

残余心血管风险的研究进展

舒浩源

重庆医科大学附属第一医院心血管内科, 重庆

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摘要

即便在当今心血管疾病(CVD)的预防和治疗手段较前已获得显著的改善的情况下(如他汀调脂治疗、抗血小板治疗、控制血压等),大量患者在接受标准治疗后仍存在显著的残余心血管风险(Residual Cardiovascular Risk, RCR),RCR指尽管患者已接受基于指南推荐的标准治疗,但仍存在难以通过现有手段进一步降低的“硬终点”风险(指无法完全消除如心肌梗死、卒中、心血管死亡等心血管事件)。其定义随着对脂质代谢、炎症反应、代谢综合征的深入理解逐步扩展,现已成为心血管风险管理的重要方向。这一概念强调现代医学干预的局限性,并提示需超越传统危险因素管理,关注尚未被充分靶向的病理生理机制。本文通过查阅对比国内外相关文献,就残余心血管风险的相关概念、病理生理机制、相关生物标志物、新兴研究进展及干预策略进行综述,旨在为优化风险管理提供参考。

关键词

动脉粥样硬化, 残余心血管风险, 残余胆固醇, 个体化治疗

Research Progress on Residual Cardiovascular Risk

Haoyuan Shu

Department of Cardiovascular Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing

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Abstract

Even with significant advancements in the prevention and treatment of cardiovascular disease (CVD) today—such as statin-based lipid management, antiplatelet therapy, and blood pressure control—a substantial number of patients still face considerable residual cardiovascular risk (RCR) despite receiving standard guideline-recommended therapies. RCR refers to the persistent risk of “hard endpoints” (such as myocardial infarction, stroke, and cardiovascular death) that remains

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difficult to further reduce with current interventions, even after optimal guideline-directed treatment. The definition of RCR has evolved with deeper insights into lipid metabolism, inflammatory responses, and metabolic syndrome, and it has now become a key focus in cardiovascular risk management. This concept highlights the limitations of modern medical interventions and underscores the need to look beyond traditional risk factor management by addressing underlying pathophysiological mechanisms that remain insufficiently targeted. By reviewing and comparing relevant domestic and international literature, this article provides a comprehensive overview of RCR, including its conceptual framework, pathophysiological mechanisms, associated biomarkers, emerging research advances, and potential intervention strategies. The aim is to offer insights for optimizing risk management approaches.

Keywords

Atherosclerosis, Residual Cardiovascular Risk, Remnant Cholesterol, Personalized Therapy

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1. 背景及流行病学

1.1. 背景：从“达标治疗”到“残余风险”

LDL-C 达标和良好的血压控制是心血管疾病治疗的基石[1]，但仍有较多真实世界的研究表明，即使在血脂及血压控制达标的情况下，动脉粥样硬化性心血管疾病(ASCVD)患者仍存在较高的 MACE 复发率[2]。早在 1994 年，斯堪的纳维亚地区的辛伐他汀生存研究便首次观察到部分患者在 LDL-C 达标的情况下仍存在发生心血管事件的可能[3]，表明存在其他尚未被干预的心血管风险因素。在其之后的 PROVE IT-TIMI 22 试验发现即使 LDL-C 降低至 62 mg/dL，仍有约 22% 的患者出现心血管事件[4]，首次明确了达标治疗后残余风险的存在。2005 年，美国学者 Daniel Steinberg 在他的综述中系统地讨论了他汀治疗后“剩余风险”的机制[5]，标志着 RCR 成为正式术语。

1.2. 残余心血管风险的概念

残余心血管风险(Residual Cardiovascular Risk, 后续简称为 RCR)，指尽管患者已接受基于指南推荐的标准治疗，但经充分治疗后仍有难以通过现有手段进一步降低的“硬终点”(指无法完全消除如心肌梗死、卒中、心血管死亡等心血管事件[6])。2019 年 ESC/EAS 血脂异常管理指南正式将残余风险定义为“传统危险因素达标后仍存在的风险”，并推荐将 Lp(a)、炎症标志物等非传统标志物等作为评估指标。而后在 2021 的 ESC/EAS 指南中继续指出：残余风险不仅包括传统危险因素“残余效应”(如不完全的血压或血糖控制)，还包括非传统因素(如炎症、脂蛋白异常)[7]。其定义随着对脂质代谢、炎症反应、代谢综合征的深入理解逐步扩展，现已成为心血管风险管理的重要方向。这一概念强调现代医学干预的局限性，并提示需超越传统危险因素管理，关注尚未被充分明确的病理生理机制。

