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Research progress on the clinical application of PCSK9 inhibitors in coronary heart disease

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Abstract: Coronary heart disease (CHD) is currently an important cause of mortality among residents in China and worldwide. The incidence of CHD in China is increasing annually. Among the various factors leading to the occurrence of CHD, abnormalities in blood lipids, especially elevated low-density lipoprotein cholesterol (LDL-C), are particularly significant. Epidemiological, genetic, and clinical studies have confirmed its crucial role in the development of coronary heart disease. Therefore, effectively controlling LDL-C levels has become a paramount in preventing the onset of CHD and reducing mortality rates. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, as novel lipid-lowering medications, effectively lower LDL-C and play a significant role in preventing major adverse cardiovascular events (MACEs). This article provides a review of PCSK9 inhibitors in clinical treatment related to coronary artery atherosclerosis.

Keywords: Proprotein convertase subtilisin/kexin type 9 inhibitors; Coronary heart disease; Low-density lipoprotein cholesterol; Cardiovascular Cardiovascular events

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Coronary heart disease (CHD) is caused by damage to the inner wall of coronary arteries, which leads to the deposition of cholesterol and lipids to form plaques in the walls of the arteries and ultimately leads to narrowing of the lumen of the arteries, obstruction of blood flow or thrombosis, which can lead to myocardial ischemia or even myocardial infarction and other serious consequences. Hypercholesterolemia is an important risk factor for atherosclerosis and serious cardiovascular diseases. According to the "Summary of the 2022 Report on Cardiovascular Health and Diseases in China", the prevalence of CHD in China is increasing year by year and blood lipid levels are significantly elevated [1]. Traditional statins have been widely used in clinical practice as the cornerstone of lipid-lowering therapy for CHD. However, after using the maximum dose of statin therapy, some patients still fail to meet the requirements of lipid-lowering standards, especially for patients with familial hyperlipidemia. Accompanied by many adverse effects of the statin, some patients develop symptoms including xerostomia, abdominal pain, constipation, etc. About 1/1,000 patients develop myopathy, which is manifested as myositis, rhabdomyolysis, and some other adverse effects such as hepatic insufficiency, diabetes mellitus, hypothyroidism, etc.[2-4]. This deficiency is made up by proprotein convrtase subtilisin/kexin9 (PCSK9) inhibitors, which play an important role in the treatment of hypercholesterolemia. PCSK9 inhibitors are widely recognized as an important option for the treatment of hypercholesterolemia due to their excellent cholesterol-lowering effect.

PCSK9 is the 9th member of the proprotein convertases (PCs) family and is a secreted serine protease. It is mainly synthesized and secreted in the endoplasmic reticulum of the liver, and is also expressed in the intestines and kidneys[5]. In 2003, researchers discovered that the PCSK9 gene is closely related to cholesterol metabolism. Subsequently, researchers have found that mutant PCSK9 genes can lead to elevated levels of low-density lipoprotein cholesterol (LDL-C). The Food and Drug Administration (FDA) approval in 2015 is an important milestone in the research of PCSK9 inhibitors and marks a breakthrough in the clinical application of this class of drugs. Since then, a series of clinical trials and studies have confirmed the remarkable effectiveness of PCSK9 inhibitors in the treatment of hypercholesterolemia, making them a new option for the prevention and treatment of cardiovascular disease.

1 Mechanism of action of PCSK9

1.1 Role in blood lipids

It has been found that LDL-C binds through the LDL receptor (LDL-R) on the surface of hepatocytes, and form a complex that passes from the vasculature into the interior of the hepatocyte via the cytosolic pathway, where it is transported to the lysosomes for degradation, and then the LDL-R returns to the surface of the cell for the next cytosolization. PCSK9 binds specifically to the LDL-R, accelerating the irreversible degradation of the LDL-R and reducing the binding of LDL-R to LDL-C, thereby causing circulating levels of LDL-C to rise. Irreversible degradation and reduces the binding of LDL-R to LDL-C, which in turn results in elevated circulating LDL-C levels[6].

