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钠-葡萄糖协同转运蛋白2抑制剂在心力衰竭合并慢性肾脏病中的研究进展

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作者单位: 1.430065湖北省武汉市, 武汉科技大学医学部医学院 2.430060湖北省武汉市第三医院心内科

通信作者: 严喜胜, E-mail: yanxisheng081518@163.com

【摘要】 随着人口老龄化的日益加重, 心力衰竭及慢性肾脏病(CKD)的发病率和病死率逐年攀升。心力衰竭与CKD常合并存在, 全球约50%的心力衰竭患者合并CKD, 这类患者的预后更差, 且其治疗缺乏具体指导。近年来, 新型口服降糖药钠-葡萄糖协同转运蛋白2抑制剂(SGLT2i)在治疗心力衰竭合并CKD方面受到越来越多的关注, 其心脏及肾脏获益为心力衰竭合并CKD患者的治疗提供了新思路。本文对SGLT2i治疗心力衰竭合并CKD患者的心肾保护机制、临床证据及SGLT2i的不良反应、安全性做一综述。

【关键词】 心力衰竭; 肾疾病; 钠-葡萄糖共转运蛋白2抑制剂; 综述

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Research Progress of the Sodium-Glucose Cotransporter-2 Inhibitors in the Treatment of Heart Failure Combined with Chronic Kidney Disease

LI Hongwei¹, WAN Zhengyun¹, YAN Xisheng²

1.School of Medicine, Wuhan University of Science and Technology, Wuhan 430065, China

2.Department of Cardiology, the Third Hospital of Wuhan, Wuhan 430060, China

Corresponding author: YAN Xisheng, E-mail: yanxisheng081518@163.com

【Abstract】 With the increasing aging of the population, the incidence rate and mortality of heart failure and chronic kidney disease (CKD) rise year by year. Heart failure and CKD often coexist, and about 50% of heart failure patients worldwide have CKD. The prognosis for these patients is worse and there is a lack of specific guidance for the treatment of these patients. In recent years, the novel oral hypoglycemic agent sodium-glucose cotransporter-2 inhibitors (SGLT2i) has received increasing attention in the treatment of heart failure combined with CKD, and its significant cardiac and renal benefits provide new ideas for the treatment of patients with heart failure combined with CKD. This article provides a review of the cardiorenal protective mechanism, clinical evidence, adverse effects and safety of SGLT2i in the treatment of patients with heart failure combined with CKD.

【Key words】 Heart failure; Kidney diseases; Sodium-glucose cotransporter-2 inhibitors; Review

随着全球人口老龄化日益加重, 心力衰竭和慢性肾脏病(chronic kidney disease, CKD)的发病率逐年攀升, 目前全球约有6 400万例心力衰竭患者^[1], 且40%~50%的心力衰竭患者合并CKD^[2]。与未合并CKD的心力衰竭患者相比, 合并CKD的心力衰竭患者死亡风险增加56%^[3], 5年全因死亡率达50%~75%^[4], 已成为世界范围内的重要健康负担。心脏和肾脏之间复杂的双向作用促进了心力衰竭合并CKD的发生发展, 心力衰竭可通过引起血流动力学变化而诱发肾功能损伤, 肾功能损伤又会进一步加重心力衰竭的进展, 形成恶性循环^[5], 此外神经激素失调、炎症反应、氧化应激和代谢紊乱等机制可能在上述恶性循环中发挥重要作用。鉴于心力衰竭合并CKD发病机制复杂、不同心力衰竭类型间的异质性、治疗心力衰竭的药物对肾脏的作用等, 心力衰竭合并CKD患

