·综述·

钠-葡萄糖共转运蛋白2抑制剂在老年2型糖尿病合并常见心血管疾病中的应用进展

张辉[1],李泱[2],刘传斌[1*]
([1]中国人民解放军总医院京西医疗区,北京 100144;[2]中国人民解放军总医院第六医学中心心血管病学部,北京 100048)

【摘 要】 老年2型糖尿病(T2DM)患者常有多病共存现象,而合并心血管疾病(CVD)最为常见,是其致残、致死的首要原因。钠-葡萄糖共转运蛋白2抑制剂(SGLT2i)是一种新型降糖药物,其心血管保护作用受到广泛关注,在老年T2DM与CVD共病的治疗上展现出良好的前景。本文就SGLT2i在T2DM合并心力衰竭、高血压、动脉粥样硬化、心肌梗死等常见CVD中的应用研究进展作一综述。

【关键词】 糖尿病, 2型;钠-葡萄糖共转运蛋白2抑制剂;老年共病;心血管疾病;心力衰竭
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Advances in application of sodium-glucose co-transporter 2 inhibitor in elderly type 2 diabetes mellitus patients with concomitant common cardiovascular diseases

Zhang Hui[1], Li Yang[2], Liu Chuanbin[1*]
([1]Western Medical Branch, Chinese PLA General Hospital, Beijing 100144, China; [2]Senior Department of Cardiology, Sixth Medical Centre, Chinese PLA General Hospital, Beijing 100048, China)

【Abstract】 Elderly patients with type 2 diabetes mellitus (T2DM) often have multiple coexisting diseases, and the complication of cardiovascular diseases (CVD) is the most common, which is the primary cause of disability and death. Sodium-glucose co-transporter protein 2 inhibitor (SGLT2i) is a novel hypoglycemic agent, which has received widespread attention for its cardio-protective effects, and shows good prospects for the treatment of co-morbidities of T2DM and CVD in the elderly. In this article, we reviewed the progress of SGLT2i in T2DM combined with heart failure, hypertension, atherosclerosis, myocardial infarction and other common CVD.

【Key words】 diabetes mellitus, type 2; sodium-glucose co-transporter protein 2 inhibitor; geriatric co-morbidities; cardiovascular diseases; heart failure
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Corresponding author: *Liu Chuanbin*, *E-mail*: *doctor_liuchuanbin@126.com*

随着人口老龄化加剧,2型糖尿病(type 2 diabetes mellitus, T2DM)患病率和多病共存现象增加[1]。共病是指个体患有2种或2种以上的疾病,其发病与年龄增长密切相关[2]。调查显示,我国糖尿病患者约有1.4亿,而77%~90%的T2DM患者存在多病共存现象,超过三分之一的T2DM患者合并心血管疾病(cardiovascular disease, CVD),显著增加其心血管事件和全因死亡的风险[3,4]。钠-葡萄糖共转运蛋白2抑制剂(sodium-glucose co-transporter 2 inhibitor, SGLT2i)是一种新型降糖药,可通过抑制肾脏近端小管葡萄糖重吸收来降低血糖,单独使用不增加低血糖风险[5]。多项研究显示,SGLT2i除了可以安全、稳定地降低血糖外,还对CVD展现出巨大的治疗潜力,可以降低血压[6]、减少主要心血管不良事件(major adverse cardiovascular events, MACE)[7]、改善心力衰竭(heart failure, HF)症状[8,9]等,为老年T2DM合并CVD共病患者的治疗提供了新的思路。

1 SGLT2i与T2DM合并心力衰竭

SGLT2i作为HF“新四联”药物之一,不仅用于T2DM合并HF患者的治疗,还能降低T2DM患者

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通信作者:刘传斌, E-mail: doctor_liuchuanbin@126.com

