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降脂药物对动脉粥样硬化斑块逆转的影响及作用机制

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摘　要

冠状动脉粥样硬化斑块的形成与进展是心血管疾病发生的核心病理过程，其破裂引发的血栓形成是冠心病患者不良预后的主要诱因。低密度脂蛋白胆固醇(LDL-C)作为动脉粥样硬化的关键致病因素，是降脂治疗的核心靶点。降脂药物在心血管疾病治疗中具有双重作用，不仅能调节血脂代谢，还可通过其它机制稳定斑块并促进其消退。长期有效降低LDL-C水平，可显著减少心血管事件发生率，改善患者临床预后。本文系统综述了不同降脂策略在冠心病患者群体中表现出的斑块逆转效应及潜在作用机制，以期为冠心病的早期防治与治疗策略提供理论依据。

关键词

降脂药物，冠状动脉粥样硬化，斑块逆转，作用机制

The Effect and Mechanism of Lipid-Lowering Drugs on the Regression of Atherosclerotic Plaques

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Abstract

The formation and progression of coronary atherosclerotic plaques represent the core pathological process underlying the development of cardiovascular diseases, and thrombosis triggered by their rupture is the main inducer of adverse prognosis in patients with coronary heart disease. As a key pathogenic factor of atherosclerosis, low-density lipoprotein cholesterol (LDL-C) is the core target of lipid-lowering therapy. Lipid-lowering drugs exert a dual effect in the treatment of cardiovascular diseases: they not only regulate lipid metabolism but also stabilize plaques and promote their regression through other mechanisms. Long-term effective reduction of LDL-C levels can significantly decrease the incidence of cardiovascular events and improve patients' clinical prognosis. This article systematically reviews the plaque regression effects and potential mechanisms of different lipid-lowering strategies in patients with coronary heart disease, aiming to provide a theoretical basis for the early prevention, treatment, and therapeutic strategy optimization of coronary heart disease.

Keywords

Lipid-Lowering Drugs, Coronary Atherosclerosis, Plaque Regression, Mechanism of Action

1. 引言

冠状动脉粥样硬化是一种慢性炎症性疾病[1]，其病理基础是冠状动脉内膜下脂质沉积、血管平滑肌细胞凋亡及炎症细胞浸润共同驱动的富含脂质斑块形成[2]。当斑块稳定性降低或受到侵蚀时，易破裂并暴露脂质核心，激活凝血系统形成血栓，导致心肌梗死等严重心血管事件，是冠心病患者死亡和致残的主要原因[3]。流行病学与临床研究证实，他汀类药物作为降脂治疗的基石，能够降低低密度脂蛋白胆固醇(LDL-C)水平，其降脂疗效和心血管保护作用已得到充分证实[4]。降脂药物除调节血脂外，还具备稳定斑块、抑制进展及促进消退的独特作用[5]，而斑块消退作为一种潜在的治疗策略，近年来成为心血管领域研究热点[6]，众多临床试验聚焦于此，旨在探索不同干预措施对冠状动脉粥样硬化斑块消退的影响及作用机制[7]。本文总结相关研究，阐述不同干预手段在斑块逆转方面的研究进展，探讨其可能存在的潜在作用机制，为改善心血管疾病患者的预后提供依据。

2. 降脂药物的斑块逆转作用

2.1. 他汀类药物

他汀类药物通过抑制羟甲基戊二酸单酰辅酶 A (HMG-CoA)还原酶，减少内源性胆固醇合成，同时反馈性上调肝细胞表面低密度脂蛋白受体(LDL-R)表达，加速血液中 LDL 的清除，从而有效降低 LDL-C 水平[8]。此外，他汀还具有抗炎、抗氧化、改善内皮功能、抑制炎症反应和稳定动脉粥样硬化斑块等多效性作用[9]。

