·综述·

心力衰竭与糖尿病共病及其临床用药研究现状

李慧颖[1],白永怿[1,2],刘宏斌[1,2,3*]

([1]解放军总医院第二医学中心心血管内科,北京 100853;[2]解放军总医院国家老年疾病临床医学研究中心,北京 100853;[3]慢性心衰精准医学北京市重点实验室,北京 100853)

【摘 要】 心力衰竭和糖尿病是现代两种重大的流行病,二者之间交互影响。临床常见心力衰竭与糖尿病共病,对临床用药安全提出了新的挑战。本文从流行病学、临床症状及预后风险、生理病理机制及用药选择4个方面对"心力衰竭与糖尿病共病"的研究现状进行系统阐述,并重点论证将心力衰竭和糖尿病单病药物应用于共病患者的安全性及有效性,为临床用药决策提供指导。

【关键词】 心力衰竭;糖尿病;共病

【中图分类号】 R541.6;R587.1 【文献标志码】 A 【DOI】 10.11915/j.issn.1671-5403.2021.01.014

Status quo of research on comorbidity of heart failure and diabetes and its clinical medication

LI Hui-Ying[1], BAI Yong-Yi[1,2], LIU Hong-Bin[1,2,3*]

([1] Department of Cardiology, the Second Medical Center of Chinese PLA General Hospital, Beijing 100853, China; [2] National Clinical Research Center for Geriatric Diseases, Chinese PLA General Hospital, Beijing 100853, China; [3] Beijing Key Laboratory of Chronic Heart Failure Precision Medicine, Beijing 100853, China)

【Abstract】 Heart failure and diabetes are two most frequent conditions in the modern times that interact with each other. Comorbidity of heart failure and diabetes is clinically common, posing new challenges to the safety of clinical medication. This paper provides a systematical review of the status quo of research on the comorbidity in the aspects of epidemiology, clinical symptoms and risk of prognosis, physiological and pathological mechanism, and drug selection, focusing on the safety and effectiveness of using drugs for heart failure and diabetes for patients with the comorbidity, to provide guidance for decision making in clinical medication.

【Key words】 heart failure; diabetes; comorbidity

This work was supported by the Medical Big Data Research and Development Project of PLA General Hospital (2018MBD-026) *and National Key Research and Development Plan of China* (2017YFC0840103).

Corresponding author: LIU Hong-Bin, E-mail: liuhbin301@163.com

心力衰竭和糖尿病是现代两种重大流行病,二者皆占用了全球范围内相当比例的医疗资源。心力衰竭是各种心脏疾病的终末期复杂临床综合征,院内死亡率和再住院风险高。糖尿病是最常见的慢性代谢性疾病,可导致心、脑、肾、血管、神经等组织和器官的严重并发症,远期危害大。心力衰竭与糖尿病共病的现象临床非常多见,而二者的共病机制从未被系统阐明,且共病状态对临床预后及用药有着潜在的深远影响。本文就心力衰竭-糖尿病共病的流行病学、临床症状及预后风险、生理病理机制及用药选择方面的研究进展进行系统综述。

1 心力衰竭-糖尿病共病的流行病学

1974年Framingham研究首先明确心力衰竭与糖尿病二者之间的流行病学关联:45~74岁的男性糖尿病患者发生充血性心力衰竭的比例是未患糖尿病男性的2倍之上,同阶段女性人群中该比例达5倍之高,糖尿病独立于共存的高血压或冠状动脉性疾病之外预测了心力衰竭[1];与此类似,Thrainsdottir等[2]研究发现任何形式的糖代谢紊乱都与心力衰竭之间

收稿日期:2020-02-06;接受日期:2020-03-04

基金项目:解放军总医院医疗大数据研发项目(2018MBD-026);国家重点研发计划重点专项课题(2017YFC0840103)

通信作者:刘宏斌,E-mail:liuhbin301@163.com

有很强的相关性。相应地,心力衰竭患者较无心力衰竭患者更易合并糖尿病。有研究表明心力衰竭患者每10年患2型糖尿病的风险比经治疗的高血压患者高18%~22%[3];Amato等[4]也发现心力衰竭独立于年龄、性别、糖尿病家族史等因素预测了2型糖尿病的发生。

