·综　述·

动脉粥样硬化性心血管疾病高危人群胆固醇管理的临床研究进展

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[摘　要]　严格控制胆固醇水平可以有效减少人群心血管病事件的发生,低密度脂蛋白胆固醇升高是动脉粥样硬化性心血管疾病的独立危险因素,可作为衡量胆固醇控制水平的主要指标。传统的管理胆固醇药物包括他汀类、胆固醇吸收抑制剂、胆酸螯合剂、贝特类临床疗效确切,而新型降胆固醇药物包括前蛋白转化酶枯草溶菌素9抑制剂、微粒体甘油三酯转运蛋白抑制剂、反义寡核苷酸(ApoB-100合成抑制剂)等同样取得了不错的临床疗效。文章将对胆固醇药物特点及其不良反应进行综述,以期找出最合理的胆固醇管理方案。

[关键词]　动脉粥样硬化性心血管疾病;低密度脂蛋白胆固醇;他汀类;前蛋白转化酶枯草溶菌素9抑制剂

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Clinical research of cholesterol management for the people with high-risk atherosclerotic cardiovascular disease

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[**Abstract**]　Control of cholesterol levels can reduces the incidence of atherosclerotic cardiovascular disease(ASCVD). Increased low-density lipoprotein cholesrerol has been an independent risk factor of ASCVD. Statins, cholesrerol absorption inhibitor, bile acid sequestrant have been proved effectively for reduction of low-density lipoprotein cholesterol. New type therapeutic drugs proprotein convertase subtilisin/kexin type 9 inhibitors, microsomal triglyceride transfer protein inhibitor, antisense oligonucleotide inhibitors, peroxisome proliferator-activated receptor-α have also achieved clinical benefit in recent clinical trials. In this article, we will review the efficacy and safty of cholesterol-lowering drugs, so that we can find out the most effective plan of cholesterol management.

[**Key word**]　atherosclerotic cardiovascular disease; low-density lipoprotein cholesrerol; statin; proprotein convertase subtilisin/kexin type 9 inhibitor

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1　研究背景

《中国心血管病2018》报告指出,中国成人胆固醇水平呈现逐年上升的趋势,对中国31个省163 461例成人胆固醇水平调查显示,年龄≥18岁的成人平均胆固醇水平高达4.7 mmol/L[1]。低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)升高是动脉粥样硬化性心血管疾病的独立危险因素,每降低1 mmol/L的LDL-C,心血管疾病的总死亡率和患病率下降22%[2]。基于多项大型临床研究结果,2019欧洲心脏病杂志(ESC)和欧洲动脉粥样硬化学会(EAS)推荐对降低LDL-C的靶标值作出更为严格的管理,新版指南依据SCORE量表将需要进行降胆固醇治疗的目标人群分为极高危、高危、中危以及低危4类,其中对极高危的动脉粥样硬化性心血管疾病(atherosclerotic cardiovascular disease, ASCVD)人群,

LDL-C推荐靶标值为<1.4 mmol/L且降幅>50%,而对于2年内有主要不良心血管事件发生的极高危ASCVD人群,则可考虑降低为LDL-C<1.0 mmol/L,对于高危ASCVD人群推荐LDL-C靶标值为<1.8 mmol/L且降幅>50%,而中、低危人群的LDL-C靶标值分别为<2.6 mmol/L、<3.0 mmol/L[3-6]。本文将对降胆固醇药物的特点及不良反应进行综述,以期找出最合理的治疗方案。