1.2 Pro-inflammatory effects

Studies have demonstrated that the inflammatory response plays a role at all times in myocardial infarction, influencing myocardial healing and repair [7]. PCSK9 can convert leukocytes to a pro-inflammatory state, leading to the production of pro-inflammatory cytokines that play a direct role in the development of atherosclerosis. It acts directly through pro-inflammatory oxidation of LDL and modification of plaque components, thereby inducing a cytokine, chemokine and adhesion molecule-mediated inflammatory response that promotes atherosclerosis formation and development [8-9]. Atherosclerosis-associated inflammatory factors including tumor necrosis factor-α (TNF-α), interleukin (IL)-6 and IL-1β have been found to be well inhibited by PCSK9 inhibitors [10].

1.3 Platelet activation

Recently, it has been demonstrated that PCSK9 enhances platelet activation. PCSK9 in plasma directly enhances platelet activation by binding to platelet CD36 and activating downstream signaling pathways. Platelet activation releases inflammatory mediators such as thromboxane A2 and 5-hydroxytryptophan, which promote platelet adhesion and aggregation, lead to atherosclerosis, aggravate microvascular obstruction, and contribute to the expansion of the area of the post-infarction area of the myocardial infarction [11].

1.4 Apoptosis

PCSK9 can promote ox-LDL-induced endothelial cell apoptosis and cause endothelial dysfunction in atherosclerosis through the c-Jun amino-terminal kinase/p38 mitogen-activated protein kinase pathway. Meanwhile, some studies have shown that knockdown of PCSK9 gene by siRNA can inhibit ox-LDL-induced endothelial cell apoptosis through the Bcl-2/Bax pathway, both demonstrating the pro-apoptotic effect of PCSK9[12-13].

2 Clinical use of PCSK9 inhibitors

Numerous researchers have found that PCSK9 inhibitors have great potential in the prevention of atherosclerotic disease. By lowering LDL-C levels, PCSK9 inhibitors significantly inhibit cholesterol deposition and plaque formation in the arterial vasculature, reducing patients' risk of major adverse cardiovascular events (MACEs), such as myocardial infarction and stroke. It has been stated that Lp(a) is a complex of LDL-C, ApoB100 and ApoA, which is considered to be independently associated with the development of coronary artery disease and is not affected by a decrease in the level of LDL-C. Statins cannot reduce LP(a), and PCSK9 inhibitors are better able to reduce the level of this type of lipoproteins in comparison with statins, thus preventing the occurrence of cardiovascular events[14-15]. Moreover, in many studies, PCSK9 inhibitors have been found to have additional effects beyond LDL-C reduction, such as inhibiting inflammation[6,16], controlling platelet activation[17], and regulating apoptosis of vascular endothelial cells[12], etc. They further reduce the formation of atherosclerosis, prevent plaque rupture, and prevent the development of MACEs.

2.1 Application of PCSK9 inhibitors in the treatment of hypercholesterolemia

The ODYSSEY trial[18] is a series of large-scale studies on the efficacy and safety of PCSK9 inhibitors, mainly focusing on the efficacy and safety of the two currently listed drugs, evolocumab and alirocumab, in different patient groups. Among them, the ODYSSEY LONG TERM trial[19] and ODYSSEY FH I and II trials[20] were conducted on patients with hypercholesterolemia and familial hypercholesterolemia respectively, which confirmed that PCSK9 inhibitors have good efficacy in reducing LDL-C in the short term. The LDL-C levels were observed to be lowered by about 61.9% in comparison with those of the control group in 24 weeks. The MACEs events were lowered by 48%, which not only has a significant effect, but also has the effect of lowering LDL-C. The ODYSSEY COMBO I and II trials demonstrated that the addition of a PCSK9 inhibitor to maximal statin therapy further reduced LDL-C and was more effective than ezetimibe[21].

2.2 Potential of PCSK9 Inhibitors in preventing atherosclerotic disease

Researchers comparing the use of PCSK9 inhibitors with basal statins in an acute coronary syndrome population in the ODYSSEY OUTCOMES trial confirmed a reduction in LDL-C levels of approximately 55% and a 15% reduction in all-cause mortality. It was also observed that the application of PCSK9 in patients with LDL-C≥100 mg/dL (2.6 mmol/L) inhibitors resulted in greater benefits [22].

