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SGLT2 抑制剂联合 GLP–1 受体激动剂治疗 2 型糖尿病合并心血管疾病的研究进展

赵喆，杨丹丹 综述 詹晓蓉 审校

(哈尔滨医科大学附属第一医院内分泌三科，哈尔滨 150001)

[摘 要] 目前糖尿病患病率越来越高，且相当大一部分合并心血管疾病，SGLT2抑制药及GLP-1受体激动药可从降糖、减重、降压、保护肾功等多个角度间接及直接地减少糖尿病患者的心血管不良事件和心血管病病死率。

[关键词] 2型糖尿病；心血管事件；钠葡萄糖协同转运蛋白2抑制剂；胰高血糖素样肽-1受体激动剂

Research advance in SGLT2 inhibitor combined with GLP-1 receptor agonist in the treatment of type 2 diabetes with cardiovascular disease

ZHAO Zhe, YANG Dandan, ZHAN Xiaorong

(Third Department of Endocrinology, First Affiliated Hospital of Harbin Medical University, Harbin 150001, China)

Abstract At present, the prevalence of diabetes mellitus is getting higher and higher, and a considerable part of them have cardiovascular disease. SGLT2 inhibitors and GLP-1 receptor agonists can reduce cardiovascular adverse events and cardiovascular mortality in diabetic patients from the angles of reducing blood sugar, weight, blood pressure and kidney function.

Keywords type 2 diabetes mellitus; cardiovascular events; sodium glucose cotransporter 2 inhibitors; glucagon like peptide 1 receptor agonists

糖尿病(diabetes mellitus，DM)患者的数量从1980年的1.08亿增加到2014年的4.22亿，预计到2040年将达到6.42亿。相当大比例的DM患者具有高心血管疾病(cardiovascular diseases，CVD)风险[1]。在2015年，约380万人死于DM，CVD是主要的病因[2]。在2018年，ADA首次将T2DM患者分为显性CVD患者和无CVD患者[3]。在前者中，生活方式管理和二甲双胍治疗后，建议联合使用减少心血管不良事件和心血管病病死率的降糖药物：钠葡萄糖共转运体2抑制药(sodium glucose cotransporter 2 inhibitors，SGLT2i)或胰高血糖素样肽-1受体激动药(glucagon like peptide 1 receptor agonists，GLP-1 RA)[3]。

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通信作者 (Corresponding author)：詹晓蓉，Email: xiaorongzhan@sina.com

1 SGLT2i 和 GLP-1 RA 降低血糖、体重、血压的协同作用

SGLT2是参与肾脏葡萄糖再吸收的主要共转运体，SGLT2i可抑制近端肾单位的再吸收，增加尿葡萄糖排泄量达80 g/d[4-6]。而GLP-1受体刺激增加胰岛素分泌、降低胰高血糖素分泌、减缓胃排空(尤其是对短效GLP-1受体激动剂)和增加饱腹感，从而降低血糖[7-11]。

SGLT2i增加热量排泄[12]。但SGLT2i亦通过调节器官间神经(迷走神经分支和交感神经)网络来限制体重减轻，从而引起食欲旺盛并抑制棕色脂肪组织(brown adipose tissue，BAT)诱导的能量消耗[13]。而GLP-1受体激动剂则通过降低食欲[10]、延迟胃排空来减少摄食过多或通过各种下丘脑机制的能量消耗来影响体重[14]。

SGLT2i和GLP1 RA均诱导血液动力学效应，降低血压、动脉僵硬度和血液黏稠性[15-20]。SGLT2i渗透性利尿剂的作用，导致血压降低。已获批准的SGLT2i在慢性肾病(chronic kidney disease，CKD)的3a期能够改善肾功能，也可能有助于降低血压[16-17]。GLP-1RA治疗可降低T2DM患者的收缩压和舒张压[21]。

一项前瞻性随机研究[22]显示：联合用药的安全性和有效性优于两种单药治疗，HbA1c的降低、第2周和第28周空腹血糖的基线变化、第28周餐后2 h血糖降低、体重减轻和收缩压降低均非常显著。在一项为期28周的随机双盲实验[23]中，达格列净、艾塞那肽(每周1次)联合大剂量胰岛素强化对肥胖胰岛素抵抗的及血糖控制不良(HbA1c≥8.0%和≤11.0%)的T2DM患者的治疗中，也显示出安全性和有效性。达格列净、艾塞那肽的双重治疗可减轻体重、脂肪组织、空腹和餐后血糖以及收缩压。该研究还发现：达格列净联合艾塞那肽的治疗导致体重、糖尿病前期危险和收缩压的持续下降(在24和52周)，而没有糖尿病的肥胖成年人对此耐受良好。

2 SGLT2i 和 GLP1RA 对心血管事件的协同作用

SGLT2i促进钠尿和渗透性利尿，导致血浆容量减少，心脏前、后负荷降低，血压(blood pressure，BP)降低以及动脉僵硬(arterial stiffness，AS)改善，从而改善心力衰竭(heart failure，HF)患者的心内膜下血流[24]。除对传统的CVD危险因素或线粒体心肌细胞途径的影响外，还可能引起轻微、持续的高酮血症，如由SGLT2i(主要是β-羟基丁酸酯)引起的高酮血症，被心脏自由吸收，并优先于脂肪酸被氧化[25-26]。这种燃料变化在线粒体水平上改善了氧消耗转化为工作效率的转导[25-26]。很小的能量供应变化也可转化为功能上的巨大差异，并且在持续使用SGLT2i数月或数年后仍有改善心功能的结果[26]。