2 胆固醇药物治疗

2.1 他汀类

他汀类药物通过竞争性抑制3-羟基-3-甲基戊二酸单酰辅酶A(HMG-CoA)活性,降低肝脏中胆固醇的合成。细胞内胆固醇浓度的降低导致肝细胞表面低密度脂蛋白受体(low-density lipoprotein receptor,LDLR)表达,使得从血液中提取的低密度脂蛋白(low-density lipoproteim,LDL)量增加,致使循环LDL-C浓度降低。降低LDL-C水平是他汀类药物预防ASCVD的主要机制,除此之外他汀类药物抗炎和抗氧化作用同样与降低ASCVD发生率相关[7-9]。他汀类药物在一级和二级预防中显著降低ASCVD的发病率和死亡率。荟萃分析共纳入26个随机对照试验共17 000例患者,结果表明LDL-C每降低1 mmol/L可降低5年全因死亡率10%、心血管死亡率20%、主要不良心血管事件(major adverse cardiovascular events,MACE)23%以及卒中风险17%,对人群的服药时间进行亚组分析,结果表明他汀类药物服药时间越长获益越大,坚持服药1年以上的人群ASCVD发生率下降幅度高于只服药1年的人群。研究表明,对非糖尿病且10年ASCVD发生风险<7.5%的人群进行了20年的随访,持续口服他汀类药物可使全因死亡率下降18%[10]。Meta分析纳入28项随机对照试验,研究结果表明>75岁的人群坚持口服他汀类药物依然可有效较少MACE事件的发生[11],而对于有高胆固醇血症的青少年,他汀类同样表现出了良好的安全性与耐受性[12]。横纹肌溶解是他汀类药物最严重的不良反应,发生率约为1/10万~3/10万,单纯肌肉疼痛发生率约10%~15%,最新研究表明其可能是一种免疫介导的坏死性炎性肌病[13]。他汀类虽可引起肝酶升高,但鲜有实质性的损害,而新发糖尿病的发病风险主要呈剂量依赖性,他汀类药物不会增加罹患癌症的风险[14-15]。

2.2 胆固醇吸收抑制剂

依折麦布是一种抑制肠道摄取胆固醇而不影响脂溶性营养素吸收的降脂药物。依折麦布通过抑制胆固醇吸收(最可能通过与NPC1L1蛋白相互作用),降低了脂蛋白胆固醇在肝脏中的循环量,肝脏反应性上调LDLR,从而导致血液中清除更多的LDL,单药依折麦布可降低高胆固醇血症患者LDL-C 15%~22%[16-17]。在IMPROVE-IT试验研究中,18 144例患者随机分为他汀类或他汀加依折麦布组,随访7年共5 314例患者存在ASCVD事件,辛伐他汀联合依折麦布组ASCVD事件减少170例,辛伐他汀组的平均LDL-C为1.8 mmol/L,而服用依折麦布联合辛伐他汀的患者平均LDL-C为1.4 mmol/L,并且联合用药组缺血性卒中的发生率降低了21%,该实验的亚组分析指出对于糖尿病或具有ASCVD高风险的患者辛伐他汀联合依折麦布表现出了更好的疗效[3,18]。对于年龄≥75岁的老年人,依折麦布作为一级预防用药,具有潜在的预防ASCVD事件的作用,但还需进一步验证[19]。当治疗目标对他汀类药物不能耐受或即使使用最大剂量仍然无法有效控制LDL-C时,依折麦布可作为二线治疗与他汀类药物联合使用。依折麦布的不良反应有肝酶升高和肌肉痛,尚未发现严重的不良反应。

2.3 前蛋白转化酶枯草溶菌素9(proprotein convertase subtilisin/kexin type 9,PCSK9)抑制剂

PCSK9是一种含丝氨酸的蛋白,由肝细胞合成分泌,PCSK9与LDL竞争性结合LDLR,导致机体通过溶酶体降解LDL的水平降低,引起血浆LDL浓度升高。利用单克隆抗体PCSK9抑制剂,降低血浆中PCSK9的水平,导致肝细胞表面LDLR表达的增加,达到降低循环LDL的效果[20]。目前批准上市的PCSK9抑制剂是两种完全的人单克隆抗体阿莫罗布单抗(Alirocumab)和依洛尤单抗(Evolocumab)。GLAGOV试验结果表明在患者已经接受他汀类治疗的基础上,加用Evolocumab可有效减少冠状动脉粥样硬化斑块体积,但并不能改变斑块的组成成分[21-22]。他汀类药物可增加循环PCSK9水平,因此PCSK9抑制剂与他汀类联合用药可增加疗效[23-24]。最新临床试验表明PCSK9抑制可以有效降低高危ASCVD患者的LDL-C水平,并减少ASCVD事件的发生[25-28]。两项大型的多中心临床试验对比了PCSK9抑制剂联合他汀类与单药他汀类的疗效,并已完成随访。在FOURIER试验中,27 564例已经接受他汀类药物治疗但LDL-C水平仍然高于1.8 mmol/L的ASCVD患者随机分为Evolocumab组或安慰剂组对照组。Evolocumab在48周时LDL-C的中位值从基