The FOURIER study, the first large, multicenter, double-blind cardiovascular outcome study of PCSK9 inhibitors, with 27,564 participants, confirmed the excellent lipid-lowering effect of PCSK9 inhibitors, i.e., the ability to reduce LDL-C by up to 59% on top of statin, and absolute lipid level by 1.45 mmol/L[23]. Moreover, its sub-study, the FOURIER-OLE trial, confirmed that the use of PCSK9 inhibitors in the treatment of patients with coronary artery disease significantly reduces the risk of MACEs, resulting in a decrease of cardiac events by approximately 15% during 3 years of follow-up. Meanwhile, the GLAGOV trial observed by intravascular ultrasound (IVUS) that the use of PCSK9 inhibitor treatment on top of statin treatment could more significantly reduce the plaque size and degree of obstruction, confirming that PCSK9 inhibitors can effectively reduce the size of plaques and reverse the plaque effect [24].

PCSK9 inhibitors have been applied in the clinics as lipid-lowering drugs, and their prominent LDL-lowering ability is their key advantage, which can reduce the development of cardiovascular events safely. PCSK9 inhibitors seem to be able to compensate for, or even replace, statins, which can play a protective and therapeutic role for people at high risk of cardiovascular disease. In the study of CHD, the inflammatory response is recognized as an important factor involved in is disease progression. Thus, control of the inflammatory response is particularly critical. In a domestic clinical study, it was concluded that PCSK9 inhibitors can effectively improve the early systemic inflammatory response in patients with myocardial infarction, significantly reduce the levels of IL-1β, IL-6, TNF-α and other related inflammatory factors, and thus achieve the role of cardioprotection[25]. In addition to the above trials, many other studies are exploring the efficacy and safety of PCSK9 inhibitors, such as FURTHER, MENDEL, also showed that PCSK9 inhibitors have good safety while achieving better lipid-lowering effect as well as the prevention of cardiovascular disease significant results [26-27]. These large clinical trials have demonstrated that PCSK9 inhibitors have excellent lipid-lowering effects in the treatment of coronary artery disease while significantly reducing cardiovascular events, with less hepatic or renal impairment and fewer myositis, myalgia, diabetes, and neurocognitive events compared to statins[28].

3 Safety and side effects of PCSK9 inhibitors

PCSK9 inhibitors are generally considered relatively safe drugs that significantly reduce the incidence of adverse cardiovascular events, without causing serious liver or kidney abnormalities, and affecting blood glucose[29-30]. However, they may have some side effects. The following are some common side effects and safety concerns.

3.1 Injection site reactions

Because PCSK9 inhibitors are used via the injection route of administration, some patients may experience injection-related reactions such as pain, redness, swelling, tingling, or bruising at the injection site[31].

3.2 Immunogenic reactions

In some studies and case reports, some patients have experienced reactions related to the immunogenicity of PCSK9 inhibitors, such as anaphylactic reactions, hives, drug rashes, skin rashes and swelling at the injection site. A SPIRE trial was also stopped in progress due to more severe allergenicity problems[32]. Such adverse reactions, however, did not increase significantly in the clinical trials of evolocumab and alirocumab, which are currently available [33].

3.3 Neurocognitive side effects

In some previous studies, patients using PCSK9 inhibitors may experience mild neurocognitive side effects such as memory loss or poor concentration [34]. However, these observations are inconsistent, and more studies are needed to further clarify their relationship with the drug. While some studies have suggested an association with excessively low LDL-C levels, the EBBINGHAUS trial concluded that low levels of plasma cholesterol do not induce cognitive impairment [35].

4 Current status of PCSK9 inhibitors

According to the different mechanisms of action of PCSK9 inhibitors, they are mainly classified into drugs that inhibit PCSK9 at the nucleic acid level, such as small interfering RNA (siRNA), antisense oligoneucleotides (ASOs), drugs that inhibit the binding of PCSK9 to LDL-C and LDL-R, such as monoclonal antibodies (mAb), antibody-mimicking proteins, and small molecules that alter the catalytic site of the PCSK9 protein[19]. Alirocumab and evolocumab are listed drugs. Among these drugs, inclisiran is a small interfering RNA.Its main mode of administration is subcutaneous injection, which has been used clinically, but due to its price and mode of administration, some patients stop taking the drug. While other types of PCSK9 inhibitors are under research and many drugs have reached phase III clinical stage, their mode of application is oral and seems to be more popular[36].