2.2. 依折麦布

依折麦布是广泛应用于临床的降脂药物[10]，可以特异性结合回肠绒毛刷状缘尼曼－匹克 C1 型类似

蛋白 1 (NPC1L1)，阻断肠道胆固醇吸收[11]。IMPROVE-IT 试验结果显示在 ACS 患者中，依折麦布与他汀联合使用可进一步降低低密度脂蛋白水平并有效改善心血管疾病的预后[12]。PRECISE-IVUS 多中心随机对照试验将 246 例冠心病患者随机分配至阿托伐他汀联合依折麦布治疗组和阿托伐他汀单药治疗组，结果显示联合治疗组和阿托伐他汀单药治疗组患者(LDL-C)水平分别为 1.64 mmol/L 和 1.90 mmol/L ($P < 0.001$)，LDL-C 达标率分别为 72%与 47% ($P = 0.001$)，IVUS 结果显示，冠状动脉斑块发生逆转的患者比率分别为 78%和 58% ($P = 0.004$) [13]。ZIPANGU 试验结果显示，单纯他汀类药物治疗前后斑块体积百分比无显著变化(48.5% ± 10.2% vs. 48.2% ± 10.4%, $P = 0.4$)，但他汀类药物和依折麦布联合治疗的患者明显减少(50.0% ± 9.8% vs. 49.3% ± 9.8%, $P = 0.03$) [14]。因此，该药物单药治疗可在一定程度上降低心血管事件的发生率[15]，与他汀类药物联用可产生协同效应，进一步降低 LDL-C 水平[12]。

2.3. PCSK9 抑制剂

前蛋白转化酶枯草溶菌素 9 (PCSK9)通过与肝细胞表面的 LDL-R 结合，促进其降解，增加血浆 LDL-C 水平[16]。而 PCSK9 抑制剂(如阿利西尤单抗、依洛尤单抗)可阻断这一过程，增加 LDL-R 数量，进而降低 LDL-C 水平[17]。对于接受最大耐受剂量他汀类药物治疗后，LDL-C 水平仍未达标的患者，可使用 PCSK9 抑制剂以降低心血管事件风险[18]。一项近红外光谱研究(2021 年，日本)纳入 53 例有冠状动脉疾病(CAD)病史且接受过 NIRS-IVUS 检查的患者。一组接受 PCSK9 抑制剂和他汀类药物(21 例患者)，另一组仅接受他汀类药物(32 例患者)。结果显示：PCSK9 抑制剂显著降低非罪犯冠状动脉斑块的脂质成分，表明其在调节斑块脂质成分、促进斑块稳定和消退方面具有重要作用，为冠状动脉疾病的治疗提供了新的靶点[19]。PACMAN-AMI 研究(2022 年，欧洲)招募 300 例急性心肌梗死患者，在罪犯血管 PCI 后 24 小时内，在高强度他汀(瑞舒伐他汀，20 mg/日)基础上，患者随机接受阿利西尤单抗(150 mg/2 周，$n = 148$)或安慰剂($n = 152$)，治疗 52 周。连续血管内超声(IVUS)显示，与安慰剂相比，阿利西尤单抗组非梗死相关冠状动脉的斑块逆转更明显，这为急性心肌梗死患者的二级预防提供了新的研究方向[20]。一项关于 PCSK9 抑制剂在急性冠脉综合征患者中疗效的研究(2023 年，欧洲)纳入 265 例 STEMI 或 NSTEMI 患者，PCI 后冠状动脉造影显示非梗死相关动脉近端存在非阻塞性粥样硬化病变(直径狭窄 > 20%且<50%)。患者随机分为两组，治疗组接受每两周皮下注射 150 毫克阿利西尤单抗，对照组注射安慰剂，两组均在高强度他汀类药物治疗基础上随访 52 周。结果发现，斑块体积减少、脂质成分减少和纤维帽增厚的“三联消退”现象的发生与阿利西尤单抗治疗和更高的基线脂质积聚独立相关，表明阿利西尤单抗对特定患者冠状动脉粥样硬化斑块的消退和稳定具有积极作用，为改善此类患者的心血管预后提供了可能[19]。ARCHITECT 研究(2024 年，西班牙)纳入 104 例无临床 ASCVD 的家族性高胆固醇血症患者(中位年龄 53.3 岁，女性 51.9%)，在高强度他汀治疗基础上接受阿利西尤单抗(150 mg/14 天)治疗。研究发现，该治疗对于基线斑块负荷较高及不稳定核心较大的患者，可能产生更大的斑块负荷逆转，这为家族性高胆固醇血症患者的个体化治疗提供了参考[21]。一项荟萃分析(2024 年，美国)纳入 51 项随机对照试验($n = 9113$，22%女性)。高强度降脂治疗组包括他汀(HIS)、HIS + 二十碳五烯酸(EPA)、HIS + 依折麦布、低强度他汀(LIS)、LIS + EPA、LIS + 依折麦布、PCSK9 抑制剂等。研究发现与降脂治疗相关的斑块逆转主要由高强度他汀(HIS)驱动，显著降低斑块总体积(TAV)和百分比体积(PAV)，进一步强调了高强度他汀在斑块消退治疗中的核心地位，同时提示联合其他降脂药物可能是未来研究方向[22]。

