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达格列净治疗心血管疾病的疗效及其机制

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【摘要】 目前, 动脉粥样硬化性心血管疾病(ASCVD)、心力衰竭(HF)、心房颤动(AF)等心血管疾病尚无治愈方法, 只能通过药物长期治疗来延缓病情进展, 患者发病率及病死率较高。钠-葡萄糖协同转运蛋白2抑制剂——达格列净为一种相对较新的口服降糖药物, 目前研究较为广泛, 但部分研究发现, 无论患者是否合并糖尿病, 达格列净均可以降低心血管疾病患者的心血管死亡率或因HF住院率, 因而其在心血管疾病治疗中也可发挥重要作用。本文综述了达格列净治疗ASCVD、HF、AF的疗效及其机制, 以期为中心血管疾病的预防及治疗提供新思路。

【关键词】 心血管疾病; 动脉粥样硬化性心血管疾病; 心力衰竭; 心房颤动; 达格列净; 综述

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Effect and Mechanism of Dapagliflozin in the Treatment of Cardiovascular Diseases

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【Abstract】 At present, there is no cure for atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), atrial fibrillation (AF) and other cardiovascular diseases, which can only be delayed by long-term drug treatment, and the morbidity and mortality of patients are relatively high. The sodium-glucose cotransporter 2 inhibitor, dapagliflozin, is a relatively new oral hypoglycemic drug, which has been widely studied. However, some studies have found that dapagliflozin can reduce the cardiovascular mortality or hospitalization rate due to HF in patients with cardiovascular disease regardless of whether the patients are complicated with diabetes, so it can also play an important role in the treatment of cardiovascular disease. This article reviewed the effect and mechanism of dapagliflozin in the treatment of ASCVD, HF and AF, in order to provide new ideas for the prevention and treatment of cardiovascular diseases.

【Key words】 Cardiovascular diseases; Atherosclerotic cardiovascular disease; Heart failure; Atrial fibrillation; Dapagliflozin; Review

目前, 动脉粥样硬化性心血管疾病(atherosclerotic cardiovascular disease, ASCVD)、心力衰竭(heart failure, HF)、心房颤动(atrial fibrillation, AF)等心血管疾病的发病率及病死率逐年上升, 临床上多采用药

物长期治疗来控制病情进展^[1-3]。钠-葡萄糖协同转运蛋白2抑制剂(sodium-glucose cotransporter 2 inhibitors, SGLT2i)可以通过抑制肾近端小管的钠-葡萄糖协同转运蛋白(sodium-glucose cotransporter, SGLT)2来减少葡萄糖的肾脏重吸收, 进而增加尿糖的排泄, 从而降低

血糖水平,其中达格列净为一种相对较新的口服降糖药物,目前研究较为广泛^[4]。研究表明,无论患者是否合并糖尿病,达格列净均可以降低心血管疾病患者的心血管死亡率或因HF住院率,这表明达格列净在心血管疾病治疗中也可发挥重要作用^[5]。本文通过回顾相关文献,总结了达格列净治疗ASCVD、HF、AF的效果及其机制,以期对心血管疾病的诊治提供新思路。