有研究[27]将7 020名患者随机分为恩格列净组(10或25 mg/d；因两组有相似的结果，均进行分析)及安慰剂组，接受平均3.1年的标准治疗。与安慰剂组相比，恩格列净组的CVD(主要是HF恶化)病死率降低了38%，HF住院率降低了35%，而非致命性心肌梗死(myocardial infarction，MI)的发生率没有显著降低。有研究[28]给予3种不同的SGLT2i——坎格列净、达格列净、恩格列净，对HF具有相同的有益效果；这种效应是药物类效应[28-29]。

利拉鲁肽可改善氧化应激、内皮功能、动脉刺激性、左室心肌张力、收缩和解舒张、氨基末端脑钠肽前体(amino-terminal pro-brain natriuretic peptide，NT-proBNP)[30]。在9 340名高CVD风险T2DM患者(平均随访3.8年)的LEADER试验[31]中，4 668名患者随机分为利拉鲁肽组，其余患者随机分为安慰剂组。主要终点是CVD事件、非致死性MI或非致命性卒中死亡。主要预后下降13%，CVD病死率下降22%，全因病死率下降15%。而非致死性MI，HF和卒中住院病例分别减少了12%，13%和11%。且利拉鲁肽组糖尿病微血管病变(肾或视网膜)的发生率低于安慰剂组，主要是肾病发生率较低。

SGLT2i减少了HF住院率和CVD病死率，而GLP-1 RA减少了由非致死性心肌梗死和卒中引起的CVD病死率，尽管这些在逐一考虑时没有统计学意义[31]。此外，liraglutide增强左心功能，有助于减少HF事件，特别是在射血分数降低的HF(heart failure with reduced ejection fraction，HFrEF)中。与对照组相比，利拉鲁肽组的每搏输出量和心输出量明显增加[30,32-33]。如果将SGLT2i和GLP-1 RA一起给药，可能降低患者CVD病死率，并可能在CVD事件上有更大的获益。

3 SGLT2i 和 GLP1 RA 改善肾功能的协同作用

纳入7 020例T2DM患者的EMPA-REG OUTCOME试验[11]研究了恩格列净长期对高CVD危险患者肾的影响。实验中4 124例患者接受恩格列净治疗，其余患者服用安慰剂。恩格列净组新增或恶化的肾病发生率为12.7%，安慰剂组为18.8%。恩格列净组血清肌酐(serum creatinine，SC)水平增加一倍的发生率为1.5%，安慰剂组为2.6%。恩格列净组开始肾替代治疗的发生率为0.3%，安慰剂组为0.6%。恩格列净对蛋白尿无明显影响。这些数据表明：在高CVD风险T2DM患者中，与安慰剂和常规护理相比，恩格列净使临床肾事件的风险显著降低。

在LEADER实验[34]中9 340名高危T2DM患者被随机分成利拉鲁肽(1.8 mg/d)组和安慰剂组，平均随访3.84年，随访CVD和肾事件。利拉鲁肽组发生肾事件的人数少于安慰剂组，相对危险度减少百分比(relative risk reduction，RRR)为22%。主要是利拉鲁肽组的新发持续性大量白蛋白尿少于安慰剂组，RRR为26%。

恩格列净和利拉鲁肽组合对肾具有累加的有利作用。恩格列净可以减少新发病或恶化的肾病、SC加倍的速度，需要肾替代疗法，而恩格列净对蛋白尿没有显著影响[34]。利拉鲁肽可减少T2DM患者新发的大量白蛋白尿，增强了恩格列净的作用，并大大降低肾病的发生；肾功能恶化的有效衰减可保护心脏并可能抵消与CVD风险相关的其他风险因素[35-36]，这在T2DM患者中更为有效[37]。

SUSTAIN-6实验[38]中3 297例高CVD风险的T2DM患者在标准护理方案下随机接受每周1次(0.5 mg或1.0 mg)索马鲁肽或安慰剂治疗104周，新发或恶化的肾病发生率低于安慰剂组。

考虑EMPA-REG OUTCOME[11]，LEADER[34]，SUSTAIN-6[38]的结果以及将CVD结局试验转化为临床实践，中欧和东欧糖尿病专家组专家委员会[39]建议：在高风险T2DM患者(伴有CVD或CKD等合并症)中使用SGLT2i或GLP-1-RA作为二甲双胍后的第二步；如果两种药物都在高CVD风险患者中给药，预计其效益会高于单药治疗的效果。

4 结语

SGLT-2联合GLP-1 RA治疗高CVD风险T2DM患者，可显著降低血糖、体重、血压，降低CVD风险以及心血管及肾不良事件的发生率，从根本上改善患者生活质量和长期生存[32,40-42]。然而，GLP-1 RA和SGLT2i的长期生存研究还没有完成，需要更多的前瞻性长期对照研究来证明这一结论。

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