HF住院风险。T2DM是HF的重要危险因素,T2DM患者的HF患病率为12%[10]。HF在老年T2DM患者中更为常见[11]。DAPA-HF研究表明,SGLT2i可使射血分数降低的心力衰竭(heart failure with reduced ejection fraction, HFrEF)患者心血管原因死亡率降低18%、全因死亡率降低17%、首次HF恶化事件降低30%[8]。DELIVER研究显示,与安慰剂组相比,SGLT2i能使T2DM合并射血分数轻度降低的心力衰竭(heart failure with mildly reduced ejection fraction, HFmrEF)或射血分数保留的心力衰竭(heart failure with preserved ejection fraction, HFpEF)患者主要复合终点(恶化HF事件或心血管死亡)风险降低19%[9]。对于T2DM合并急性HF,SOLOIST-WHF研究和EMPULSE研究都表明,SGLT2i能显著降低这类患者的急诊就诊率、心血管死亡率或HF住院率[12,13]。因此,最新的指南和专家共识除了建议使用SGLT2i用于各种急、慢性HF外,对合并高危心血管风险或心血管疾病的T2DM患者也推荐使用SGLT2i以预防HF住院[14,15]。多数研究认为,SGLT2i可能通过利尿、降压、促进红细胞生成等途径调节血流动力学,改善心肌能量代谢,调节心肌离子稳态,减轻炎症反应和心肌纤维化,改善心脏重构,抑制心外膜脂肪组织-SGLT2介导的代谢重构等途径治疗HF[16]。

2 SGLT2i与T2DM合并高血压

SGLT2i在降低患者血糖的同时还可以降低血压,但降压作用较弱。调查显示,高血压是T2DM患者最常见合并症[17]。SACRA研究[6]发现,相较安慰剂,SGLT2i能显著降低伴有夜间高血压的T2DM患者白天、24 h、晨起和夜间收缩压(systolic blood pressure, SBP)及白天、24 h舒张压(diastolic blood pressure, DBP)。Sjöström等[18]对13项SGLT2i临床试验数据进行荟萃分析,发现无论T2DM患者基线血压如何,相较安慰剂,SGLT2i均能使患者血压适度降低,且对合并高血压T2DM患者的降压作用略强。以上研究表明,SGLT2i降低患者血压幅度有限,但耐受性和安全性良好,不增加心率和低血压风险,对老年患者比较友好。目前的研究认为,SGLT2i的降压作用可能有多种机制,主要包括利尿引起的血容量减少、利钠和体质量减轻,而其减弱交感神经兴奋、改善内皮功能、降低动脉僵硬度等也有一定作用[19]。

3 SGLT2i与T2DM合并动脉粥样硬化

SGLT2i对动脉粥样硬化(atherosclerosis, AS)有显著疗效,可调节血脂、稳定斑块、减缓AS的进展,但对外周血管疾病(peripheral arterial disease, PAD)的作用尚存在争议。老年T2DM患者往往有多重心血管危险因素共存,合并AS的比率很高,显著增加其死亡风险[20,21]。多数研究显示,SGLT2i可以降低总胆固醇(total cholesterol, TC)、血清甘油三酯(triglyceride, TG),同时升高高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C),虽然也略微升高低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C),但不增加LDL-C/HDL-C比值。此外,SGLT2i还可改善不同LDL亚类的比例,降低小而密低密度脂蛋白胆固醇(small dense low-density lipoprotein cholesterol, sdLDL-C),而被氧化的sdLDL-C被认为是AS的主要元凶之一[22]。Han等[23]发现,与格列美脲相比,SGLT2i可显著减轻小鼠炎症反应和胰岛素抵抗,并减小主动脉弓/主动脉瓣AS斑块面积。Chen等[24]研究发现,SGLT2i可使小鼠颈动脉斑块脂质含量总体降低、胶原含量增加、斑块帽与斑块高度比增加,提示其有助于减缓斑块的发展,稳定斑块。然而,SGLT2i对PAD的作用尚存在争议。Lee等[25]发现,相比其他降糖药物,SGLT2i可以降低T2DM患者下肢PAD或截肢的风险。然而,CANVAS研究[7]却得到了相反的结果。此外,也有研究显示,SGLT2i在对T2DM患者心血管疾病发挥益处的同时并不增加下肢不良事件的风险[26]。在作用机制上,SGLT2i能调节血脂、改善血管内皮糖萼、减轻血管内皮功能障碍、减少氧化应激、减轻炎症反应,这些对改善患者AS都能起到有益的作用[27]。