1 达格列净治疗ASCVD的效果及其机制

1.1 达格列净治疗ASCVD的效果

ASCVD包括外周动脉闭塞性疾病、冠状动脉粥样硬化性心脏病(急性冠脉综合征、稳定性心绞痛、缺血性心肌病等)、缺血性脑卒中^[6],而心肌梗死作为急性冠脉综合征的一种,是HF和心源性死亡的主要原因之一^[7]。大量研究表明,达格列净对ASCVD患者有明显的益处^[8-12]。达格列净不但可以改善心肌梗死模型小鼠受损的心功能,而且可以抑制心室重塑^[8]。DAYEM等^[5]采用达格列净治疗100例冠状动脉介入术后患有急性冠脉综合征的非糖尿病患者,也得出了相同的结论。ZELNIKER等^[12]研究显示,N末端脑钠肽前体(N-terminal pro-brain natriuretic peptide, NT-proBNP)及高敏肌钙蛋白T(high-sensitivity cardiac troponin T, hs-cTnT)水平升高(即NT-proBNP>165 ng/L, hs-cTnT>15.5 ng/L)的ASCVD合并T2DM患者经达格列净治疗后,其动脉粥样硬化事件发生率降低,且接受达格列净治疗的患者主要不良心血管事件(major adverse cardiovascular events, MACE)发生率低于接受安慰剂治疗的患者。MAO等^[13]在急性心肌梗死合并2型糖尿病患者中发现,与不使用达格列净者相比,使用达格列净者再住院率降低。但CESARO等^[14]对143例接受达格列净治疗的糖尿病合并ASCVD患者随访1年发现,27例患者不得不提前停药,其中17例患者发生泌尿生殖感染、7例患者治疗效果不佳[糖化血红蛋白(glycosylated hemoglobin, HbA_{1c})未达到目标或下降不明显]、3例患者不想继续使用该药物进行治疗。

总之,达格列净可有效改善ASCVD患者心功能,抑制心室重塑,且安全性较好,但同时要定期监测其泌尿生殖感染等不良反应的发生情况。此外,达格列净治疗ASCVD的效果还需要更多大型的循证医学证据进一步证明。

1.2 达格列净治疗ASCVD的机制

(1)调节肠道菌群。研究表明,达格列净可以改变心肌梗死模型小鼠肠道微生物区系结构,使肠道乳杆菌科、脱硫弧菌科等有益菌的丰度增加,其中乳杆菌科可通过调节交感神经张力和心肌收缩力而改善小鼠预后,但脱硫弧菌科与心肌梗死之间的关系仍不清楚^[7]。(2)抑制心肌酶释放。一项动物研究显示,长

期服用达格列净可预防缺血性心脏病模型大鼠发生心肌缺血再灌注损伤,其机制为达格列净可通过激活磷脂酰肌醇-3-激酶(phosphatidylinositol 3-kinase, PI3K)/蛋白激酶B(protein kinase B, PKB)/哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin, mTOR)信号通路而升高PI3K、PKB、mTOR的磷酸化水平,进而抑制细胞凋亡和心肌细胞中肌酸激酶同工酶(creatine kinase muscle/brain subtype, CK-MB)、乳酸脱氢酶(lactate dehydrogenase, LDH)的释放^[15-16]。(3)抑制炎症递质的释放。研究显示,达格列净可以通过降低缺血性心脏病模型大鼠的一氧化氮合酶、诱导型一氧化氮合酶mRNA表达而降低循环炎症递质水平[如肿瘤坏死因子 α (tumor necrosis factor- α , TNF- α)和白介素(interleukin, IL)-1 β],进而抑制心脏脂质过氧化和减轻动脉粥样硬化、内皮功能障碍、血管平滑肌功能障碍^[16]。也有研究发现,达格列净可能通过抑制心肌缺血再灌注损伤模型小鼠体内炎症因子(IL-6)的表达而降低体内铁调素水平(因为IL-6可促进转录激活因子3与铁调素启动子的结合,进而增加铁调素水平^[17]),进而抑制心肌内出血和心室重构^[18]。