线时的2.38 mmol/L降低到平均0.78 mmol/L。经过平均2.2年的随访，Evolocumab治疗显著降低了主要终点的风险（复合心血管死亡、心肌梗死、卒中、不稳定心绞痛住院或冠状动脉血管重建）15%，但是两组的全因死亡率和心血管死亡率无差异[4]。ODDYSSEY试验纳入了18 924例1年内发生过急性冠脉综合征或不稳定心绞痛的患者，虽然已接受最大耐受剂量他汀类药物治疗，但LDL-C仍然≥1.8 mmol/L，试验组加用Alirocumab，对照组给予安慰剂。试验组12个月时LDL-C的平均水平从2.38 mmol/L降低到1.24 mmol/L。在平均2.8年的随访后，主要结果（包括冠心病死亡、非致死性心肌梗死、缺血性中风或需要住院治疗的不稳定心绞痛）相对降低15%[5]。此外，在ODDYSSEY试验中联合用药组降低了全因死亡率，减少了再住院的人数，但不能降低心血管死亡率，但该结果还需要进一步临床试验进行验证[29-31]。现有临床研究结果表明尽可能地降低LDL-C依然是预防ASCVD的有效手段，尤其是那些有新发心梗的患者[32]。虽然有一些案例报道PCSK9抑制剂会引起患者的认知障碍，但是EBBINGHAUS研究结果表明PCSK9抑制剂并不会增加神经系统损害，这与FOURIER和ODDYSSEY试验的安全性终点一致[33]。最常见的不良反应为注射部位的瘙痒及流感样症状。考虑到成本效益的问题，PCSK9抑制剂的使用尚难普及[34-35]。

2.4　微粒体甘油三酯转运蛋白（microsomal triglyceride transfer protein，MTP）抑制剂

MTP将甘油三酯（TG）和磷脂从内质网转移到载脂蛋白B（ApoB），这是极低密度脂蛋白（very low density lipoprotein，VLDL）形成的必要步骤，抑制MTP可以防止VLDL在肝脏和肠中的形成[36]。MTP抑制剂洛美他派（Lamitapide）更多的用于家族性高胆固醇血症患者的治疗，同时作为他汀类的辅助治疗可有效降低LDL-C的水平[37-38]，但是该药物对ASCVD结局的影响尚未确定[39]。洛美他派的使用可能会引起肝脏脂肪含量的增加，以及胃肠道反应，胃肠道不良反应呈剂量依赖性，但会随着药物使用时间的延长而降低[40]。因此，使用洛美他派的患者需了解药物，做好定期检测肝功能指标的准备。

2.5　反义寡核苷酸

反义寡核苷酸米泊美生（Mipomersen），能够结合ApoB-100上的信使RNA（mRNA），引发mRNA分子的选择性降解。经皮下注射后，寡核苷酸优先转运到肝脏，与特定的mRNA结合，阻止ApoB的翻译，从而减少致动脉粥样硬化的脂质和脂蛋白的产生，包括LDL-C。对于高LDL-C血症合并ASCVD的患者，米泊美生可有效降低LDL-C水平[41]。米泊美生可以降低家族性高胆固醇血症患者的LDL-C，并有潜在的降低ASCVD的效果[42]。尽管可以有效降低LDL-C，但是注射部位反应、肝脂肪变性、肝酶升高和流感样症状等安全终点事件的增加，可能会极大限制米泊美生的使用[43]。

2.6　其他胆固醇管理药物

靶向抑制PCSK9的小分子干扰RNA（siRNA）：在一项入组了1 617例ASCVD或高风险的ASCVD患者的临床研究中，这些患者尽管接受最大耐受剂量他汀类药物（联用或不联用依折麦布）但LDL-C水平仍升高。在该研究中，受试人群在0、3个月各皮下注射1次Inclisiran（一种siRNA制剂），此后每6个月皮下注射1次，结果表明Inclisiran可持续降低LDL-C水平超过1年，且尚未发现任何不良反应，该试验还对比了单倍剂量（150 mg）与双倍剂量（300 mg）药物注射的临床结果，使用双倍剂量的人群LDL-C水平更低，且不会增加不良反应[44-45]。

