induces P-selectin expression, fostering platelet-leukocyte aggregates, while LOX-1-ox-LDL interaction activates integrins αIIbβ3 and α2β1, enhancing platelet aggregation through cytoskeletal reorganization and receptor redistribution. These dual receptor pathways synergize via fibrinogen crosslinking, elevating thrombotic risk[16]. Moreover,11-Dehydrothromboxane B2 (11-dh-TxB2), a stable urinary metabolite of TXA2 (half-life ~45 minutes), serves as a critical biomarker for platelet activation. A 2017 prospective cohort study identified a direct correlation between PCSK9 and 11-dh-TxB2[17]. Future studies are needed to further elucidate the interaction network of PCSK 9 with different platelet agonists to optimize the precise intervention strategies for thrombotic diseases.

Mass apoptosis after endothelial cell injury disrupts endothelial integrity and increases permeability, thereby promoting endothelial dysfunction and atherogenesis. In terms of alleviating atherosclerosis and inducing plaque regression, PCSK 9 inhibitors may be achieved through the inhibition of endothelial cell apoptosis. The serum PCSK 9 level had good predictive value in terms of carotid intima-wall thickness and was an independent indicator of factors other than homeostatic model assessment (HOMA) score, obesity, LDL-C, lipoprotein (a) and inflammatory markers[18]. In rabbit models, evolocumab outperformed atorvastatin in reducing atherosclerotic plaque volume, fibrosis, and necrotic core composition[19]. Similarly, alirocumab therapy in humans reduced plaque lipid content and increased fibrous tissue, enhancing plaque stability. These findings underscore PCSK9 inhibitors' dual role in vascular protection and plaque remodeling[20].

## 5. Efficacy and safety of PCSK9 inhibitors

Alirocumab, the first FDA-approved PCSK9 inhibitor, achieved LDL-C reductions of 59.5% to 62.0% compared to placebo in the ODYSSEY OUTCOME trial, with 79% of participants reaching the LDL-C target of <70 mg/dL. When combined with statins, evolocumab demonstrated a 59% LDL-C reduction from baseline and a 15% risk reduction. In a 501-patient trial, inclisiran showed LDL-C reductions of 42% after one dose and up to 56% after two doses. Pooled data from nine ODYSSEY Phase III trials (n=4,880) revealed that alirocumab 75/150 mg biweekly combined with statins achieved LDL-C reductions of 43.6%-62.9% at week 24 in patients with prior ischemic stroke, significantly lowered lipoprotein (a), and attained LDL-C goals in 74.1%-84.8% of those with MI/stroke history (vs. 63.7%-74.7% in controls). Subgroup analyses confirmed consistent efficacy across populations, with comparable reductions in LDL-C, non-HDL-C, and apolipoprotein B regardless of prior cardiovascular events and similar adverse event rates[21].

Safety debates focus on four aspects: ① Neurocognitive events: Most studies (including FOURIER sub-analyses and meta-analyses) show no significant difference between alirocumab/evolocumab and placebo (evolocumab 1.6% vs 1.5%; alirocumab 1.2% vs 0.5%), with low LDL-C (25 mg/dL) not increasing risk. However, the combined analysis of ODYSSEY LONG TERM and OSLER study suggested slightly increased events in the treatment group (OR 1.29) and the mechanism was unclear[22]. ② Muscle safety: Alirocumab shows higher myopathy rates versus placebo (5.4% vs 2.9%, P<0.006), while Evolocumab shows no difference (5% vs 4.8%). ③ Metabolic effects: No statistical differences in new-onset diabetes (evolocumab 8.1% vs 7.7%; alirocumab 1.8% vs 2%), though cautious use in diabetic or high ASCVD-risk populations is advised[23]. ④ Mortality: Alirocumab reduced all-cause serious adverse events (OR 0.92), while

evolocumab may increase mortality risk[24].Overall, PCSK9 inhibitors demonstrate favorable tolerability, but long-term effects still require evidence-based validation. Mechanism and adverse reactions of PCSK9 inhibitors is shown in Table 1.