总体来讲,心力衰竭患者共病糖尿病的比例为27%~48%。PARADIGM-HF研究发现8 399例射血分数减低的心力衰竭(heart failure with reduced ejection fraction, HFrEF)患者中35%有糖尿病病史,13%患有未经诊断的糖尿病[5];I-Preserve研究中,4 128例射血分数保留的心力衰竭(heart failure with preserved ejection fraction, HFpEF)患者中有27%同时患有糖尿病[6];ESC-HFA注册研究中,9 428例门诊慢性心力衰竭患者的糖尿病共病率为36.5%[7];OPTIMIZE-HF注册研究的48 612例住院心力衰竭患者中42%患有糖尿病[8];本课题组在对多中心、包含2万余份样本的心力衰竭专病数据库的分析发现,31.67%的心力衰竭患者有糖尿病病史。

2 心力衰竭-糖尿病共病患者的临床症状及预后

合并糖尿病的心力衰竭患者有更高的美国纽约心脏病学会(New York Heart Association, NYHA)分级,即NYHAⅢ/NYHAⅣ级患者所占比例更多[9,10]。且无症状心力衰竭共病糖尿病者更易出现心脏结构和功能异常,包括糖尿病相关的左心室质量、相对壁厚和左房大小的增加,细胞外基质体积分数增加,左室收缩舒张功能障碍等[11,12],糖尿病是无症状心力衰竭患者发生症状性心力衰竭的重要预测因素[13]。

另外,共病患者全因死亡风险、心血管死亡风险和心力衰竭入院风险较心力衰竭单病患者更高[7,13];PARADIGM-HF研究中,共病患者较心力衰竭单病患者有更高的主要复合终点事件率[5];Cubbon等[9]研究发现糖尿病导致射血分数减低的慢性心力衰竭患者的2.6年全因死亡率和心血管死亡率升高近2倍,可见共病患者预后更差。

3 心力衰竭-糖尿病共病的病理生理机制

3.1 共病的宏观机制

糖尿病患者的高血糖状态诱发内皮功能障碍,更易促进血栓和冠状动脉斑块溃疡形成及血管平滑肌细胞增殖[14],其低密度脂蛋白胆固醇颗粒易导致动脉粥样硬化,引起冠状动脉血流储备不足和心肌缺血等功能性改变;糖尿病常见的并发症,如高血压、微血管功能障碍、肾功能损害等,皆可能加速心功能不全向晚期进展。另外,糖尿病患者被激活的肾素-血管紧张素-醛固酮系统(renin-angiotensin-aldosterone system, RAAS)通过增加胶原蛋白的合成、血管炎症和氧化损伤促进心肌纤维化;心脏自主神经功能损害会产生心肌区域的电不稳定性,进而导致心肌收缩和舒张功能不全,引发心力衰竭。

3.2 糖尿病性心肌病与共病的微观机制

糖尿病性心肌病也是导致糖尿病患者共病心力衰竭的基础病变和原因之一,胰岛素抵抗和高血糖状态与共病的微观机制交织在一起,引起心肌细胞多种适应性和非适应性细胞反应,最终导致心肌结构和功能不可逆转的特殊变化,不可避免地发展为心力衰竭。

3.2.1 微血管功能障碍 糖尿病患者血管内皮生长因子表达下调[15],糖基化终末产物和自由基生成增多[16],导致一氧化氮失活和内皮功能紊乱,引发内皮依赖性微血管舒张功能障碍,并且波及至冠状动脉微循环。上述功能障碍引发的心肌缺血将导致收缩蛋白丢失和心肌细胞坏死、血管周围和间质纤维化、胶原蛋白沉积和心肌细胞肥大等,从而形成糖尿病性心肌病,心肌整体功能低下导致心力衰竭。

3.2.2 代谢的改变 糖尿病患者的胰岛素抵抗状态促进糖代谢向脂肪酸代谢转移,心肌细胞葡萄糖转运蛋白表达下降、葡萄糖摄取减少,同时游离脂肪酸(free fatty acid, FFA)的释放增加。过度摄取和使用FFA会加大氧耗量而且降低心肌效率,超过糖尿病患者的β-氧化能力之后所产生二酰基甘油和神经酰胺等有毒脂质中间体在心肌细胞和心外膜组织内积累,活性氧族的生成也随之增加[17],加之炎症细胞浸润,最终导致线粒体功能障碍、心肌细胞凋亡和心肌效率降低。