ATP-柠檬酸裂解酶（ATP citrate lyase，ACL）抑制剂：在他汀类不耐受的人群中ACL联合依折麦布，可有效降低LDL-C水平，并可降低高敏C反应蛋白（hsCRP）[46]。研究表明，在最大耐受他汀类的基础上加用ACL，可降低LDL-C 19.2 mg/dL，且不会增加不良反应事件[47]。

除LDL-C的管控外，提高血浆高密度脂蛋白胆固醇（high-density lipoprotein cholesterol，HDL-C）和降低脂蛋白Lp（a）的水平同样可以有效预防ASCVD事件。胆固醇酯转移蛋白抑制剂（cholesteryl ester transfer protein inhibitors，CETP）是血浆HDL-C的主要调节器。研究表明，安塞曲匹（Anacetrapib）可以提高HDL-C水平104%，降低LDL-C 17%，并在平均随访4.1年后减少了9%的MACE，但由于该试验纳入30 000万人，最终因绝对获益较低，该药物未能成功上市[48]。在稳定的他汀类治疗基础上，加用安塞曲匹，与安慰剂对照组相比可降低LDL-C 37%，提高HDL-C 118%，但是在减少MACE方面两组并没有差异[49]。Meta分析结果表明CETP类药物可以提高血浆HDL-C 100%~130%，降低LDL-C约30%，有减少心血管死亡率的趋势，但并不能减少全因死亡率[50]。最新研究表明对于Lp（a）>90~100 mg/dL的人群，Lp（a）减少80%~90%可降低ASCVD事件15%~20%，Lp(a)绝对值降低50~90 mg/dL，可降低ASCVD事

件20%~40%,Lp(a)绝对值降低65.7 mg/dL所带来的获益与LDL-C降低38.67 mg/dL相当[51-53]。由此可见寻找可有效降低Lp(a)的治疗手段非常有必要。研究表明,PCSK9抑制剂可降低Lp(a)水平26.9%,但这并未降低心血管疾病的风险,但是在该试验中Lp(a)降低>37 nmol/L时,发病人群明显减少[54]。对于Lp(a)高于正常值或有基础心脏病的人群,反寡义核苷酸可有效降低血浆Lp(a)水平,在以20 mg/周注射时,可降低血浆Lp(a)80%,但是其是否可以减少ASCVD事件需要进一步验证[55]。

3 总 结

目前最新的大型临床研究以及指南的数据均来自国外,我国尚缺乏相关领域的实践。事实上关于ESC与EAS对于高危ASCVD人群LDL-C<1.4 mmol/L的指南推荐,是否合乎我国国情尚存疑虑。赵冬教授团队对我国普通人群进行了长达20年的队列研究随访,分析LDL-C水平与ASCVD、肿瘤性死亡以及出血性脑卒中之间的关系,结果显示:LDL-C水平与ASCVD风险正相关,与肿瘤性死亡不相关,与出血性脑卒中负相关。且LDL-C <1.8 mmol/L相关的出血性脑卒中风险远远高于LDL-C≥1.8 mmol/L相关的出血性脑卒中风险(HR:6.10 *vs.* 3.77),此结果在高血压人群中更加显著[56]。降低胆固醇水平可有效减少ASCVD事件的发生,而LDL-C仍然是现阶段治疗的主要靶点,对于血压正常的患者,建议强化治疗LDL-C<1.4 mmol/L,而对于血压高的患者需要同时控制好血压。另外依折麦布、PCSK9抑制剂等与他汀类联合用药可更好地降低LDL-C水平,有减少ASCVD的趋势,联合用药降胆固醇或许是更好的治疗选择策略。

[参考文献]

[1] 胡盛涛,高润霖,刘立生,等.《中国心血管病报告2018》概要[J]. 中国循环杂志,2018,34(3):209-220

[2] BAIGENT C,BLACKWELL L,EMBERSON J,et al. Efficacy and safety of more intensive lowering of LDL cholesterol:a meta-analysis of data from 170,000 participants in 26 randomised trials[J]. Lancet,2010,376(9753):1670-1681

[3] CANNON C P,BLAZING M A,GIUGLIANO R P,et al. Ezetimibe added to statin therapy after acute coronary syndromes[J]. N Engl J Med,2015,372(25):2387-2397

[4] SABATINE M S,GIUGLIANO R P,KEECH A C,et al. Evolocumab and clinical outcomes in patients with cardiovascular disease[J]. N Engl J Med,2017,376(18):1713-1722