1.3. 流行病学

1.3.1. 总体人群风险

2006 年 REACH 注册研究[8]对 68,236 例稳定型动脉粥样硬化患者进行了为期 4 年的随访，研究显

示,即使是在已经接受他汀治疗的达标人群中,心血管事件年发生率仍高达 6.5%。2015 年 IMPROVE-IT 试验对 LDL-C 降至 53 mg/dL 的急性冠脉综合征患者中进行了 7 年的随访,结果表明主要不良心血管事件(Major Adverse Cardiovascular Events, 后简称 MACE)风险仍可达 32.7% [9]。而女性冠心病患者在接受血运重建后,10 年死亡率较男性高 15% [10]; 大于 75 岁急性心梗患者在 1 年内的再住院率可高达 40% [11]。

1.3.2. 特定高危因素亚组

既往的 LEADER 试验表明即便是在血糖控制良好的 2 型糖尿病患者中,人群的心血管死亡风险仍较非糖尿病人群高 2~4 倍 [12]; CRIC 研究对 eGFR < 60 mL/min/1.73m² 的慢性肾病(CKD)患者进行了为期 5 年的随访,其总体心血管事件风险为 28.3%,显著高于肾功能正常人群(9.1%) [13]。

1.3.3. 地域差异

一项全球性前瞻性队列研究对来自全球共计 21 个国家(涵盖高、中、低收入国家)的超过 135,000 名参与者进行了为期平均 9.3 年的随访。低收入国家患者的心血管残余风险是高收入国家的 1.8 倍,可能与饮食习惯、医疗资源不足、危险因素控制率低(如血压达标率仅 10%)相关 [14]。

2. 残余心血管风险的机制及靶点

RCR 的靶点多样,其病理生理机制复杂且多维度,涉及了脂质代谢异常、炎症与免疫失调、代谢紊乱、内环境高凝倾向等多个方面,且各方面不同的信号通路间存在交叉影响,以下将分类讨论。

2.1. 脂质代谢异常

2.1.1. 残余胆固醇(Remnant Cholesterol, RC)

研究表明,残余胆固醇是动脉粥样硬化的独立危险因素 [15]。残余胆固醇是指血液中富含甘油三酯的脂蛋白(Triglyceride-Rich Lipoproteins, TRL)在代谢过程中形成的“残余颗粒”中所携带的胆固醇。这类残余颗粒体积较小(直径约 30 nm~80 nm),因此更易穿透血管内皮进而滞留于动脉内膜 [16]。这些脂质分子被巨噬细胞吞噬后在胞内堆积,形成泡沫细胞,大量的泡沫细胞在血管内皮堆积形成脂质条纹乃至脂质斑块,大量的脂质沉积进而诱发血管内炎症反应,从而增加不良心血管事件发生的风险。哥本哈根城市心脏研究表明:受访人群中残余胆固醇水平每升高 1 mmol/L,心肌梗死的风险增加约 2.8 倍 [17]。2020 年哥本哈根城对 25,480 名未接受降脂治疗的心梗受试者进行了进一步的研究,结果表明由 VLDL 胆固醇主导的心血管事件约占据了全部 apoB 脂蛋白相关心肌梗死风险的 50% [18]。

2.1.2. 脂蛋白(a)

Lp(a)由 LDL 样颗粒与载脂蛋白 a [apo(a)]通过二硫键连接而成。其中 apo(a)与纤溶酶原高度同源,可抑制纤溶活性并促进血栓形成 [19] [20]。其主要的致动脉粥样硬化机制包括氧化修饰与炎症激活两方面 [21]。Lp(a)易被氧化的特性更容易促进泡沫细胞形成 [22],与此同时 apo(a)也可通过结合氧化磷脂(OxPL)激活内皮细胞 NF- κ B 通路,促进 IL-6 等促炎因子的释放,介导免疫炎症反应 [23]。2018 年美国医学会杂志中的一项孟德尔随机化分析显示: Lp(a)水平每降低 100 nmol/L,冠心病风险可以降低 29% [24],对其作为冠心病治疗靶点的潜在价值给予了肯定和支持。

2.1.3. HDL 功能

高密度脂蛋白(HDL)是由多种脂质和脂蛋白组成的复合体,正常结构的 HDL 具有保护心血管的功能 [25]。但临床研究表明,应用胆固醇酯转移蛋白(CETP)抑制剂特异性升高血浆 HDL-C 水平非但不能改善心血管结局,反而增加了心血管事件和死亡风险,也不能对家族性高胆固醇血症患者的动脉粥样硬化