3.2.3 钙离子失稳态 糖尿病患者心肌细胞收缩和调节蛋白以及表达异常,导致肌原纤维ATP酶活性下降和收缩力降低[18];肌浆网Ca^{2+}-ATP酶活性被长期高糖状态下的心肌细胞氧化应激灭活[19],肌浆网Ca^{2+}固存效率低下,导致胞浆Ca^{2+}超载和舒张功能受损。钙离子稳态的这些扰动与肌原纤维重塑有关,并与糖尿病性心肌病患者的舒张功能障碍有关,是引发心力衰竭的微观因素。

3.3 心力衰竭与胰岛素抵抗互为因果

随着心力衰竭的进展和神经体液激活,代偿性肾上腺素能驱动导致脂肪分解和FFA浓度升高,心脏代谢谱向与胰岛素抵抗/糖尿病相似的方向转

移[20]。这些代谢改变不仅可能损害心肌能量学、降低了机械工作的效率,也会促进全身的胰岛素抵抗,形成心力衰竭导致代谢改变、而代谢改变又导致心力衰竭的恶性循环。

4 心力衰竭-糖尿病共病的临床用药研究

4.1 心力衰竭相关药物用于共病

药物治疗是心力衰竭的防治关键,下文简述血管紧张素转换酶抑制剂(angiotensin converting enzyme inhibitor, ACEI)、血管紧张素Ⅱ受体拮抗剂(angiotensin-Ⅱ receptor blocker, ARB)、血管紧张素受体脑啡肽酶抑制剂(angiotensin receptor-neprilysin inhibition, ARNI)、β 受体阻滞剂、盐皮质激素受体拮抗剂(mineralocorticoid receptor antagonist, MRA)几类常见的心力衰竭药物作用于心力衰竭-糖尿病共病的研究进展。

4.1.1 ACEI 和 ARB 1999 年的 TRACE 研究证实了 ACEI 类药物在心肌梗死后心力衰竭-糖尿病共病患者中的重要意义,它可以显著降低共病患者发展为重度心力衰竭的风险[21]。Shekelle 等[22]的荟萃分析同样得出无论是否合并有糖尿病,ACEI 在心力衰竭患者中都有同样获益的结论。对于 ARB 类药物,CHARM 研究先后证实了坎地沙坦使 HFrEF 患者糖尿病发病率减低[23]及有效降低共病患者死亡率的结论[10]。目前仅有少量小规模研究认为 ARB 类药物用于心力衰竭-糖尿病共病患者疗效欠佳。

4.1.2 ARNI 以诺欣妥(沙库巴曲缬沙坦钠)为代表的 ARNI 类心力衰竭药物对共病患者有益的原因,一是由于脑啡肽酶可刺激脂解,增加脂质氧化,故而抑制脑啡肽酶可能有助于改善血糖参数,二是由于胰高血糖素样肽-1(glucagon-like peptide-1, GLP-1)不仅被二肽基肽酶-4(dipeptidyl peptidase-4, DDP-4)降解,也被脑啡肽酶降解,GLP-1 受体信号的增强可能有助于解释诺欣妥的降糖作用[24]。这类心力衰竭药物良好的血糖控制效果在对糖尿病合并心力衰竭患者的研究中已得到充分证实[25]。

4.1.3 β 受体阻滞剂 陆续有证据表明 β 受体阻滞剂不仅能降压、减慢心率,还能增加心肌葡萄糖利用、减轻脂肪酸对心肌的损害,有效减少糖尿病患者心血管事件的发生。Haas 等[26]分析证实了 β 受体阻滞剂对心功能Ⅱ~Ⅲ级心力衰竭共病糖尿病患者的疗效和安全性,体现了 β 受体阻滞剂在共病治疗中的重要价值。卡维地洛、琥珀酸美托洛尔和比索洛尔已被证实显著降低合并有糖尿病的症状性心力衰竭患者的发病率和死亡率,推荐用于心力衰竭-糖尿病共病患者。

4.1.4 MRA MRA 类药物螺内酯对非心力衰竭患者的血糖水平有负面影响,近期一项荟萃分析显示螺内酯对患者空腹血糖和胰岛素水平影响不甚明显,但有使患者糖化血红蛋白升高的风险[27],临床上应谨慎用于共病患者;而国内临床上难以获得的 MRA 类药物依普利酮在伴或不伴有糖尿病的 HFrEF 患者中可能具有一致疗效[28],可能比螺内酯更有利于共病患者[29]。