2 达格列净治疗HF的效果及其机制

2.1 达格列净治疗HF的效果

有研究指出,无论左心室射血分数如何, HF患者服用达格列净12周后其相关不适症状均得到了明显改善^[19-20]。相关研究也显示,达格列净可以降低慢性HF患者左心房体积指数、左心室质量,从而改善患者心脏结构及功能^[21]。一项纳入118例急性HF患者的前瞻性研究表明,入院后尽早开始服用达格列净与缩短患者住院时间有关^[22]。一项纳入6 263例左心室射血分数>40%的HF患者的研究发现,无论患者目前服药种类及状态如何,口服达格列净均可减少HF恶化或心血管死亡事件的发生^[23]。对于合并肾功能异常的射血分数降低的心力衰竭(heart failure with reduced ejection fraction, HFrEF)患者,达格列净可以明显减慢肾小球滤过率的下降速度,其可通过改善患者的肾功能来延缓肾脏疾病进展^[24]。《2021 ESC急性心力衰竭诊断和治疗指南》^[25]及《2022 AHA/ACC/HFSA心力衰竭管理指南》^[26]均建议,在所有已接受血管紧张素受体脑啡肽酶抑制剂(angiotensin receptor-neprilysin inhibitor, ARNI)、 β -受体阻滞剂和盐皮质激素受体拮抗剂(mineralocorticoid receptor antagonist, MRA)治疗的HFrEF患者中,无论其是否患有糖尿病,均应添加SGLT2i来达到降低HF住院率和心血管疾病死亡率的目的。

研究显示,达格列净可导致HFrEF患者肾小球滤过率短暂下降,但这通常不会使患者出现肾小管损

伤,这可能是血流动力学改变的结果,此外,从长远来看,达格列净对患者的预后有一定好处^[27]。还有研究显示,HFrEF患者口服达格列净后其血浆血红蛋白(hemoglobin, HGB)、血细胞比容(hematocrit, HCT)升高,且1个月时其肾小球滤过率随着血浆血红蛋白水平升高而下降^[23]。另一项研究发现,HFrEF稳定期患者规律口服达格列净3个月后明尼苏达心力衰竭生活质量问卷(Minnesota Living with Heart Failure Questionnaire, MLHFQ)评分随着血红蛋白水平升高而降低^[24]。研究表明,秋水仙碱联合达格列净可协同治疗高尿酸血症合并HF患者,其可缩短患者治疗时间,所以对于HF合并痛风患者,用达格列净抗HF的同时,需注意其合并症用药疗程^[28]。一项涉及11 007例接受口服达格列净治疗的HF患者的随机试验显示,女性患者预后优于男性,但达格列净对HF患者的治疗效果不受性别影响^[29],欧振飞等^[30]研究也得出了相似结果。研究显示,口服达格列净可使心血管疾病患者血压轻度降低,也可使收缩压 <120 mmHg(1 mmHg=0.133 kPa)的HF患者复发率和死亡率升高,因此,使用达格列净治疗HF患者时需密切关注患者血压变化,适时调整用药方案^[31]。据报道,达格列净可能会引起继发性的红细胞增多症和尿路感染等相关并发症,而恩格列净较达格列净更易引起尿路感染^[32-33]。还有研究表明,HF患者服用达格列净后可引起心室重塑^[34]。

总之,达格列净可改善HF患者疾病相关不适症状,缩短住院时间,降低不良事件发生率、再住院率,延缓疾病进展,但应注意观察患者肾小球滤过率、血浆HGB及HCT等相关化验指标病理性升高或生理性一过性升高情况,还应注意合并症、性别、血压等对疗效的影响及相关不良反应发生情况。

2.2 达格列净治疗HF的机制

(1)降低促炎蛋白水平。据报道,达格列净可通过降低HF患者循环中促炎蛋白单核细胞趋化蛋白1(monocyte chemoattractant protein-1, MCP-1)、生长刺激表达基因2蛋白(growth stimulation expressed gene 2, ST2)水平来降低炎症因子表达水平,从而降低动脉僵硬,抑制心肌纤维化,进而缓解临床症状^[35]。YEOH等^[36]对3 048例HF患者随访1年发现,与不口服达格列净的HF患者相比,规律口服达格列净的HF患者血清内皮素1(endothelin-1, ET-1)水平降低,考虑可能是达格列净通过抑制肾脏近端小管分泌ET-1而抑制心肌细胞肥大及心肌纤维化。(2)激活PKB/糖原合成酶激酶3(glycogen synthesis kinase, GSK3)、丝裂原活化的细胞外信号调节激酶(mitogen-activated extracellular signal-regulated kinase, MEK)/细胞外调节蛋白激酶(extracellular regulated protein kinase, ERK)