发展起到明显的改善[26] [27]。因而提出了 HDL 功能异常影响心血管事件的学说, 近年来胆固醇流出力(CEC)被视为胆固醇逆转过程中反应 HDL 亚类整体功能的指标。Rohatgi 等在 2924 例无心血管疾病的人群中研究发现, 胆固醇流出能力最高分位人群心血管事件的发生率较最低分位人群可降低 67%, 提示 CEC 可能是冠心病新的风险预测因子及治疗靶点[28]。

2.2. 炎症与免疫失调

2.2.1. NLRP3 炎症小体

NLRP3 炎症小体是一种多蛋白复合物, 在调节先天免疫系统和炎症信号传导中发挥着关键作用, 其形成通路包括胆固醇结晶与氧化低密度脂蛋白(ox-LDL)经 TLR4/NF- κ B 通路的诱导转录及组织蛋白酶 B 等物质促使复合体组装, 最终在与募集接头蛋白 ASC 及 pro-caspase-1 结合后形成具有功能的炎症小体[29] [30]。其可催化前体白细胞介素转化为活性形式, 同时促进 IL-1 β 和 IL-18 释放, 活化的 IL-1 β 可通过 MyD88/IRAK4 通路, 促进血管内皮黏附分子(例如 VCAM-1)的表达, 进而增强单核细胞浸润介导巨噬细胞死亡并释放促炎内容物(如 HMGB1), 驱动斑块进展, 加速动脉斑块的进展与不稳定性[31]。CANTOS 试验显示靶向抑制 NLRP3 炎症小体的下游效应分子可显著降低心血管事件风险, 支持 NLRP3 炎症小体在动脉粥样硬化中所具有的关键作用。

2.2.2. IL-6 通路

白介素(IL-6)是重要的炎症细胞因子之一, 可以由多种类型细胞合成和分泌, 包括单核细胞、T 细胞、成纤维细胞和内皮细胞[32]。肝脏可通过 IL-6R 信号上调 CRP 等急性期蛋白的合成及升高纤维蛋白原等促凝因子水平加重内皮功能障碍, 促进血栓形成。IL-6 还可与 TNF- α 共同作用, 激活 JNK 和 IKK β 通路, 使 IRS-1/2 的丝氨酸位点磷酸化, 阻碍其酪氨酸磷酸化及下游 GLUT4 转运, 造成胰岛素信号通路障碍, 加重胰岛素抵抗[33] [34]。另外, IL-6 在胞膜和可溶性受体的信号传导中作用不同, 通过膜结合受体的经典 IL-6 信号通路主要起到再生和保护性的作用, 而可溶性 IL-6R 的 IL-6 反式信号通路通常被认为是促进自身炎症水平升高的主要通路。故对反式信号通路的特异性阻断相较于对 IL-6 通路的完全阻断存在更大的获益[35]。

2.3. 代谢综合征

代谢综合征(Metabolic Syndrome, MetS)是指人体的蛋白质、脂肪、碳水化合物等物质发生代谢紊乱的病理状态, 是一组复杂的代谢紊乱症候群, 其核心病理生理机制与心血管事件密切相关。

2.3.1. 胰岛素抵抗

胰岛素信号传导链是维持葡萄糖稳态、脂质代谢平衡及血管功能的核心通路。因其传导功能障碍引发的胰岛素抵抗不仅是 2 型糖尿病(T2DM)的核心病理机制, 也与动脉粥样硬化等心血管疾病密切相关。信号通路障碍机制涉及胰岛素受体底物浓度下降、胰岛素受体敏感性降低、炎症通路过度激活等多个方面[36] [37]。且即使在通过降糖、降压、调脂等传统治疗控制了基本危险因素的情况下, 胰岛素抵抗异常仍可通过内皮功能障碍及心肌代谢重构等方面对 RCR 产生影响[38]。另外, 糖尿病患者体内的小血小板 P2Y₁₂ 受体表达上调, 可导致阿司匹林或氯吡格雷治疗后残余血小板活性升高, 出现抗血小板药物抵抗[39]。

2.3.2. 冠状结构(CLS)及脂肪组织炎症

ACCORD 研究对 10,251 名 2 型糖尿病患者的研究表明, 强化降糖(HbA_{1c} < 6.0%)与标准治疗(HbA_{1c} 7.0%~7.9%)相比并未显著降低心血管事件风险, 且全因死亡率高于标准组, 提示 MACE 风险除代谢紊乱