4.2 糖尿病相关药物用于共病

糖尿病患者血糖水平的长期控制依赖于降糖药物,以下简述二肽基肽酶-4 抑制剂、钠-葡萄糖协同转运蛋白 2(sodium-glucose cotransporter 2, SGLT-2)抑制剂和胰高血糖素样肽-1 受体激动剂、二甲双胍及磺酰脲类降糖药作用于心力衰竭-糖尿病共病的研究进展。

4.2.1 DPP-4 抑制剂 阿格列汀、利格列汀、沙格列汀和西格列汀是 DPP-4 抑制剂类代表药物。虽然有研究证明 DPP-4 抑制剂对心力衰竭住院风险的影响为中性[30],然而大多数临床试验不能证明其在心力衰竭或心力衰竭高危患者中应用的合理性。例如在 SAVOR TIMI-53 研究中,沙格列汀组心血管事件发生率与安慰剂组相似,但心力衰竭住院风险却增加了 27%[31]。将 DPP-4 抑制剂灵活用于心力衰竭-糖尿病共病患者尚需一定时间。

4.2.2 SGLT-2 抑制剂 以坎格列净、达格列净、恩格列净为代表的 SGLT-2 抑制剂类降糖药可以使糖尿病患者获得心力衰竭方面的获益。CANVAS 项目证实,坎格列净能够使心血管疾病风险高的糖尿病患者的心力衰竭住院风险降低 33%[32]。CVD-REAL 研究也证实了 SGLT-2 抑制剂与其他降糖药相比能够相对降低心力衰竭住院风险的 39%[33]。推荐将 SGLT-2 抑制剂用于共病患者。

4.2.3 GLP-1 受体激动剂 阿必鲁肽、杜拉鲁肽、艾塞那肽、利拉鲁肽、利西拉肽和索马鲁肽是治疗 2 型糖尿病的 GLP-1 受体激动剂类代表药物。这类药物大多显示对心血管结局有益,对心力衰竭住院风险的影响为中性。在 LEADER 等随机对照试验中[34-37],合并心力衰竭患者的比例为 14%~23.6%,与安慰剂组相比,各类型 GLP-1 激动剂组患者发生心力衰竭住院的风险皆没有差异,因此可考虑将之用于共病患者。

4.2.4 二甲双胍及磺酰脲类降糖药 心力衰竭不是二甲双胍的使用禁忌;而磺酰脲类药物对于心力

衰竭患者,尚无大型随机对照试验证实其有益。有研究显示磺脲类药物与心力衰竭患者出院后的全因死亡率之间无关联[38];而更多的观察性研究表明,与二甲双胍[39,40]或DPP-4抑制剂[41]等更新的制剂相比,磺酰脲类药物可能与心力衰竭事件的风险增加有关。因此对于心力衰竭高危患者和已确诊心力衰竭患者,磺酰脲类药物的应用不甚适合。

5 总 结

综上,心力衰竭-糖尿病共病在临床上很常见,共病患者较单病患者的临床症状更重、预后更差,医师在临床决策上需要进行更多方面的权衡与考量。心力衰竭-糖尿病共病的机制奠定共病用药的基础,有待进一步研究;一部分经典及新型心血管系统药物及糖尿病治疗药物被推荐用于心力衰竭-糖尿病共病患者,也有一些单病药物在共病患者中的使用需格外谨慎,未来心力衰竭-糖尿病共病的灵活治疗还需要临床医师及科研工作者的共同努力。

【参考文献】

[1] Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study[J]. Am J Cardiol, 1974, 34(1): 29-34. DOI: 10.1016/0002-9149(74)90089-7.

[2] Thrainsdottir IS, Aspelund T, Thorgeirsson G, *et al*. The association between glucose abnormalities and heart failure in the population-based Reykjavik study[J]. Diabetes Care, 2005, 28(3): 612-616. DOI: 10.2337/diacare.28.3.612.

[3] Kostis JB, Sanders M. The association of heart failure with insulin resistance and the development of type 2 diabetes[J]. Am J Hypertens, 2005, 18(5Pt1): 731-737. DOI: 10.1016/j.amjhyper.2004.11.038.

[4] Amato L, Paolisso G, Cacciatore F, *et al*. Congestive heart failure predicts the development of non-insulin-dependent diabetes mellitus in the elderly. The Osservatorio Geriatrico Regione Campania Group[J]. Diabetes Metab, 1997, 23(3): 213-218.