者的治疗目前仍在探索中^[6]。

近年来, 钠-葡萄糖协同转运蛋白2抑制剂(sodium-glucose cotransporter-2 inhibitors, SGLT2i)的使用越来越普遍, 尽管最初作为降糖药物被开发和使用, 但随机对照试验已经证实, SGLT2i不仅能够给2型糖尿病(type 2 diabetes mellitus, T2DM)患者带来主要心血管获益, 也适用于未合并T2DM的心力衰竭及CKD患者^[7], 在延缓CKD进展方面, SGLT2i甚至优于传统血管紧张素转换酶抑制剂(angiotensin converting enzyme inhibitors, ACEI)^[8]。本文对SGLT2i治疗心力衰竭合并CKD的心肾保护机制、临床证据及SGLT2i的不良反应和安全性做一综述。

1 钠-葡萄糖协同转运蛋白(sodium-glucose cotransporter, SGLT)2和SGLT2i

SGLT是一种依赖钠转运葡萄糖的同向转运蛋白。SGLT在人体内广泛存在, 目前共发现6种SGLT, 其中SGLT1和SGLT2

相关研究最多,二者主要与调节葡萄糖稳态相关^[9]。SGLT1在肠道、心脏和肾脏中均有表达,其中表达在肾脏近曲小管S3段的SGLT1负责重吸收肾小球滤过液中约10%的葡萄糖,而SGLT2主要表达于肾脏近曲小管S1段,负责重吸收肾小球滤过液中90%的葡萄糖^[10]。

SGLT2i最早可追溯到苹果树提取物“根皮苷”,这种药物因选择性差且胃肠道不良反应明显而未获准用于临床^[11]。为解决这一问题,研究者对“根皮苷”的结构进行了修饰,研发出了SGLT2i类药物^[12]如列净类降糖药,包括达格列净、恩格列净、索格列净等。SGLT2i类药物可竞争性地阻断SGLT2,降低肾小球滤过液中葡萄糖的重吸收,从而降低血糖^[13]。近年研究表明,SGLT2i不仅能改善糖尿病患者心血管结局,还降低非糖尿病患者心力衰竭事件发生风险^[7],为此,《2021 ESC急性和慢性心力衰竭诊断和治疗指南》^[14]将SGLT2i纳入心力衰竭的四联治疗。随着大型随机对照试验的开展,SGLT2i在延缓肾功能下降和改善CKD患者预后方面的作用亦得到了证实^[15]。SGLT2i在心血管和肾脏保护方面的优势使其成为治疗心力衰竭合并CKD患者的潜在选择。

2 SGLT2i治疗心力衰竭合并CKD的心肾保护机制

CKD是心力衰竭最常见的共病之一,可能与心力衰竭和CKD具有共同传统危险因素(包括高龄、糖尿病、吸烟、肥胖等)以及二者之间潜在的相互作用有关^[16]。目前二者共病的病理生理学机制仍在广泛研究中,主要包括血流动力学紊乱、神经激素系统激活、缺氧、炎症、氧化应激、能量代谢失衡等^[17],而SGLT2i可能通过改善上述病理生理学过程而对心脏及肾脏起保护作用。

2.1 改善血流动力学

既往研究表明,心排量降低导致的肾脏灌注不足是心力衰竭患者肾功能恶化的主要驱动因素^[18]。近年随机对照试验表明,静脉充血和中心静脉压升高可能在心力衰竭患者肾功能恶化中发挥关键作用^[19],其可能通过升高肾静脉压力以及肾间质静水压而降低肾脏灌注及肾小球滤过率,从而导致CKD进展^[20]。另一可能原因是静脉充血使得血液从有效循环转移至内脏容量血管,致使腹内压升高,进而导致肾毛细血管及肾小管受压,加重肾功能不全^[21-22]。SGLT2i可竞争性地阻断SGLT2受体,抑制肾小球滤过后的钠和葡萄糖的重吸收,促进尿钠及尿糖排泄,从而降低心脏前负荷并减轻静脉充血。除了抑制SGLT2外,SGLT2i能够干扰近端肾小管上皮细胞中与SGLT2共定位的 Na^+-H^+ 交换体3(Na^+-H^+ exchanger 3, NHE-3),减弱葡萄糖和钠的重吸收,维持钠离子向致密斑的输送,在管球反馈的作用下入球小动脉收缩,肾小球内压降低,从而对肾脏起到保护作用^[23]。此外,对于心力衰竭合并CKD患者,传统利尿剂会引起血管内、外容量同时减少,而SGLT2i可更多地减少组织间液量,在不影响灌注的前提下降低前负荷及减轻静脉充血^[24],这体现了SGLT2i治疗心力衰竭合并CKD患者的优势。