因素以外,也可由如炎症、氧化应激等残余风险机制主导[40]。而脂肪组织除能量储备功能外也同样具备活跃的内分泌功能[41]。在代谢异常的患者中,过度肥大的内脏脂肪细胞常导致局部缺氧及 HIF-1 α 通路的异常激活,促进促炎因子(如 MCP-1、IL-6)分泌,形成巨噬细胞浸润的炎症环境,进而导致全身血管炎症反应及自身免疫功能紊乱[42]。CLS 是巨噬细胞吞噬脂肪细胞的脂肪微环境,其在内脏脂肪组织(VAT)中的组织学密度被认为可用于预测肥胖的代谢紊乱进展。研究表明,肥胖人群中的 CLS 密度明显更高,可占组织体积的 3.9%,而在非肥胖人群中其组织占比仅为 0.46% [43]。

2.3.3. 三甲胺-N-氧化物(Trimethylamine N-Oxide, TMAO)

TMAO 是一种由肠道微生物代谢胆碱、左旋肉碱等膳食成分产生的代谢产物,近年来被证实与心血管疾病密切相关,其机制不仅包括通过调控胆固醇代谢和炎症反应促进动脉粥样硬化进展[44],还能通过调控血小板上的钙信号通路、抑制 NO/cGMP 通路以及协同膜受体等作用促进血小板的异常活化,激活全身性低度炎症反应[45];此外,其还能促进促炎细胞因子(如 IL-6、TNF- α)释放,间接增强血小板活性,最终诱发血栓形成。

2.4. 高凝倾向

2.4.1. 血小板高反应性(HPR)

HPR 是指血小板在体外或体内对激活剂(如 ADP、胶原、花生四烯酸)的反应性显著增强,导致血小板过度活化,表现为血小板过度聚集和促血栓形成倾向[46]。在接受抗血小板治疗的患者中, HPR 可显著增加血栓事件风险,心血管残余风险人群中约 20%~30%存在 HPR;在 PCI 术后患者的随访研究中,该类患者支架内血栓风险可较对照组增加 2~3 倍[47],因此,识别和管理 HPR 对于改善 ACS 患者的预后具有重要意义。

2.4.2. 微血管功能障碍

微血管功能障碍(Microvascular Dysfunction, MVD)是稳定型冠心病患者再发 MACE 的独立预测因子,其定义为直径小于 500 μm 的小血管结构或功能异常,通常表现为血管内皮依赖性舒张功能受损、血管通透性增加、血管重塑及灌注异常,病理机制通常与氧化应激和炎症反应密切相关。微血管病变可导致心肌灌注储备(CFR)下降,增加再发 MACE 风险[48]。

3. 管理策略

3.1. 生活管理

戒烟限酒作为一项传统的心血管疾病预防手段被各个地区提倡,而饮食管理在心血管残余风险的调控中同样起着至关重要的作用。研究显示,合理的饮食调配可影响脂质摄入及体内炎症水平,显著降低残余心血管风险。PREDIMED 试验显示,地中海饮食使主要心血管事件风险降低 30% (HR = 0.70, 95% CI 0.54~0.92) [49]。而限时进食(Time-Restricted Eating, TRE)可以通过调节进食带来的血糖波动对胰岛素分泌的影响,改善胰岛素敏感性和血压[50]。除此之外,每周 ≥ 150 分钟中等强度有氧运动(如快走、游泳等)可显著降低内脏脂肪和残余胆固醇水平。

3.2. 综合血脂管理

CTT 分析显示, LDL-C 每降低 1 mmol/L 可使主要心血管事件风险降低 22%,而作为目前 LDL-C 管理基石的他汀药物的降脂效果存在局限性,具体表现为:他汀类药物剂量每增加一倍, LDL-C 水平仅进一步降低约 6%,表明单纯增加他汀剂量可能无法显著提高降脂效果,揭示了联合其他降脂药物治疗的必

要性[51]。依折麦布 + 辛伐他汀的联合治疗可使 ACS 患者 7 年 MACE 风险降低 6.4% [9]，FOURIER 试验及 ODYSSEY OUTCOMES 试验同样表明在他汀基础上加用 PCSK9 抑制剂可有效降低主要终点风险 [52] [53]。除传统的降 LDL-C 治疗外，针对 Lp(a) 的治疗策略同样也得到了广泛关注：以英克斯兰及奥尔帕西兰为代表的 siRNA 类药物可显著降低载脂蛋白水平 [54]，靶向 apo(a) mRNA 的反义寡核苷酸类药物 (Pelacarsen) 2 期临床研究数据提示其可将脂蛋白(a)降低 80% [55]。这些药物的成功开发将为高 Lp(a) 患者提供全新的治疗选择。