5 Discussion

Since the first PCSK9 inhibitor was launched, there has been tremendous progress in the field, driven by continued research. PCSK9 inhibitors have shown great potential in clinical applications. They have been widely used in the treatment of hypercholesterolaemia and have shown significant reductions in LDL-C levels. In addition, PCSK9 inhibitors are thought to have a potentially important role in the prevention of cardiovascular disease by improving atherosclerotic lesions. Combination with statins may further improve therapeutic efficacy. Although PCSK9 inhibitors have shown significant benefits in clinical use, their safety and potential side effects must be taken into account. In most cases, mild side effects such as headache and myalgia are manageable and can be managed by adjusting the dose or treatment regimen. However, more comprehensive studies and observations are needed on the potential safety concerns of PCSK9 inhibitors in the long term.

Research and clinical application of PCSK9 inhibitors continues to face a number of challenges and limitations. One of these is the improvement of dosage forms to increase patient convenience and compliance. In addition, the development of individualised therapy and personalized medicines is an important direction for the future. By studying individual genetic differences and biomarkers, patient response to PCSK9 inhibitors can be

better predicted, leading to personalized treatment strategies.

In conclusion, the progress of research into PCSK9 inhibitors has brought hope for the treatment of cardiovascular disease. Through further research and clinical practice, their potential in the prevention and treatment of hypercholesterolaemia and cardiovascular disease can be better understood and provide a more reliable basis for the development of personalized treatment.

Conflict of interest None

Reference:

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· 研究进展 ·

前蛋白转化酶枯草溶菌素 9 抑制剂在冠状动脉粥样硬化性心脏病中的应用进展

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摘要：冠状动脉粥样硬化性心脏病（冠心病）是目前我国乃至世界范围内导致居民死亡的重要原因。在我国范围内冠心病的患病率正逐年上升。在导致冠心病发生的诸多原因中，血脂异常尤其是低密度脂蛋白胆固醇（LDL-C）升高尤为重要，在流行病学、遗传学以及临床研究中，均已证实其在冠心病发生发展中发挥重要作用。因此有效地控制 LDL-C 水平已成为预防冠心病发生、降低死亡率的重中之重。前蛋白转化酶枯草溶菌 9（PCSK9）抑制剂作为新型的降脂药物可以很好的降低 LDL-C，对预防不良心血管事件（MACEs）发生发挥重要作用。本文将对 PCSK9 抑制剂在冠状动脉硬化相关临床治疗问题上进行综述。

关键词：前蛋白转化酶枯草溶菌 9 抑制剂；冠状动脉粥样硬化性心脏病；低密度脂蛋白胆固醇；心血管事件

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Abstract: Coronary heart disease (CHD) is currently an important cause of mortality among residents in China and worldwide. The incidence of CHD in China is increasing annually. Among the various factors leading to the occurrence of CHD, abnormalities in blood lipids, especially elevated low-density lipoprotein cholesterol (LDL-C), are particularly significant. Epidemiological, genetic, and clinical studies have confirmed its crucial role in the development of CHD. Therefore, effectively controlling LDL-C levels has become paramount in preventing the onset of CHD and reducing mortality rates. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, as novel lipid-lowering medications, effectively lower LDL-C and play a significant role in preventing major adverse cardiovascular events (MACEs). This article provides a review of PCSK9 inhibitors in clinical treatment related to coronary artery atherosclerosis.

Keywords: Proprotein convertase subtilisin/kexin type 9 inhibitors; Coronary heart disease; Low-density lipoprotein cholesterol; Cardiovascular events

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冠状动脉粥样硬化性心脏病（冠心病）是因为冠状动脉血管内壁出现损伤，促使胆固醇和脂质在血管壁内沉积形成斑块，并最终导致血管腔狭窄、血流阻塞或血栓形成，进而引发心肌缺血甚至心肌梗死等严重后果。高胆固醇血症是引发动脉粥样硬化以及严重心血管疾病发生的重要的危险因素。根据《中国心血管健康与疾病报告 2022 概要》指出，我国冠心病患病率正在逐年上升，且血脂水平明显升高[1]。传统的他汀类药物作为冠心病降脂治疗的基石，已经在临床上被广泛使用。然而在使用最大剂量他汀治疗后，仍有部分患者达不到降脂标准的要求，尤其对家族性高脂血症患者收效甚微。同时伴随有许多该药物的不良反应，部分患者出现口干、腹痛、便秘等，约 1/1 000 患者出现肌病，具体表现为肌炎、肌溶解，另外一些不良反应为肝功能不全、糖尿病、甲状腺功能减退等[2-4]。而前蛋白转化酶枯草溶菌素 9（proprotein convrtase subtilisin/kexin9, PCSK9）抑制剂正好填补了这个缺口，PCSK9 抑制剂在高胆固醇血症治疗中具有重要作用，由于其出色的降胆固醇效果，PCSK9 抑制剂被广泛认为是治疗高胆固醇血症的一种重要选择。