2.4. 二十碳五烯酸乙酯(IPE)

二十碳五烯酸乙酯(IPE)最初作为饮食辅助药物用于治疗成人高甘油三酯血症[23]，具有里程碑意义的 REDUCE-IT 试验，该实验(2019 年)纳入 8179 例接受他汀治疗的高 TG 患者(TG 135~499 mg/dL)，随

机给予 IPE 4 g/d 或安慰剂，中位随访 4.9 年。结果显示，IPE 组心血管死亡、心肌梗死等缺血事件风险较安慰剂组显著降低，且冠状动脉斑块脂质成分减少[24]。因此在他汀治疗基础上加用 IPE 可使高 TG (≥150 mg/dL)患者的主要心血管事件发生率显著降低[24]。EVAPORATE 试验(2020 年)纳入 80 例他汀治疗中 TG 持续升高(≥200 mg/dL)的冠心病患者接受 IPE 4 g/d 或安慰剂治疗 18 个月。多层螺旋 CT 显示，与安慰剂相比，IPE 组低密度脂蛋白、斑块体积显著消退[25]。EPA/DHA 与斑块消退相关性研究，该研究(2020 年，美国)纳入 31 例接受他汀类药物治疗的稳定型 CAD 患者，分为两组。一组每天给予 3.36 克 EPA 和 DHA，另一组不使用 EPA/DHA (对照组)。研究表明，EPA 和 DHA 的下游产物——特异性促炎症消退介质(SPM)，通过刺激炎症消退途径，可能预防他汀类药物治疗下 LDL-C 控制良好的 CAD 患者的斑块进展，提示了 EPA 和 DHA 在稳定型 CAD 患者斑块管理中的潜在益处，为心血管疾病抗炎治疗提供了新视角[26]。

3. 探讨斑块逆转的作用机制

3.1. 他汀类药物的多靶点调控机制

斑块逆转涉及清除脂质和坏死核心，恢复内皮功能及抑制血管平滑肌细胞增殖[27]。他汀类药物通过抑制肝细胞 HMG-CoA 还原酶，阻断胆固醇生物合成的关键步骤，降低 LDL-C 水平，延缓疾病进展[28]。其多效性效应可能与斑块逆转密切相关，包括：1) 增加 NO 生物利用度：上调血管内皮一氧化氮(NO)合酶活性，增加 NO 水平，调节血管张力、血小板聚集及血管平滑肌细胞增殖[29]。2) 抗炎与抗氧化效应：减轻全身炎症反应和氧化应激，降低 CRP 水平，减少 TNF-α、IL-6 等促炎因子释放，抑制动脉粥样硬化斑块发展[30]。3) 改变斑块成分：增加致密斑块钙化比例，促进抗炎 M2 巨噬细胞表型，有助于斑块消退、钙化和稳定[31]。尽管这些分子机制令人信服，但在临床常用剂量下，其独立于降低 LDL-C 作用之外的“多效性”对改善心血管的贡献程度仍存争议[32]。

3.2. 依折麦布的肠道胆固醇吸收抑制机制

依折麦布选择性阻断空肠刷状缘 NPC1L1 蛋白，抑制肠道胆固醇吸收，减少跨膜转运，从而降低血清胆固醇水平[33]。研究表明依折麦布治疗可促进动脉粥样硬化斑块消退[34]，其分子机制包括：1) NPC1L1 依赖性途径：依折麦布与 NPC1L1 结合后，改变其构象或干扰其与游离胆固醇的结合[35]。2) 破坏 CAV1-膜联蛋白 2 异复合体：已有研究表明依折麦布在体内有效破坏 CAV1-膜联蛋白 2 异复合体，减少肠细胞胆固醇吸收、乳糜微粒形成和分泌以及胆汁中胆固醇重吸收，耗尽肝脏胆固醇库，上调肝细胞表面 LDL-R 表达，降低血清 LDL-C 水平[36]。其临床获益主要归因于 LDL-C 的额外降低。目前尚缺乏强有力的临床证据表明，在同等LDL-C降低水平下，依折麦布比他汀类药物具有显著独立的多效性优势。其斑块逆转作用可能主要源于对循环 LDL-C 水平的协同强化控制[37]。