2.2 抑制神经激素系统

心力衰竭和CKD患者普遍存在交感神经系统的慢性激活。心力衰竭合并CKD引发的动脉充盈不足或静脉充血可

反射性激活交感神经系统,刺激肾素-血管紧张素-醛固酮系统,导致血管升压素、去甲肾上腺素等神经激素过度分泌^[25]。神经激素系统的长期慢性激活不仅加重原有的水钠潴留,增加心脏和肾脏循环的负担,还通过复杂的信号通路促进心脏及肾脏的纤维化,使心肾功能进一步恶化^[26]。SGLT2i产生的利尿效应通过减少心脏及肾脏传入大脑信号而抑制交感神经系统激活,从而纠正液体潴留^[27]。动物实验表明,达格列净能够降低神经源性高血压模型小鼠心脏和肾脏组织中酪氨酸羟化酶以及去甲肾上腺素水平,从而降低交感神经系统活性^[28],恩格列净能够抑制糖尿病模型兔的肾交感神经过度活动^[29]。研究显示,达格列净可降低心力衰竭合并CKD患者肌肉交感神经活动^[30]。此外,SGLT2i可改善交感神经活动的昼夜节律,从而影响全身肾素-血管紧张素系统的活动^[31-32]。有研究表明,SGLT2i短暂的利尿作用可能导致全身肾素-血管紧张素系统的适度激活,这种激活对于维持正常的肾小球滤过可能起着重要作用。但研究者在长期接受治疗的心力衰竭合并CKD患者中并没有观察到肾素-血管紧张素系统被激活^[33]。此外,SGLT2i还可以选择性地减轻心力衰竭患者的间质水肿,这可能会减轻容量不足引发的反射性神经激素系统激活^[34]。

2.3 改善缺氧、延缓心肾损伤

发生心力衰竭和CKD时心脏及肾脏长期处于缺血缺氧状态,心肌和肾小管细胞利用氧气能力下降,进而对心脏及肾脏的结构及功能产生不利影响^[35-36]。缺氧诱导因子1(hypoxia-inducible factor 1, HIF-1)的 α 亚基即HIF-1 α 表达上调可促进心脏和肾脏损伤的进展^[37]。与HIF-1 α 相反,HIF-2 α 可抑制缺氧诱导的细胞应激反应和炎症反应,并在心脏和肾脏中发挥细胞保护作用^[38]。研究发现,SGLT2i可通过降低近端小管上皮细胞的线粒体耗氧来抑制缺氧诱导的HIF-1 α 积聚,降低HIF-1 α 及其靶基因的表达^[39]。动物实验进一步证明,SGLT2i可降低小鼠肾小管中HIF-1 α 表达水平,减少间质纤维连接蛋白,从而减轻肾损伤^[40];同时,SGLT2i还可以通过上调Sirtuin-1对特定赖氨酸残基进行脱乙酰作用而直接选择性地激活HIF-2 α ^[41-42],从而减轻心肌细胞缺氧损伤及肾细胞纤维化和炎症反应^[43]。HIF-2 α 还是促红细胞生成素产生的主要生理刺激物,SGLT2i可以通过上述机制提高促红细胞生成素水平,改善贫血,从而改善心脏和肾脏组织的氧合,起到心血管和肾脏保护作用。此外,SGLT2i还可通过抑制SGLT2以及NHE-3而减少肾小管重吸收钠,降低腺苷三磷酸(adenosine triphosphate, ATP)依赖性肾小管工作量和氧需求,缓解肾脏缺氧^[44]。