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PCSK9 是前蛋白转化酶枯草杆菌蛋白酶家族的第 9 个成员，是一种分泌性丝氨酸蛋白酶。主要在肝脏内质网中合成分泌，在肠道、肾脏等部位也有表达[5]。2003 年，研究人员发现了 *PCSK9* 基因与胆固醇代谢密切相关。随后，研究人员又发现某些突变型 *PCSK9* 基因能够导致低密度脂蛋白胆固醇（low-density lipoprotein cholesterol，LDL-C）水平升高，2015 年美国食品和药品监督管理局（FDA）的批准是 PCSK9 抑制剂研究的重要里程碑，标志着这一类药物在临床应用中的突破。此后，一系列临床试验和研究证实了 PCSK9 抑制剂在高胆固醇血症治疗中的显著效果，使其成为心血管疾病预防和治疗的一种新选择。

1　PCSK9 的作用机制

1.1　*血脂方面的作用*　研究发现 LDL-C 通过肝细胞表面的低密度脂蛋白受体（low-density lipoprotein receptor，LDL-R）结合，共同形成复合物，经胞吞途径从血管内进入肝细胞内部，转运至溶酶体内降解，随后 LDL-R 返回至细胞表面进行下一次胞吞。PCSK9 与 LDL-R 特异性的结合，加速 LDL-R 不可逆降解，减少了 LDL-R 与 LDL-C 的结合，进而使得循环中 LDL-C 水平升高[6]。

1.2　*促炎作用*　许多研究均证实了炎症反应在心肌梗死中的各个时期均发挥作用，影响心肌愈合和修复[7]。研究发现 PCSK9 可以将白细胞转换为促炎状态，从而导致促炎细胞因子的产生，这些因子在动脉粥样硬化的发展中直接作用。它直接通过 LDL 的促炎性氧化和斑块成分的修饰而发生作用，从而引起细胞因子，趋化因子和黏附分子介导的炎症反应，促进动脉硬化形成与发展[8-9]。已经发现的动脉粥样硬化相关的炎症因子：肿瘤坏死因子-α（tumor necrosis factor-alpha，TNF-α），白细胞介素（interleukin，IL）-6 和 IL-1β，PCSK9 抑制剂都有较好的抑制作用[10]。

1.3　*血小板活化作用*　最近有研究证明 PCSK9 有增强血小板活化的作用。血浆中的 PCSK9 通过与血小板 CD36 结合从而激活下游信号传导途径直接增强血小板活化，血小板活化后可释放血栓素 A2、5-羟色胺等炎性介质，这些炎性介质通过促进血小板黏附和聚集而致动脉粥样硬化，加重微血管阻塞并对心肌梗死后面积扩展有促进作用[11]。

1.4　*凋亡*　PCSK9 可通过 c-Jun 氨基端激酶/p38 丝裂原活化蛋白激酶途径，促进动脉粥样硬化中 ox-LDL 诱导的内皮细胞凋亡，引起内皮功能障碍。同时有研究表明，通过 siRNA 敲除 *PCSK9* 基因可通过 Bcl-2/Bax 途径抑制 ox-LDL 诱导的内皮细胞凋亡，均证明了 PCSK9 促凋亡作用[12-13]。