3.3. 抗炎治疗

3.3.1. 秋水仙碱

2019 年 Jean-Claude Tardif 等在秋水仙碱心血管预后试验(colchicine cardiovascular outcomes trial, COLCOT)中发现，经 0.5mg 秋水仙碱治疗后，急性心肌梗死患者(起病时间 < 1 月)的首次心血管事件发生率较安慰剂组可降低 23%，而总缺血性心血管事件的风险则可降低达 34%，其作用机制与秋水仙碱的抑制微管聚合、阻断 NLRP3 活化相关[56]。但秋水仙碱与 ARB 类药物同经肝脏代谢，二者均有致肾功能恶化的风险，目前尚无大规模的临床研究探索二者合用对肾功能影响，故在长期使用 ARB 类药物的患者中加用秋水仙碱应当谨慎。

3.3.2. 免疫制剂

卡拉单抗(Canakinumab)是一种人源性单克隆抗体，其可选择性地阻滞 IL-1 β 与 IL-1 受体的结合，2017 年的 CANTOS 试验对 10,061 例存在心血管事件且 C 反应蛋白(hsCRP)水平升高的患者进行了研究，结果显示，使用卡拉单抗 150 mg 组和 300 mg 组患者的心血管事件风险较对照组分别降低 15%和 14% [57]。2021 年的 RESCUE 实验中，使用 ziltivekimab 治疗 12 周的患者 hsCRP 的中位水平较对照组存在显著降低，提示了其在合并肾功能不全的冠心病患者中的治疗潜力[58]。

3.4. 代谢干预

代谢紊乱是 RCR 的重要驱动因素，以 SGLT2 抑制剂和 GLP-1 受体激动剂为代表的代谢调节药物已被证实可通过血糖控制及多个靶器官的保护作用降低心血管风险[59] [60]，近年来肠道环境对心血管疾病的影响逐渐得到重视，通过补充特定益生菌改善肠道菌群环境可能是心血管疾病预防和治疗的新思路。

肠道菌群调节

嗜粘蛋白阿克曼氏菌(*Akkermansia muciniphila*，以下简称 AKK)是一种于 2004 年从人类粪便样本中分离得到的椭圆形革兰氏阴性细菌。该菌定植于人类肠道黏膜层，能够利用肠道黏液层中的黏蛋白作为其主要营养来源。研究表明，AKK 通过增强肠道屏障功能，发挥抗炎作用，并在改善血糖稳态和胰岛素敏感性方面具有潜在功效，该菌的生长和定植与多酚类物质及鱼油的摄入密切相关，因此膳食中增加鱼油、浆果等多酚含量丰富的食物可能有助于提升肠道内 AKK 的丰度[61] [62]。此外，氧化三甲胺(TMAO)的前体物质三甲胺(Trimethylamine, TMA)也主要由肠道特定微生物群(如梭菌属 *Clostridia*、普雷沃菌属 *Prevotella* 等)代谢产生，其经肠道吸收后在肝脏中转化为 TMAO [63]。通过补充特定益生菌竞争性改善肠道菌群组成，可有效干预肠道微环境，降低有害菌群丰度，从而减少 TMAO 的生成。

3.5. 血栓预防

血栓预防主要通过抑制血小板活化或阻断凝血级联反应，从而减少动脉或静脉系统血栓形成，最终降低心血管不良事件的发生风险。目前临床常用的预防策略主要包括以阿司匹林、氯吡格雷为代表的抗血小板治疗，以及以华法林、利伐沙班为代表的抗凝治疗。然而，在高出血风险患者中，血栓预防治疗

往往面临挑战。血小板蛋白酶活化受体-1 (protease-activated receptor-1, PAR-1)拮抗剂作为一种新型治疗药物,因其能够特异性抑制凝血酶介导的血小板活化而受到广泛关注[64]。此外,基于凝血因子 XI (FXI)的靶向抗血栓药物通过特异性结合 FXI 并将其稳定在酶原构象,从而有效抑制其被 FXIIa 或凝血酶激活[65]。与传统的抗血栓治疗方案相比,这类新型靶向药物在保持抗血栓疗效的同时,具备更低的出血风险。

4. 展望

尽管当前心血管疾病管理已显著改善血脂、血压、血糖等传统危险因素水平,但残余心血管风险仍持续存在,揭示了同类疾病表现下深层病理机制的异质性以及传统干预手段的局限性。现有的 RCR 治疗仍缺乏针对非传统危险因素发生机制的有效干预,且虽基因、代谢组相关检查技术为 RCR 分型提供了可能,但其检测项目复杂、成本高昂,限制了临床转化应用。因此,亟需开发具有良好成本效益的临床实用型生物标志物检测体系,以促进 RCR 评估的临床普及。未来研究需通过整合新型生物标志物、探索开发精准靶向疗法、优化“药物 + 生活方式”多模态干预策略,实现 RCR 的个体化风险评估与精准治疗。

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