2.4 抑制炎症反应、减轻氧化应激

心力衰竭和CKD共病会使全身处于炎症状态,这种炎症状态会引发血管内皮功能受损和氧化应激,导致心脏和肾脏纤维化重构,使心脏和肾脏功能进一步恶化^[25]。研究表明,SGLT2i在体外和动物模型中可减轻炎症和氧化应激,进而使炎症标志物(白介素6、白介素1 β)、血小板反应性指标(P-选择素)和氧化负荷指标(活性氧)明显降低,抗氧化水平指标(超氧化物歧化酶、谷胱甘肽和总抗氧化能力)升

高^[45-47]。心力衰竭合并CKD时心肌细胞处于氧化应激状态, SGLT1与Na⁺-H⁺交换体1(Na⁺-H⁺ exchanger 1, NHE-1)表达上调, 胞质内钠水平增加, 从而促进经由膜结合钠-钙交换转运蛋白的钙内流以及促进经由线粒体表面结合钠-钙交换转运蛋白的钙从线粒体转移到胞质中来提高胞质内钙水平^[48-49]。胞质内钙水平升高可降低钙瞬变和肌浆网钙储备, 导致心肌收缩功能减弱。SGLT2i通过直接抑制心肌细胞表面NHE-1和SGLT1, 以逆转氧化应激诱导的钠超载及钙超载, 改善线粒体功能, 延缓心脏电生理重构及纤维化, 进而使心脏获益。另外, 哺乳动物雷帕霉素靶蛋白复合物1(mammalian target of rapamycin complex 1, mTORC1)通过抑制自噬、促进氧化应激和炎症等多种机制而促进CKD的发生发展^[50]。研究表明, 达格列净可抑制近端肾小管细胞中mTORC1的激活, 从而缓解肾小管间质纤维化^[51]。此外, SGLT2i发挥抗炎作用的可能机制还包括影响腺苷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)/SIRT1/过氧化物酶体增殖物激活受体 γ 辅助激活因子1 α (peroxisome proliferator activated receptor γ coactivator-1 α , PGC-1 α)信号传导、各种细胞因子、NLRP3炎症小体^[52-53]和富含亮氨酸重复序列的Nod样受体蛋白炎症小体(Nods contain leucine-rich repeats, NOD-LRRs)等^[54]。

2.5 纠正心肾能量代谢

心力衰竭和CKD共病时, 心脏及肾脏能量代谢供需平衡被破坏, 能量代谢失衡进一步加重心肾损伤。在这种情况下, 酮体作为一种超级燃料, 能够在消耗更少氧气的同时生成更多的ATP, 进而提升心脏及肾脏的能量利用效率^[55]。SGLT2i能够通过抑制SGLT2而使进入细胞的葡萄糖减少, 导致脂肪分解、酮体生成增多。在这种情况下, 心脏和肾脏能量利用均从葡萄糖转化为脂肪酸和酮体, 增加了心脏和肾脏的额外能量来源, 同时减少了脂肪组织产生的细胞内脂质毒性^[56]。在动物模型中, SGLT2i通过诱导代谢向禁食样代谢反应转变而抑制了mTORC1过度激活, 从而改善线粒体功能^[57]。SGLT2i还可以通过激活SIRT1/PGC-1 α /FGF21信号通路而促进酮体生成及细胞自噬, 进而发挥肾功能保护作用^[58]。研究表明, SGLT2i并非通过增加酮体氧化途径而升高 β -羟丁酸水平而抑制氧化应激、炎症和纤维化, 进而延缓肾功能下降^[59], 但该结论还需要更多的动物实验进一步证实。另外, SGLT2i对心力衰竭和CKD的传统危险因素亦产生影响。除了通过降低血糖控制T2DM的进展而达到心肾保护作用外, SGLT2i还可以通过抑制葡萄糖吸收促进热量丢失, 减轻体质量和肝脏及皮下脂肪^[60]。恩格列净还可通过增强脂肪褐变以减轻肥胖诱导的炎症。同时, SGLT2i还可以促进尿酸排泄, 降低血清尿酸水平, 减少高尿酸血症介导的炎症和动脉粥样硬化以实现心肾保护作用^[61]。