2　PCSK9 抑制剂的临床应用

临床试验表明，PCSK9 抑制剂与他汀类药物联合应用可以显著降低 LDL-C 水平。同时，众多研究人员也发现 PCSK9 抑制剂在动脉粥样硬化疾病预防中具有巨大潜力。通过降低 LDL-C 水平，PCSK9 抑制剂对动脉血管内的胆固醇沉积和斑块形成有明显的抑制作用，从而降低患者主要不良心脏事件（major adverse cardiovascular events，MACEs）的风险，如心肌梗死和卒中。有研究表示脂蛋白（a）[lipoprotein（a），Lp（a）]是 LDL-C、载脂蛋白（apolipoprotein，Apo）B100 和 ApoA 的复合物，认为其与冠心病发生独立相关，且不受 LDL-C 水平下降影响，而他汀类药物并不具备降低 Lp（a）能力，PCSK9 抑制剂相较于他汀类药物能更好的降低该类脂蛋白水平，从而预防心血管事件的发生[14-15]。并且在众多研究中发现，PCSK9 抑制剂具有除降低 LDL-C 额外的作用，如抑制炎症反应[6,16]、控制血小板活化[17]、调节血管内皮细胞凋亡[12]等。进一步减少动脉硬化的形成，防止斑块破裂，预防 MACEs 发生。

2.1　*PCSK9 抑制剂在高胆固醇血症治疗中的应用*　ODYSSEY 试验[18]是一系列关于 PCSK9 抑制剂疗效和安全性的大型研究，主要是对目前已经上市的依洛尤单抗和阿利西尤单抗两种药物在不同患者群体中的疗效和安全性。其中 ODYSSEY LONG TERM 试验[19]、ODYSSEY FH Ⅰ和Ⅱ试验[20]分别对超高胆固醇血症以及家族性高胆固醇血症患者进行研究，证实 PCSK9 抑制剂在短期内具有良好的降低 LDL-C 疗效，在 24 周内观察 LDL-C 水平较对照组能够降低约 61.9%，MACEs 事件降低 48%，其不仅具有显著的降脂效果并且能够显著减少心血管事件的风险，且耐受性良好，不会增加额外不良反应。ODYSSEY COMBO Ⅰ和Ⅱ试验则证实在最大剂量他汀治疗基础上加用 PCSK9 抑制剂能够进一步降低 LDL-C 且较依折麦布等效果更加显著[21]。

2.2　*PCSK9 抑制剂在动脉粥样硬化疾病预防中的潜力*　研究人员在 ODYSSEY OUTCOMES 试验中对急性冠状动脉综合征人群中使用 PCSK9 抑制剂与基础他汀药物进行比较，结果证实 LDL-C 水平降低约 55%，全因死亡率降低 15%，且 LDL-C≥100 mg/dL（2.6 mmol/L）的患者应用 PCSK9 抑制剂后收益更大[22]。而另一项关于 PCSK9 抑制剂的首个大型多中心双盲的心血管结局研究——FOURIER 研究中，参与人数 27 564，证实了 PCSK9 抑制剂出色的降脂效果，即能够在他汀类药物的基础上进一步降低 LDL-C 高达 59%，绝对血脂水平降低 1.45 mmol/L[23]。并且其子研究 FOURIER-OLE 试验中，在长达 3 年的随访中，证实了使用 PCSK9 抑制剂治疗冠心病患者可以显著降低 MACEs 的发生风险，使心脏事件的发生率减少了约 15%。同时，GLAGOV 试验通过血管内超声（intravascular ultrasound，IVUS）进行观察，在他汀治疗基础上使用 PCSK9 抑制剂治疗能够显著降低斑块的体积和阻塞程度，证实了 PCSK9 抑制剂具有良好的降低斑块大小、逆转斑块作用[24]。

PCSK9 抑制剂作为降脂为主的药物被开发应用于临床，突出的降低 LDL 能力是其关键优势，能够良好的降低心血管事件发生同时具有良好的安全性。PCSK9 抑制剂似乎可以弥补甚至替代他汀类药物，对心血管疾病高危人群起到保护和治疗作用。在冠心病的研究中，炎症反应被认为是参与疾病进展的重要因素。因而有效的控制炎症反应尤为关键。在一项国内的临床研究认为 PCSK9 抑制剂能有效改善心肌梗死患者早期全身炎症反应，明显降低 IL-1β、IL-6、TNF-α 等相关炎性因子水平，进而达到保护心脏的作用[25]。