[5] SCHWARTZ G G,STEG P G,SZAREK M,et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome[J]. N Engl J Med,2018,379(22):2097-2107

[6] TASK FORCE MEMBERS,ESC COMMITTEE FOR PRACTICE GUIDELINES (CPG),ESC NATIONAL CARDIAC SOCIETIES. 2019 ESC/EAS guidelines for the management of dyslipidaemias:lipid modification to reduce cardiovascular risk[J]. Atherosclerosis,2019,290:140-205

[7] MARGARITIS M,SANNA F,ANTONIADES C. Statins and oxidative stress in the cardiovascular system[J]. Curr Pharm Des,2017,doi:10.2174/1381612823666170926130338

[8] CHEN L W,LIN C S,TSAI M C,et al. Pitavastatin exerts potent anti-inflammatory and immunomodulatory effects via the suppression of AP-1 signal transduction in human T cells[J]. Int J Mol Sci,2019,20(14):3534

[9] DE LA CRUZ J A,MIHOS C G,HORVATH S A,et al. The pleiotropic effects of statins in endocrine disorders[J]. Endocr Metab Immune Disord Drug Targets,2019,19(6):787-793

[10] FORD I,MURRAY H,MCCOWAN C,et al. Long-term safety and efficacy of lowering low-density lipoprotein cholesterol with statin therapy:20-year follow-up of west of scotland coronary prevention study[J]. Circulation,2016,133(11):1073-1080

[11] CHOLESTEROL TREATMENT TRIALISTS' COLLABORATION. Efficacy and safety of statin therapy in older people:a meta-analysis of individual participant data from 28 randomised controlled trials[J]. Lancet,2019,393(10170):407-415

[12] ANAGNOSTIS P,VAITSI K,KLEITSIOTI P,et al. Efficacy and safety of statin use in children and adolescents with familial hypercholesterolaemia:a systematic review and meta-analysis of randomized-controlled trials[J]. Endocrine,2020,69(2):249-261

[13] STROIE O P,BOSTER J,SURRY L. Statin-induced immune-mediated necrotizing myopathy:an increasingly recognized inflammatory myopathy[J]. Cureusm,2020,12(5):7963

[14] CRAVEIRO N S,SILVA LOPES B,TOMÁS L,et al. L-TRUST:long-term risk of cancer in patients under statins therapy. A systematic review and meta-analysis[J]. Pharmacoepidemiol Drug Saf,2019,28(11):1431-1439

[15] YEBYO H G,ASCHMANN H E,KAUFMANN M,et al. Comparative effectiveness and safety of statins as a class and of specific statins for primary prevention of cardiovas-

cular disease: a systematic review, meta-analysis, and network meta-analysis of randomized trials with 94,283 participants[J]. Am Heart J, 2019, 210: 18-28

[16] STITZIEL N O, WON H H, MORRISON A C, et al. Inactivating mutations in NPC1L1 and protection from coronary heart disease[J]. N Engl J Med, 2014, 71(22): 2072-2082

[17] PHAN B A, DAYSPRING T D, TOTH P P. Ezetimibe therapy: mechanism of action and clinical update [J]. Vasc Health Risk Manag, 2012, 8: 415-427

[18] GIUGLIANO R P, CANNON C P, BLAZING M A, et al. Benefit of adding ezetimibe to statin therapy on cardiovascular outcomes and safety in patients with versus without diabetes mellitus: results from IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial)[J]. Circulation, 2018, 137(15): 1571-1582

[19] OUCHI Y, SASAKI J, ARAI H, et al. Ezetimibe lipid-lowering trial on prevention of atherosclerotic cardiovascular disease in 75 or older(EWTOPIA 75): a randomized, controlled trial[J]. Circulation, 2019, 140(12): 992-1003

[20] CATAPANO A L, PIRILLO A, NORATA G D. New pharmacological approaches to target PCSK9[J]. Curr Atheroscler Rep, 2020, 22(7): 24

[21] NICHOLLS S J, PURI R, ANDERSON T, et al. Effect of evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV randomized clinical trial [J]. JAMA, 2016, 316(22): 2373-2384

[22] NICHOLLS S J, PURI R, ANDERSON T, et al. Effect of evolocumab on coronary plaque composition [J]. J Am Coll Cardiol, 2018, 72(17): 2012-2021