3 SGLT2i治疗心力衰竭合并CKD的临床证据

3.1 SGLT2i在不同类型心力衰竭合并CKD患者中的心肾获益

目前已经发表了多项针对SGLT2i治疗心力衰竭疗效的大型随机对照试验, 这些试验重点关注达格列净、恩格列净和索格列净等SGLT2i对不同类型心力衰竭的治疗效果, 其中肾

脏结局作为次要临床结局指标^[62-67]。尽管未见专门针对心力衰竭合并CKD患者的研究, 但以上研究均根据基线估算肾小球滤过率(estimated glomerular filtration rate, eGFR)进行了亚组分析, 其中eGFR $<60 \text{ ml} \cdot \text{min}^{-1} \cdot (1.73 \text{ m}^2)^{-1}$ 亚组符合改善全球肾脏病预后组织(Kidney Disease: Improving Global Outcomes, KDIGO)对CKD的定义^[68], 可以根据其亚组分析结果推断SGLT2i对不同类型心力衰竭合并CKD的治疗效果。

3.1.1 射血分数降低的心力衰竭(heart failure with preserved ejection fraction, HFpEF)合并CKD

糖尿病患者心血管结局研究(cardiovascular outcome trails, CVOTs)证实, SGLT2i能改善T2DM患者心血管、肾脏临床预后^[62]。近年来, DAPA-HF研究^[63]和EMPEROR-Reduced研究^[64]进一步明确, SGLT2i可以延缓非糖尿病HFpEF患者心力衰竭恶化, 降低其心血管死亡风险及改善其肾脏结局。两项研究均纳入了左心室射血分数(left ventricular ejection fraction, LVEF) $\leq 40\%$ 的慢性心力衰竭患者, DAPA-HF研究^[63]排除了eGFR $<30 \text{ ml} \cdot \text{min}^{-1} \cdot (1.73 \text{ m}^2)^{-1}$ 或肾功能快速下降的患者, 结果显示, 相较于eGFR $\geq 60 \text{ ml} \cdot \text{min}^{-1} \cdot (1.73 \text{ m}^2)^{-1}$ 亚组, 达格列净可降低eGFR $<60 \text{ ml} \cdot \text{min}^{-1} \cdot (1.73 \text{ m}^2)^{-1}$ 亚组的HFpEF患者复合心血管事件发生风险。EMPEROR-Reduced研究^[64]剔除了eGFR $<20 \text{ ml} \cdot \text{min}^{-1} \cdot (1.73 \text{ m}^2)^{-1}$ 或需要透析治疗的HFpEF患者, 该研究观察了eGFR变化斜率以及复合肾脏终点, 结果显示, 恩格列净能够降低HFpEF患者eGFR变化斜率、复合肾脏终点发生风险。EMPEROR-Reduced研究的预先指定分析指出, 恩格列净对HFpEF患者主要临床结局及肾脏复合终点的作用与患者入组时eGFR、蛋白尿状态无关。在eGFR为20~60 $\text{ml} \cdot \text{min}^{-1} \cdot (1.73 \text{ m}^2)^{-1}$ 的HFpEF合并CKD患者中, 恩格列净亦能使患者心肾获益^[65]。

3.1.2 射血分数保留的心力衰竭(heart failure with preserved ejection fraction, HFpEF)/射血分数轻度降低的心力衰竭(heart failure with mildly reduced ejection fraction, HFmrEF)合并CKD