[5] Kristensen SL, Preiss D, Jhund PS, *et al*. Risk related to pre-diabetes mellitus and diabetes mellitus in heart failure with reduced ejection fraction: insights from prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial[J]. Circ Heart fail, 2016, 9(1): e002560. DOI: 10.1161/CIRCHEARTFAILURE.115.002560.

[6] Kristensen SL, Mogensen UM, Jhund PS, *et al*. Clinical and echocardiographic characteristics and cardiovascular outcomes according to diabetes status in patients with heart failure and preserved ejection fraction. A report from the irbesartan in heart failure with preserved ejection fraction trial (I-Preserve)[J]. Circulation, 2017, 135(8): 724-735. DOI: 10.1161/CIRCULATIONAHA.116.024593.

[7] Dauriz M, Targher G, Laroche C, *et al*. Association between diabetes and 1-year adverse clinical outcomes in a multinational cohort of ambulatory patients with chronic heart failure: results from the ESC-HFA heart failure long-term registry[J]. Diabetes Care, 2017, 40(5): 671-678. DOI: 10.2337/dc16-2016.

[8] Greenberg BH, Abraham WT, Albert NM, *et al*. Influence of diabetes on characteristics and outcomes in patients hospitalized with heart failure: a report from the organized program to initiate lifesaving treatment in hospitalized patients with heart failure (OPTIMIZE-HF)[J]. Am Heart J, 2007, 154(2): 277.e1-8. DOI: 10.1016/j.ahj.2007.05.001.

[9] Cubbon RM, Adams B, Rajwani A, *et al*. Diabetes mellitus is associated with adverse prognosis in chronic heart failure of ischaemic and non-ischaemic aetiology[J]. Diab Vasc Dis Res, 2013, 10(4): 330-336. DOI: 10.1177/1479164112471064.

[10] MacDonald MR, Petrie MC, Varyani F, *et al*. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme[J]. Eur Heart J, 2008, 29(11): 1377-1385. DOI: 10.1093/eurheartj/ehn153.

[11] From AM, Scott CG, Chen HH. The development of heart failure in patients with diabetes mellitus and pre-clinical diastolic dysfunction: a population-based study[J]. J Am Coll Cardiol, 2010, 55(4): 300-305. DOI: 10.1016/j.jacc.2009.12.003.

[12] Swoboda PP, McDiarmid AK, Erhayiem B, *et al*. Diabetes mellitus, microalbuminuria, and subclinical cardiac disease: identification and monitoring of individuals at risk of heart failure[J]. J Am Heart Assoc, 2017, 6(7): e005539. DOI: 10.1161/JAHA.117.005539.

[13] Shindler DM, Kostis JB, Yusuf S, *et al*. Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) Trials and Registry[J]. Am J Cardiol, 1996, 77(11): 1017-1020. DOI: 10.1016/s0002-9149(97)89163-1.

[14] Cas AD, Khan SS, Butler J, *et al*. Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure[J]. JACC Heart failure, 2015, 3(2): 136-145. DOI: 10.1016/j.jchf.2014.08.004.

[15] Yoon YS, Uchida S, Masuo O, *et al*. Progressive attenuation of myocardial vascular endothelial growth factor expression is a seminal event in diabetic cardiomyopathy: restoration of microvascular homeostasis and recovery of cardiac function in diabetic cardiomyopathy after replenishment of local vascular endothelial growth factor[J]. Circulation, 2005, 111(16): 2073-2085. DOI: 10.1161/01.CIR.0000162472.52990.36.

[16] 李婉娇,李强. 糖尿病性心肌病的发病机制及治疗方法研究进展[J]. 中华老年多器官疾病杂志, 2019, 18(7): 536-539. DOI: 10.11915/j.issn.1671-5403.2019.07.115.
Li WJ, Li Q. Progress in the research on pathogenesis and treatment of diabetic cardiomyopathy[J]. Chin J Mult Organ Dis Elderly, 2019, 18(7): 536-539. DOI: 10.11915/j.issn.1671-5403.2019.07.115.

[17] Cherian S, Lopaschuk GD, Carvalho E. Cellular cross-talk between epicardial adipose tissue and myocardium in relation to the pathogenesis of cardiovascular disease[J]. Am J Physiol Endocrinol Metab, 2012, 303(8): E937-E949. DOI: 10.1152/ajpendo.00061.2012.

[18] Malhotra A, Sanghi V. Regulation of contractile proteins in diabetic heart[J]. Cardiovasc Res, 1997, 34(1): 34-40. DOI: 10.1016/s0008-6363(97)00059-x.