Table 1. Mechanism and adverse reactions of represent drugs of PCSK9 inhibitors

| Drug Name | Mechanism | Adverse Reaction |
|---|---|---|
| Alirocumab | Targeting to bind with PCSK9 | Local injection site reaction, Pruritus, Upper respiratory, Tract symptoms |
| Evolocumab | Targeting to bind with PCSK9 | Local injection site reaction, Pruritus, Upper respiratory, Tract symptoms |
| Inclisiran | Blocking the intracellular translation of PCSK-9 mRNA | Local injection site reaction |

## 6. Conclusion

PCSK9 inhibitors demonstrate multidimensional synergistic effects in ischemic stroke prevention and treatment, encompassing lipid-lowering, anti-inflammatory, antithrombotic, and plaque-stabilizing actions. However, current research predominantly focuses on long-term cardiovascular benefits, while acute-phase neuroprotective mechanisms remain unclear. For instance, whether PCSK9 inhibitors preserve blood-brain barrier integrity, suppress oxidative stress during ischemia-reperfusion injury, or alleviate neuroinflammation via microglial polarization regulation requires bidirectional validation through animal models and clinical translational studies. Although most studies indicate no increased neurocognitive risk, the potential indirect cognitive impairment from extremely low LDL-C levels through altered neuronal cholesterol metabolism necessitates mechanistic exploration and long-term follow-up. Future research should: 1) Decipher PCSK9's anti-inflammatory and neurorestorative targets within the neurovascular unit; 2) Optimize risk stratification and dosing regimens using biomarker-guidance and genetic polymorphism analysis; 3) Establish long-term safety/efficacy profiles beyond randomized trial limitations. Comprehensive clinical implementation of PCSK9 inhibitors demands a paradigm shift from "lipid-centric" approaches to "neurovascular network modulation," requiring interdisciplinary collaborations to bridge mechanistic insights and clinical evidence gaps. This transformation will enable tailored therapeutic strategies addressing both systemic vascular protection and CNS-specific neurorepair processes.

## References


*[1] Handelsman Y, Lepor N E. PCSK9 Inhibitors in Lipid Management of Patients With Diabetes Mellitus and High Cardiovascular Risk: A Review. J. Am. Heart Assoc. 2018, 7, e008953.*

*[2] Ilut S, Pirlog B O, Pirlog R, Nutu A, Vacaras V, Armean SM. Recent Advances on the Roles of PCSK-9 Inhibitors in the Management of Acute Ischemic Stroke Patients. Int J Mol Sci. 2022, 23(18): 10221. Published 2022 Sep 6. doi:10.3390/ijms231810221*

*[3] Schwartz G G, Steg P G, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med. 2018, 379(22): 2097-2107. doi:10.1056/NEJMoa1801174*

*[4] Watts G F, Chan D C, Somaratne R, et al. Controlled study of the effect of proprotein convertase subtilisin-kexin type 9 inhibition with evolocumab on lipoprotein(a) particle kinetics. Eur Heart J. 2018, 39(27): 2577-2585. doi:10.1093/eurheartj/ehy122*

*[5] Jia L, Betters J L, Yu L. Niemann-pick C1-like 1 (NPC1L1) protein in intestinal and hepatic cholesterol transport. Annu Rev Physiol. 2011, 73: 239-259. doi:10.1146/annurev-physiol-012110-142233*

*[6] German C A, Shapiro M D. Small Interfering RNA Therapeutic Inclisiran: A New Approach to Targeting PCSK9. BioDrugs. 2020, 34(1): 1-9. doi:10.1007/s40259-019-00399-6*

*[7] Qin J, Liu L, Su X D, et al. The effect of PCSK9 inhibitors on brain stroke prevention: A systematic review and*