由于HFpEF和HFmrEF临床表型的多样性以及病理生理学机制的异质性和复杂性, 相关研究并未发现传统改善HFpEF预后的药物〔包括 β -受体阻滞剂、ACEI/血管紧张素II受体拮抗剂(angiotensin II receptor blockers, ARB)/血管紧张素受体-脑啡肽酶抑制剂(angiotensin receptor-neprilysin inhibitors, ARNI)、醛固酮受体拮抗剂(mineralocorticoid receptor antagonist, MRA)〕对HFpEF/HFmrEF患者预后有益^[66]。为此, EMPEROR-Preserved研究^[67]和DELIVER研究^[69]针对SGLT2i对LVEF $>40\%$ 的慢性心力衰竭患者的心肾获益进行了探究。其中, EMPEROR-Preserved研究^[67]排除了eGFR $<20 \text{ ml} \cdot \text{min}^{-1} \cdot (1.73 \text{ m}^2)^{-1}$ 或需要透析治疗的患者, 结果显示, 恩格列净可降低HFpEF/HFmrEF患者心力衰竭住院率和因心力衰竭住院的相对风险; 此外, 恩格列净还减缓了eGFR下降率, 但未改变肾脏复合终点的风险; 亚组分析结果显示, 无论患者入组时eGFR如何, 恩格列净均可使HFpEF/HFmrEF患者心脏获益。DELIVER研究^[69]排除了

eGFR $<25\text{ ml}\cdot\text{min}^{-1}\cdot(1.73\text{ m}^2)^{-1}$ 的患者,结果显示,无论是否合并T2DM,达格列净均可降低HFpEF/HFmrEF患者心血管死亡率、因心力衰竭住院或因心力衰竭急诊就医的发生率。虽然DELIVER研究^[69]不包括肾脏次要结局指标,但其预先指定分析指出,达格列净对HFpEF/HFmrEF患者心血管获益和eGFR下降率的影响在不同肾脏疾病患者中没有统计学差异^[70]。上述研究表明,无论CKD病因、是否合并T2DM,在eGFR $\geq 25\text{ ml}\cdot\text{min}^{-1}\cdot(1.73\text{ m}^2)^{-1}$ 的HFpEF/HFmrEF患者中,SGLT2i均可降低心力衰竭事件发生风险以及延缓肾功能恶化。

3.1.3 急性心力衰竭合并CKD

目前针对SGLT2i在急性心力衰竭方面的研究较少,其有效性、安全性及用药时机均缺乏相关证据。SOLOIST-WHF研究^[71]纳入了eGFR $<30\text{ ml}\cdot\text{min}^{-1}\cdot(1.73\text{ m}^2)^{-1}$ 的T2DM合并心力衰竭患者,结果显示,索格列净降低了患者心血管死亡、住院和心力衰竭紧急就诊的风险,且其风险与eGFR无关。EMPULSE试验^[72]纳入了eGFR $<20\text{ ml}\cdot\text{min}^{-1}\cdot(1.73\text{ m}^2)^{-1}$ 的急性心力衰竭住院患者,结果显示,无论是否合并T2DM,恩格列净均可使CKD患者心脏获益;该试验中透析、肾移植或eGFR持续降低等次要结局的发生率极低(恩格列净组为0,安慰剂组为0.8%);另外,该试验还观察了恩格列净对患者出院后临床结局的影响,结果显示,出院后继续治疗组eGFR保持不变,而停药组第3个月eGFR开始下降。尽管两项研究中患者开始接受SGLT2i的时机以及治疗持续时间不同,但其均提示SGLT2i可使急性心力衰竭合并CKD患者心脏获益。推测早期启动SGLT2i治疗和出院后长期维持SGLT2i治疗均有效且安全。

最近一项荟萃分析汇集了DELIVER、EMPEROR-Preserved、DAPA-HF、EMPEROR-Reduced和SOLOIST-WHF研究的数据,结果显示,无论心力衰竭分型如何,SGLT2i均可降低心力衰竭患者总体心血管死亡或心力衰竭住院风险;根据基线eGFR进行亚组分析,结果显示,SGLT2i可使eGFR $<60\text{ ml}\cdot\text{min}^{-1}\cdot(1.73\text{ m}^2)^{-1}$ 的心力衰竭患者心血管死亡或心力衰竭住院风险降低22%,且eGFR $<60\text{ ml}\cdot\text{min}^{-1}\cdot(1.73\text{ m}^2)^{-1}$ 和eGFR $\geq 60\text{ ml}\cdot\text{min}^{-1}\cdot(1.73\text{ m}^2)^{-1}$ 亚组之间没有明显差异,进一步证实SGLT2i的心肾获益独立于eGFR^[73]。