3.3. PCSK9 与 NLRP3 炎症小体在动脉粥样硬化中的分子机制

前蛋白转化酶枯草溶菌素 9 (PCSK9)通过与 LDL-R 结合促进其溶酶体降解，导致 LDL-C 积累，与脂质代谢密切相关[38]。PCSK9 在动脉粥样硬化斑块的各种细胞成分中表达，促进炎性细胞因子分泌，调控巨噬细胞炎症反应[39]；同时在促炎环境下刺激血管平滑肌细胞(VSMCs)表达 PCSK9，导致炎症、氧化应激和细胞凋亡，直接促进动脉粥样硬化[40]。NLRP3 是一种细胞质危险信号受体，可被激活形成 NLPR3 炎症小体，促进促炎因子释放，诱导细胞凋亡，驱动动脉粥样硬化发生发展[41]-[43]。PCSK9 和 NLRP3 炎症小体之间可能存在相互作用，在缺氧条件下，可在动脉粥样硬化斑块中共同诱导细胞凋亡发生[44][45]。PCSK9 抑制剂(如阿利西尤单抗、依洛尤单抗)可特异性抑制 PCSK9，增强 LDL-C 清除，减少心血

管事件[46]。值得深入探讨的是，在临床应用中，PCSK9 抑制剂带来的卓越心血管保护作用，是否完全由强效降低 LDL-C 所驱动？要明确区分这两种贡献非常困难，因为局部 PCSK9 抑制剂潜在的多效性机制可能起到协同或修饰作用[47]。

3.4. IPE/EPA 减少心血管事件的多效性作用机制

IPE/EPA 对动脉粥样硬化斑块的作用机制涉及抗炎、抗氧化、减少斑块巨噬细胞积聚、改善内皮功能、抗血小板作用以及增强纤维帽厚度和稳定性，从而对动脉粥样硬化进展和稳定产生有利影响[48]。1) 抗炎作用：EPA 衍生的脂氧合酶代谢物可在体外减弱白三烯 B4 诱导的促炎信号和多形核白细胞迁移[49]，增强巨噬细胞吞噬作用和抗炎细胞因子 IL-10 产生[50]，并抑制中性粒细胞趋化[51]。2) 抗氧化作用：体外研究表明 EPA 抑制载脂蛋白 B 脂蛋白的氧化[52]，阻断胆固醇晶体结构域的形成[53]。3) 改善内皮功能：体外研究表明 EPA 与他汀类药物联用，可增加一氧化氮与过氧亚硝酸盐的比值，促进内皮功能逆转[54]。4) 抗血小板作用：EPA 可促进 ResolvinE1 的酶促形成，调节白细胞外渗，减少血小板聚集，并可能阻断血小板－白细胞初始相互作用[55]。值得注意的是，REDUCE-IT 试验中 IPE 显示出的显著心血管获益，强烈提示 IPE 在临床剂量下确实存在独立于传统脂质参数改善之外的多效性机制。相比之下，STRENGTH 试验中使用的 EPA + DHA 混合物却无法达到相应的疗效，其差异可能源于：① 药物形式与纯度：IPE 作为高纯度的 EPA 乙酯，而 STRENGTH 为 EPA + DHA 混合物，不同化学形式和 DHA 的加入可能影响细胞膜相互作用、胆固醇的转运、代谢途径及最终效应，可能产生反调节作用减弱 EPA 的益处[56]。② 试验人群与 EPA 差异：REDUCE-IT 入选患者心血管风险更高，集中在动脉壁和动脉粥样硬化斑块中的 EPA 更多，更容易产生多效性作用。这些对比突显了 IPE 独特的作用模式，其临床获益很可能是强效抗炎/促消退多效性与适度调脂作用协同的结果[57] [58]。

4. 结论与展望

综上所述，降脂药物能够通过延缓斑块进展、增强其稳定性乃至缩小斑块体积，从而实现动脉粥样硬化斑块的逆转。然而，现有研究多依赖于影像学手段观察到部分治疗策略所带来的斑块逆转现象，其背后的病理生理机制尚未完全阐明。因此，今后有必要探索更多促进斑块逆转的治疗策略，并深入研究其相关的分子机制，特别是不同药物剂量下其多效性机制的相对贡献，以期优化临床治疗路径、确立个体化治疗靶点，从而最终提升心血管疾病患者的预后水平。

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