[23] CAO Y X, JIN J L, SUN D, et al. Circulating PCSK9 and cardiovascular events in FH patients with standard lipid-lowering therapy[J]. J Transl Med, 2019, 17(1): 367

[24] NOZUE T. Lipid lowering therapy and circulating PCSK9 concentration [J]. J Atheroscler Thromb, 2017, 24(9): 895-907

[25] SCHMIDT A F, PEARCE L S, WILKINS J T, et al. PCSK9 monoclonal antibodies for the primary and secondary prevention of cardiovascular disease [J]. Cochrane Database Syst Rev, 2017, 4(4): 011748

[26] KOREN M J, SABATINE M S, GIUGLIANO R P, et al. Long-term efficacy and safety of evolocumab in patients with hypercholesterolemia [J]. J Am Coll Cardiol, 2019, 74(17): 2132-2146

[27] HOLLSTEIN T, KASSNER U, GRENKOWITZ T, et al. PCSK9 inhibitors in a german single-center clinical practice: real-world treatment of patients at high cardiovascular risk over 68 weeks[J]. Am J Cardiovasc Drugs, 2021, 21(1): 83-92

[28] KOSKINAS K C, WINDECKER S, PEDRAZZINI G, et al. Evolocumab for early reduction of LDL cholesterol levels in patients with acute coronary syndromes (EVOPACS) [J]. J Am Coll Cardiol, 2019, 74(20): 2452-2462

[29] SZAREK M, WHITE H D, SCHWARTZ G G, et al. Alirocumab reduces total nonfatal cardiovascular and fatal events: the ODYSSEY OUTCOMES trial [J]. J Am Coll Cardiol, 2019, 73(4): 387-396

[30] SZAREK M, STEG P G, DICENSO D, et al. Alirocumab reduces total hospitalizations and increases days alive and out of hospital in the ODYSSEY OUTCOMES trial [J]. Circ Cardiovasc Qual Outcomes, 2019, 12(11): 005858

[31] STEG P G, SZAREK M, BHATT D L, et al. Effect of alirocumab on mortality after acute coronary syndromes [J]. Circulation, 2019, 140(2): 103-112

[32] GENCER B, MACH F, MURPHY S A, et al. Efficacy of evolocumab on cardiovascular outcomes in patients with recent myocardial infarction: a prespecified secondary analysis from the FOURIER trial [J]. JAMA Cardiol, 2020, 15(8): 952-957

[33] GIUGLIANO R P, MACH F, ZAVITZ K, et al. Cognitive function in a randomized trial of evolocumab[J]. N Engl J Med, 2017, 377(7): 633-643

[34] ELAMIN A F M, GRAFTON-CLARKE C, WEN CHEN K, et al. Potential use of PCSK9 inhibitors as a secondary preventative measure for cardiovascular disease following acute coronary syndrome: a UK real-world study[J]. Postgrad Med J, 2019, 95(1120): 61-66

[35] OLRY D E LABRY LIMA A, GIMENO BALLESTER V, SIERRA SÁNCHEZ J F, et al. Cost-effectiveness and budget impact of treatment with evolocumab versus statins and ezetimibe for hypercholesterolemia in Spain[J]. Rev Esp Cardiol, 2018, 71(12): 1027-1035

[36] BLOM D J, RAAL F J, SANTOS R D, et al. Lomitapide and mipomersen-inhibiting microsomal triglyceride transfer protein(MTP)and apoB100 synthesis[J]. Curr Atheroscler Rep, 2019, 21(12): 48

[37] GIAMMANCO A, CEFALÙ A B, NOTO D, et al. Therapeutic options for homozygous familial hypercholesterolemia: the role of lomitapide[J]. Curr Med Chem, 2020, 27(23): 3773-3783

[38] NOHARA A, OTSUBO Y, YANAGI K, et al. Safety and efficacy of lomitapide in japanese patients with homozygous familial hypercholesterolemia (HoFH): results from the AEGR-733-301 long-term extension study[J]. J Atheroscler Thromb, 2019, 26(4): 368-377

[39] KHOURY E, BRISSON D, ROY N, et al. Review of the long-term safety of lomitapide: a microsomal triglycerides transfer protein inhibitor for treating homozygous familial

hypercholesterolemia[J]. Expert Opin Drug Saf,2019,18(5):403-414

[40] BLOM D J,AVERNA M R,MEAGHER E A,et al. Long-term efficacy and safety of the microsomal triglyceride transfer protein inhibitor lomitapide in patients with homozygous familial hypercholesterolemia[J]. Circulation,2017,136(3):332-335