3.2 SGLT2i在CKD患者中的心肾获益

近期在CKD患者中完成的随机对照研究^[15, 74-75]不仅探究了SGLT2i对CKD患者肾脏结局的影响,还对心血管终点事件进行了观察。其中CREDESCENCE研究^[74]发现,在eGFR为 $30\sim 89\text{ ml}\cdot\text{min}^{-1}\cdot(1.73\text{ m}^2)^{-1}$ 的T2DM合并CKD患者中,卡格列净可降低其终末期肾病、血清肌酐倍增、肾脏疾病死亡等复合肾脏结局事件、心血管病死亡和因心力衰竭恶化住院风险;此外,卡格列净可降低不同eGFR亚组T2DM合并CKD患者心血管病死亡和因心力衰竭恶化住院风险,其中对 $30\sim 45\text{ ml}\cdot\text{min}^{-1}\cdot(1.73\text{ m}^2)^{-1}$ 亚组的降低效果最明显。DAPA-CKD研究^[75]在全球范围内招募了4 303例CKD 2~4期和尿蛋白排泄率升高的患者,结果显示,无论是否合并

T2DM,达格列净均可减慢患者eGFR下降速度,逆转蛋白尿及延缓肾脏病进展,在改善CKD患者肾脏结局的同时,可降低患者心血管事件发生风险。此外,该试验的事后分析显示,达格列净对肾脏的保护作用不受患者是否同时使用ACEI或ARB治疗的影响。EMPA-KIDNEY研究^[15]纳入了eGFR $>20\text{ ml}\cdot\text{min}^{-1}\cdot(1.73\text{ m}^2)^{-1}$ 的非糖尿病相关CKD患者,结果显示,与安慰剂相比,恩格列净可降低肾功能下降及其他肾脏不良事件的发生率,但并未降低心力衰竭事件发生风险,考虑与心力衰竭发生率少于预期有关;该试验对eGFR为 $20\sim 29\text{ ml}\cdot\text{min}^{-1}\cdot(1.73\text{ m}^2)^{-1}$ 的2 282例患者进行亚组分析,结果显示,恩格列净能够减慢CKD进展和降低心血管死亡发生风险,提示SGLT2i对肾脏和心脏有双重保护作用。最近一项荟萃分析提示,与肾功能保留[GFR $>60\text{ ml}\cdot\text{min}^{-1}\cdot(1.73\text{ m}^2)^{-1}$]患者比较,SGLT2i对CKD患者的心血管益处可能更大^[76]。上述研究表明,SGLT2i能延缓不同eGFR的CKD患者的肾功能下降,降低肾脏不良事件发生率,同时还能降低心力衰竭事件发生风险,这为心力衰竭合并CKD患者的治疗提供了有力的循证依据。

4 SGLT2i的不良反应及安全性

目前临床报道的SGLT2i的主要不良反应有尿路感染、酮症酸中毒等^[77]。SGLT2i增加尿路感染的风险与其抑制近端小管SGLT2、增加尿路葡萄糖积累有关,可通过加强患者隐私部位卫生管理降低其风险^[78]。临床试验报道,接受SGLT2i治疗的T2DM患者酮症酸中毒发生率与接受安慰剂治疗的患者相似^[79],但有研究报道了罕见的血糖正常型酮症酸中毒病例^[80],因而在SGLT2i用药过程中应加强患者酮体检测。研究表明,随着肾功能进行性下降,心力衰竭合并CKD患者高钾血症发生风险变高,常导致传统治疗中ACEI/ARB和MRA剂量下调或停药^[81]。一项纳入近50 000例接受SGLT2i治疗的受试者的大型荟萃分析显示,SGLT2i可降低高钾血症的发生率而不增加低钾血症发生风险^[82],研究者在心力衰竭患者中也得到了相同的结果^[83]。此外,以上研究均未观察到药物间相互作用,尤其是SGLT2i与现有抗心力衰竭药物、降压药或利尿剂的相互作用,故SGLT2i可常规用于心力衰竭合并CKD患者。