除了上述试验,还有许多其他研究正在探索 PCSK9 抑制剂的疗效和安全性,如 FURTHER、MENDEL 同样表现出 PCSK9 抑制剂在具有良好安全性同时可以达到更好降脂效果以及预防心血管疾病的显著成效[26-27]。这些大型的临床试验在不同角度证实 PCSK9 抑制剂在冠心病治疗中,有出色的降脂效果的同时,显著降低心血管事件的发生,与他汀类药物相比没有过更多的肝肾功损害以及肌炎、肌痛、糖尿病和神经认知等事件的发生[28]。

3　PCSK9 抑制剂的安全性和副作用

PCSK9 抑制剂通常被认为是相对安全的药物,能够明显降低不良心血管事件发生,不会引起严重的肝肾功能异常,也不会对血糖造成影响[29-30]。但它们可能存在一些副作用。以下是一些常见的副作用和安全性问题。

3.1　*注射部位反应*　由于 PCSK9 抑制剂需要通过注射给药途径使用,一些患者可能会经历与注射相关的反应,如注射部位疼痛、红肿、刺痛或瘀血等[31]。

3.2　*免疫原性反应*　在一些研究和个案报告中,部分患者出现了与 PCSK9 抑制剂免疫原性相关的反应,如过敏反应、荨麻疹、药物疹、皮疹和注射部位肿胀等。一项 SPIRE 试验在进行中也因出现较严重的过敏原性问题而被迫停止[32]。但在目前已上市的依洛尤单抗和阿利西尤单抗的临床实验中这样的不良反应,并没有显著增加[33]。

3.3　*神经认知副作用*　此前的一些研究中,使用 PCSK9 抑制剂的患者可能会出现轻微的神经认知副作用,如记忆力减退或注意力差等[34]。然而,这些观察并不一致,需要更多研究来进一步明确其与药物的关系。并有研究认为与过低水平的 LDL-C 水平有关,但 EBBINGHAUS 试验认为低水平的血浆胆固醇并不会带来认知障碍[35]。这仍需进一步临床实践证明。

4　PCSK9 抑制剂的现状

根据 PCSK9 抑制剂作用机制的不同,将其主要分为在核酸水平上抑制 PCSK9 的药物如小分子干扰 RNA(smallinterfering RNA, siRNA)、反义寡核苷酸(antisense oligoneucleotides, ASOs),抑制 PCSK9 与 LDL-C 和 LDL-R 结合的药物如单克隆抗体(monoclonalantibody, mAb)、模拟抗体蛋白物,以及改变 PCSK9 蛋白催化部位的小分子肽类等[19]。已经上市的有单克隆抗体中阿利西尤单抗和依洛尤单抗。小干扰 RNA 中的英克司兰。其主要应用方式为皮下注射,已经在临床上投入使用,但由于其价格和使用方式的原因,部分患者选择停药。而其他类型 PCSK9 抑制剂正在研究中,许多药物已到达Ⅲ期临床阶段,其应用方式为口服,似乎会更受欢迎[36]。

5　讨　论

随着相关研究的不断深入,自从第一种 PCSK9 抑制剂上市以来,已取得了巨大的研究进展。它们已被广泛运用于高胆固醇血症治疗,并显示出显著的降低 LDL-C 水平的效果。此外,由于其能够改善动脉粥样硬化病变,PCSK9 抑制剂也被认为可能在预防心血管疾病方面发挥重要作用。与他汀类药物的联合应用可以进一步提高治疗效果。尽管 PCSK9 抑制剂在临床应用中显示出显著的优势,但也需要关注其安全性和潜在的副作用。通常,头痛、肌痛等轻微副作用是可控的,并且能够通过调整剂量或治疗方案进行处理。然而,对于长期使用 PCSK9 抑制剂可能存在的安全性问题,仍需进行更加全面的研究和观察。

PCSK9 抑制剂的研究和临床应用仍然面临一些挑战和限制。其中之一是剂型的改进,以提高药物的便利性和患者的依从性。此外,个体化治疗和定制化药物的发展是未来的重要方向。通过研究个体基因差异和生物标记物,可以更好地预测患者对 PCSK9 抑制剂的反应,从而实现个性化的治疗策略。

综上所述,PCSK9 抑制剂的研究进展为心血管疾病治疗带来了希望。通过进一步的研究和临床实践,可以更好地了解其在预防和治疗高胆固醇血症以及心血管疾病方面的潜力,并为制定个性化治疗方案提供更多可靠的依据。

利益冲突　无

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