[41] MÜLLER H H. Effect of mipomersen on LDL-cholesterol in patients with severe LDL-hypercholesterolaemia and atherosclerosis treated by lipoprotein apheresis: corrections of the report on the randomized MICA-study[J]. Atherosclerosis,2018,27(5):457-458

[42] DUELL P B,SANTOS R D,KIRWAN B A,et al. Long-term mipomersen treatment is associated with a reduction in cardiovascular events in patients with familial hypercholesterolemia[J]. J Clin Lipidol,2016,10(4):1011-1021

[43] FOGACCI F,FERRI N,TOTH P P,et al. Efficacy and safety of mipomersen:a systematic review and meta-analysis of randomized clinical trials[J]. Drugs,2019,79(7):751-766

[44] LANDMESSER U,HAGHIKIA A,LEITER L A,et al. Effect of inclisiran,the small-interfering RNA against proprotein convertase subtilisin/kexin type 9,on platelets,immune cells,and immunological biomarkers:a pre-specified analysis from ORION-1[J]. Cardiovasc Res,2021,117(1):284-291

[45] RAY K K,STOEKENBROEK R M,KALLEND D,et al. Effect of 1 or 2 doses of inclisiran on low-density lipoprotein cholesterol levels:one-year follow-up of the ORION-1 randomized clinical trial[J]. JAMA Cardiol,2019,4(11):1067-1075

[46] BALLANTYNE C M,BANACH M,MANCINI G B J,et al. Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia:a randomized,placebo-controlled study[J]. Atherosclerosis,2018,277:195-203

[47] RAY K K,BAYS H E,CATAPANO A L,et al. Safety and efficacy of bempedoic acid to reduce LDL cholesterol[J]. N Engl J Med,2019,380(11):1022-1032

[48] BOWMAN L,HOPEWELL J C,CHEN F,et al. Effects of anacetrapib in patients with atherosclerotic vascular disease[J]. N Engl J Med,2017,377(13):1217-1227

[49] BALLANTYNE C M,SHAH S,SAPRE A,et al. A multiregional,randomized evaluation of the lipid-modifying efficacy and tolerability of anacetrapib added to ongoing statin therapy in patients with hypercholesterolemia or low high-density lipoprotein cholesterol[J]. Am J Cardiol,2017,120(4):569-576

[50] TAHERI H,FILION K B,WINDLE S B,et al. Cholesteryl ester transfer protein inhibitors and cardiovascular outcomes:a systematic review and meta-analysis of randomized controlled trials[J]. Cardiology,2020,145(4):236-250

[51] BURGESS S,FERENCE B A,STALEY J R,et al. European prospective investigation into cancer and nutrition-cardiovascular disease(EPIC-CVD)consortium. Association of LPA variants with risk of coronary disease and the implications for lipoprotein(a)-lowering therapies:a mendelian randomization analysis[J]. JAMA Cardiol,2018,3(7):619-627

[52] LAMINA C,KRONENBERG F. Estimation of the required lipoprotein(a)-lowering therapeutic effect size for reduction in coronary heart disease outcomes:a mendelian randomization analysis[J]. JAMA Cardiol,2019,4(6):575-579

[53] MADSEN C M,KAMSTRUP P R,LANGSTED A,et al. Lipoprotein(a)-lowering by 50 mg/dL(105 nmol/L)may be needed to reduce cardiovascular disease 20% in secondary prevention:a population-based study[J]. Arterioscler Thromb Vasc Biol,2020,40(1):255-266

[54] O'DONOGHUE M L,FAZIO S,GIUGLIANO R P,et al. Lipoprotein(a),PCSK9 inhibition,and cardiovascular risk[J]. Circulation,2019,139(12):1483-1492

[55] ALKHALIL M. Lipoprotein(a)reduction in persons with cardiovascular disease[J]. N Engl J Med,2020,382(21):65

[56] SALIBA W,RENNERT H S,BARNETT-GRINESS O,et al. Association of statin use with spontaneous intracerebral hemorrhage:a cohort study[J]. Neurology,2018,91(5):400-409

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