*meta-analysis. Nutr Metab Cardiovasc Dis. 2021, 31(8): 2234-2243. doi:10.1016/j.numecd.2021.03.026*
*[8] Cordero A, Rodríguez-Mañero M, Fácila L, et al. Prevention of myocardial infarction and stroke with PCSK9 inhibitors treatment: a metanalysis of recent randomized clinical trials. J Diabetes Metab Disord. 2020, 19(2): 759-765. Published 2020 Jun 1. doi:10.1007/s40200-020-00557-6*
*[9] Bajaj N S, Patel N, Kalra R, et al. Neurological effects of proprotein convertase subtilisin/kexin type 9 inhibitors: direct comparisons. Eur Heart J Qual Care Clin Outcomes. 2018, 4(2): 132-141. doi:10.1093/ehjqcco/qcx037*
*[10] Apaijai N, Moisescu D M, Palee S, et al. Pretreatment With PCSK9 Inhibitor Protects the Brain Against Cardiac Ischemia/Reperfusion Injury Through a Reduction of Neuronal Inflammation and Amyloid Beta Aggregation. J Am Heart Assoc. 2019, 8(2): e010838. doi:10.1161/JAHA.118.010838*
*[11] Wang L, Hou H, Zi D, Habib A, Tan J, Sawmiller D. Novel apoE receptor mimetics reduce LPS-induced microglial inflammation. Am J Transl Res. 2019, 11(8): 5076-5085. Published 2019 Aug 15.*
*[12] Zheng Y, Zhu T, Li G, Xu L, Zhang Y. PCSK9 inhibitor protects against ischemic cerebral injury by attenuating inflammation via the GPNMB/CD44 pathway. Int Immunopharmacol. 2024, 126: 111195. doi:10.1016/j.intimp.2023.111195*
*[13] Giunzioni I, Tavori H, Covarrubias R, et al. Local effects of human PCSK9 on the atherosclerotic lesion. J Pathol. 2016, 238(1): 52-62. doi:10.1002/path.4630*
*[14] Landlinger C, Pouwer M G, Juno C, et al. The AT04A vaccine against proprotein convertase subtilisin/kexin type 9 reduces total cholesterol, vascular inflammation, and atherosclerosis in APOE*3Leiden. CETP mice. Eur Heart J. 2017, 38(32): 2499-2507. doi:10.1093/eurheartj/ehx260*
*[15] Yang M, Cooley BC, Li W, et al. Platelet CD36 promotes thrombosis by activating redox sensor ERK5 in hyperlipidemic conditions. Blood. 2017, 129(21): 2917-2927. doi:10.1182/blood-2016-11-750133*
*[16] Zhou L, Zhang H, Wang S, et al. PCSK-9 inhibitors: a new direction for the future treatment of ischemic stroke. Front Pharmacol. 2024, 14: 1327185. Published 2024 Jan 11. doi:10.3389/fphar.2023.1327185*
*[17] Pastori D, Nocella C, Farcomeni A, et al. Relationship of PCSK9 and Urinary Thromboxane Excretion to Cardiovascular Events in Patients With Atrial Fibrillation. J Am Coll Cardiol. 2017, 70(12): 1455-1462. doi:10.1016/j.jacc.2017.07.743*
*[18] Chan D C, Pang J, McQuillan B M, et al. Plasma Proprotein Convertase Subtilisin Kexin Type 9 as a Predictor of Carotid Atherosclerosis in Asymptomatic Adults. Heart Lung Circ. 2016, 25(5): 520-525. doi:10.1016/j.hlc.2015.10.017*
*[19] Kong Q, Liu M, Li Y, Zhu Q, Su G. Effect of evolocumab on the progression and stability of atherosclerotic plaques as evaluated by grayscale and iMAP-IVUS. Ann Palliat Med. 2020, 9(5): 3078-3088. doi:10.21037/apm-20-690*
*[20] Sun J, Lepor N E, Cantón G, et al. Serial magnetic resonance imaging detects a rapid reduction in plaque lipid content under PCSK9 inhibition with alirocumab. Int J Cardiovasc Imaging. 2021, 37(4): 1415-1422. doi:10.1007/s10554-020-02115-w*
*[21] Bruckert E, Kereiakes D J, Koren M J, et al. PCSK9 inhibition in patients with and without prior myocardial infarction or ischemic stroke: A pooled analysis of nine randomized-controlled studies of alirocumab. J Clin Lipidol. 2019, 13(3): 443-454. doi:10.1016/j.jacl.2019.04.005*
*[22] Giugliano R P, Mach F, Zavitz K, et al. Cognitive Function in a Randomized Trial of Evolocumab. N Engl J Med. 2017, 377(7): 633-643. doi:10.1056/NEJMoa1701131*
*[23] Earl G. PCSK9 inhibitors: Add-on therapy to reduce stroke risk. Nurs Crit Care (Ambler). 2019, 14(1): 42-48. doi:10.1097/01.CCN.0000549635.52054.5b*
*[24] Van Bruggen F H, Nijhuis G B J, Zuidema S U, Luijendijk H. Serious adverse events and deaths in PCSK9 inhibitor trials reported on ClinicalTrials.gov: a systematic review. Expert Rev Clin Pharmacol. 2020, 13(7): 787-796. doi:10.1080/17512433.2020.1787832*