4 SGLT2i与T2DM合并心肌梗死

动物实验表明,SGLT2i能减少心肌梗死(myocardial infarction, MI)面积和纤维化,改善心功能,但其结果仍有待临床试验验证。研究显示,有MI病史的T2DM患者MI复发风险>40%;在同年龄组中,T2DM患者MI后死亡率比非T2DM患者高两倍[28],老年T2DM合并MI预后尤其不好[29]。多数研究显示,合并MI的T2DM患者使用SGLT2i不仅可以控制血糖还使MI获益。Jiang等[30]通过结扎T2DM小鼠左前降支制作MI模型,发现SGLT2i显著减少了MI面积和心肌纤维化,改善了心功能,提高了生存率。Paolisso等[31]在一项回顾性队列研究中发现,与使用其他降糖药物的MI患者相比,使用SGLT2i的患者炎症指标更低、MI面积也更小。Furtado等[32]发现,在既往有MI病史的T2DM患者

中,SGLT2i 使 MACE 的相对风险降低 16%,并降低了 MI 的复发率。以上研究提示,SGLT2i 可能在减轻 MI 后缺血性损伤或再灌注损伤中发挥了积极作用。然而,现有的指南并不主张在疾病急性期(包括急性 MI)使用 SGLT2i,以避免发生低血容量、低血压、酮症酸中毒或急性肾损伤[33],导致 SGLT2i 用于急性 MI 的疗效和安全性证据并不充分。目前,有两项旨在评估 SGLT2i 治疗急性 MI 有效性和安全性的临床试验正在进行,即 EMPACT-MI 试验(NCT04509674)和 DAPA-MI 试验(NCT04564742)。SGLT2i 对 MI 的作用机制尚不完全清楚,除了延缓 AS 进展和稳定斑块,还可能与调节心肌细胞自噬、增强内皮功能并扩张血管、升高血浆酮体水平改善心肌能量代谢等有关[34]。

5 总 结

随着人口老龄化加剧,老年共病的问题亦日趋凸显,共病的综合管理受到广泛关注。老年 T2DM 合并 CVD 非常普遍,而 T2DM 与 CVD 相互影响,严重威胁老年人的健康,影响其生活质量。SGLT2i 作为降糖新药,在降压、降脂、保护心肌细胞方面亦有良好表现,在老年人群中安全性耐受性良好,是老年 T2DM 合并 CVD 患者的理想用药。在真实世界研究中,CVD-REAL 2 研究[35]纳入亚太、中东和北美的 470 128 例 T2DM 患者,结果表明,与使用其他降糖药物相比,SGLT2i 显著降低患者非致死性卒中 32%、非致死性 MI19%。最新的 T2DM 相关指南对 SGLT2i 用于 T2DM 合并 CVD 都作了优先推荐[20,36]。今后,SGLT2i 与降压药、降脂药等的复方制剂也许会成为老年共病的治疗方向之一。然而,SGLT2i 只获得了 HF 治疗的适应证,在 AS、高血压、MI 等 CVD 的治疗上仍处于动物实验或临床试验阶段,还有待进一步研究。此外,SGLT2i 理论上可以降压、降脂、保护心肌细胞,但其与降压药、降脂药等的相互作用如何,是否能起到协同作用,仍有待更多实验去探索。最后,现有的文献多是 SGLT2i 应用于单病的研究,SGLT2i 对 T2DM 合并 CVD 共病作用的数据多来自于亚组分析,尚缺乏针对老年 T2DM 合并 CVD 共病设计的临床试验。

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