5 小结

心力衰竭与CKD共病可加重患者病情,延长患者住院时间,增加患者死亡风险,其已成为老年社会疾病负担的重要组成部分。而SGLT2i凭借其心肾保护作用为这类患者提供了潜在的治疗选择。一方面,SGLT2i的心肾保护作用在未合并T2DM的心力衰竭和CKD患者中依旧明显;另一方面,当eGFR $<45\text{ ml}\cdot\text{min}^{-1}\cdot(1.73\text{ m}^2)^{-1}$ 时,SGLT2i因肾脏排糖能力的大幅下降而丧失抗糖尿病作用,但其心脏及肾脏保护作用仍然存在^[84],提示SGLT2i可能具有直接心肾靶向作用,作用机制包括改善血流动力学、抑制神经激素系统、减轻缺氧、抑制炎症、减轻氧化应激、改善心肾能量代谢等。SGLT2i可以通过降低血糖和直接对心肾靶向双重作用发挥其心肾保护作用,其机制还需通过更多实验和研究进一步明确和完善。

复杂的病理生理学机制以及缺乏针对心力衰竭合并CKD患者的临床研究使得这类患者的治疗缺乏指南指导, 目前主要的治疗药物包括利尿剂、血管扩张剂、正性肌力药、ACEI/ARB/ARNI、MRA, 但上述药物存在一些不良反应, 如利尿剂抵抗、肾功能进行性恶化等^[81]。与传统治疗药物相比, SGLT2i在治疗心力衰竭合并CKD方面具有一定优势。首先, SGLT2i可以通过增加肾脏排糖而改善血糖水平, 从而达到心血管和肾脏保护作用。其次, SGLT2i能够改善心脏功能、减少心力衰竭相关的住院和死亡风险。在肾脏方面, SGLT2i能够逆转蛋白尿、减缓肾功能恶化速度, 并减少与肾脏疾病相关的不良事件^[85]。

临床试验已经证实, SGLT2i对T2DM患者具有心肾保护作用^[63]。越来越多的研究也开始关注SGLT2i在非糖尿病患者中的心肾保护作用。DAPA-HF研究^[63]、EMPEROR-Reduced研究^[64]、DELIVER研究^[69]、EMPULSE试验^[72]表明, 无论是合并T2DM, SGLT2i可使不同类型心力衰竭合并CKD患者心肾获益, 这种获益在eGFR低至20 ml·min⁻¹·(1.73 m²)⁻¹的心力衰竭合并CKD患者中依旧存在; 同时, DAPA-CKD研究^[75]和EMPA-KIDNEY研究^[15]表明, 无论CKD病因及血糖状态如何, SGLT2i均能降低心力衰竭合并CKD患者eGFR、终末期肾病或肾脏原因死亡的风险。《2023 ESC糖尿病患者心血管疾病管理指南》^[86]建议, eGFR≥20 ml·min⁻¹·(1.73 m²)⁻¹的CKD合并T2DM患者使用SGLT2i治疗(I级, A); 《KDIGO 2023 CKD指南》^[87]亦建议, 使用SGLT-2i治疗eGFR≥20 ml·min⁻¹·(1.73 m²)⁻¹的成年心力衰竭合并CKD患者(I级, A)。

此外, 目前大多数临床试验常排除重度肾功能不全的患者, 尤其是GFR<20 ml·min⁻¹·(1.73 m²)⁻¹的患者, 在重度肾功能不全甚至透析患者中, SGLT2i的心肾保护作用是否存在以及其作用机制仍需更多研究进一步验证, 以更好地分析SGLT2i在心力衰竭合并不同程度肾功能不全患者中的有效性和安全性。

作者贡献: 李红薇进行文章的构思与设计, 论文撰写; 万正韵进行资料整理, 论文的修订; 严喜胜负责文章的质量控制及审校, 对文章整体负责、监督管理。

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