信号通路。研究显示,沙库巴曲缬沙坦可以增强达格列净的抗纤维化作用,而螺内酯可以弱化达格列净的抗纤维化作用,其机制为达格列净+沙库巴曲缬沙坦可通过抑制PKB/GSK3、PYK2、STAT信号通路的磷酸化{抑制PKB在苏氨酸308和丝氨酸473位点的磷酸化及其下游GSK3、酪氨酸蛋白激酶2(proline-rich tyrosine kinase 2, PYK2)、下游信号转录蛋白[如信号转导及转录激活因子3(signal transducer and activator of transcription 3, STAT3)]的磷酸化}而降低HF患者促炎细胞因子水平,抑制心肌纤维化、心室重塑;相反,达格列净+螺内酯可能通过抑制PKB、GSK3的磷酸化及激活丝裂原活化蛋白激酶MEK、ERK信号通路而增加半乳糖凝集素3(galectin 3, GAL3)、炎症因子(如IL-1 β 、IL-6)水平,从而减弱达格列净对HF患者的治疗效果^[37-38]。(3)激活腺苷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)/mTOR信号通路。MA等^[39]研究发现,达格列净可通过激活AMPK/mTOR信号通路促进HF模型大鼠心肌细胞的自噬作用,从而特异性清除活性氧和炎症细胞因子,降低心肌组织Caspase-3/7水平,减少心肌细胞凋亡,进而抑制心室重塑并改善心功能。

3 达格列净治疗AF的效果及其机制

3.1 达格列净治疗AF的效果

研究显示,不论AF患者肾小球滤过率如何,口服达格列净均可降低其不良心血管事件发生率,且肾小球滤过率偏低的AF患者可能在这方面获益更大^[40]。但目前关于达格列净治疗AF的研究很少,需要更多大样本量的多中心、前瞻性研究进一步研究其治疗效果。

3.2 达格列净治疗AF的机制

(1)激活Toll样受体4(Toll-like receptor 4, TLR4)/核因子 κ B(nuclear factor kappa-B, NF- κ B)/NOD样受体热蛋白结构域相关蛋白3(NOD-like receptor thermal protein domain associated protein 3, NLRP3)信号通路。一项随机对照试验发现,达格列净可能通过激活TLR4/NF- κ B/NLRP3信号通路,下调AF模型大鼠IL-1 β 、转化生长因子 β 1(transforming growth factor- β 1, TGF- β 1)、 β -肌球蛋白重链(β -myosin heavy chain, β -MHC)、基质金属蛋白酶2(matrix metalloproteinases 2, MMP2),从而抑制心房结构重构和电重构^[41]。(2)减轻电生理异常。研究发现,阵发性AF患者的心脏电-机械耦联间期比非阵发性AF患者长,而达格列净可降低P波指数、延迟整流钾电流,缩短动作电位时程,从而减轻电生理异常,进而降低AF发生风险^[42-43]。

目前,关于达格列净治疗AF的机制研究很少,仍然需要大量相关循证医学证据来进一步分析。

4 小结及展望

综上所述,达格列净作为心血管疾病治疗方面的新药,对于ASCVD患者,其可通过调节肠道菌群、抑制心肌酶释放、抑制炎症递质释放而改善患者心脏结构及功能,抑制心室重塑,且安全性较好;对于HF患者,其可通过降低促炎蛋白水平及激活Akt/GSK3、AMPK/mTOR信号通路而改善患者疾病相关不适症状,缩短住院时间,降低不良事件发生率、再住院率,延缓疾病进展;对于AF患者,其可通过激活TLR4/NF- κ B/NLRP3信号通路及减轻电生理异常而降低患者不良心血管事件发生率。但在用药期间要定期监测患者不良反应发生情况。此外,目前国内外关于达格列净治疗ASCVD、HF、AF的研究仍较少,尚需要更多的临床试验及动物实验进一步探讨达格列净对心血管疾病的治疗效果及其具体机制。

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本文无利益冲突。

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