[19] Teshima Y, Takahashi N, Saikawa T, *et al*. Diminished expression of sarcoplasmic reticulum Ca^{2+}-ATPase and ryanodine sensitive Ca^{2+} Channel mRNA in streptozotocin-induced diabetic rat heart[J]. J Mol Cell Cardiol, 2000, 32(4): 655-664. DOI: 10.1006/jmcc.2000.1107.

[20] SuskinN, McKelvie RS, Burns RJ, *et al*. Glucose and insulin abnormalities relate to functional capacity in patients with congestive heart failure[J]. Eur Heart J, 2000, 21(16): 1368-1375. DOI: 10.1053/euhj.1999.2043.

[21] Gustafsson I, Torp-Pedersen C, Køber L, *et al*. Effect of the angiotensin-converting enzyme inhibitor trandolapril on mortality and morbidity in diabetic patients with left ventricular dysfunction after acute myocardial infarction. Trace Study Group[J]. J Am Coll Cardiol, 1999, 34(1): 83-89. DOI: 10.1016/s0735-1097(99)00146-1.

[22] Shekelle PG, Rich MW, Morton SC, *et al*. Efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in the management of left ventricular systolic dysfunction according to race, gender, and diabetic status: a meta-analysis of major clinical trials[J]. J Am Coll Cardiol, 2003, 41(9): 1529-1538. DOI: 10.1016/s0735-1097(03)00262-6.

[23] Yusuf S, Ostergren JB, Gerstein HC, *et al*. Effects of candesartan on the development of a new diagnosis of diabetes mellitus in patients with heart failure[J]. Circulation, 2005, 112(1): 48-53. DOI: 10.1161/CIRCULATIONAHA.104.528166.

[24] Packer M. Augmentation of glucagon-like peptide-1 receptor signalling by neprilysin inhibition: potential implications for patients with heart failure[J]. Eur J Heart Fail, 2018, 20(6): 973-977. DOI: 10.1002/ejhf.1185.

[25] Seferovic JP, Claggett B, Seidelmann SB, *et al*. Effect of sacubitril/valsartan *versus* enalapril on glycaemic control in patients with heart failure and diabetes: a post-hoc analysis from the PARADIGM-HF trial[J]. Lancet Diabetes Endocrinol, 2017, 5(5): 333-340. DOI: 10.1016/s2213-8587(17)30087-6.

[26] Haas SJ, Vos T, Gilbert RE, *et al*. Are beta-blockers as efficacious in patients with diabetes mellitus as in patients without diabetes mellitus who have chronic heart failure? A meta-analysis of large-scale clinical trials[J]. Am Heart J, 2003, 146(5): 848-853. DOI: 10.1016/S0002-8703(03)00403-4.

[27] Zhao JV, Xu L, Lin SL, *et al*. Spironolactone and glucose metabolism, a systematic review and meta-analysis of randomized controlled trials[J]. J Am Soc Hypertens, 2016, 10(8): 671-682. DOI: 10.1016/j.jash.2016.05.013.

[28] Eschalier R, McMurray JJ, Swedberg K, *et al*. Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: analyses of the EMPHASIS-HF study subgroups (Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure)[J]. J Am Coll Cardiol, 2013, 62(17): 1585-1593. DOI: 10.1016/j.jacc.2013.04.086.

[29] Yamaji M, Tsutamoto T, Kawahara C, *et al*. Effect of eplerenone *versus* spironolactone on cortisol and hemoglobin A_1(c) levels in patients with chronic heart failure[J]. Am Heart J, 2010, 160(5): 915-921. DOI: 10.1016/j.ahj.2010.04.024.

[30] McGuire DK, Van de Werf F, Armstrong PW, *et al*. Association between sitagliptin use and heart failure hospitalization and related outcomes in type 2 diabetes mellitus: secondary analysis of a randomized clinical trial[J]. JAMA Cardiol, 2016, 1(2): 126-135. DOI: 10.1001/jamacardio.2016.0103.

[31] Scirica BM, Braunwald E, Raz I, *et al*. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial[J]. Circulation, 2014, 130(18): 1579-1588. DOI: 10.1161/CIRCULATIONAHA.114.010389.

[32] Neal B, Perkovic V, Matthews DR, *et al*. Canagliflozin and cardiovascular and renal events in type 2 diabetes[J]. N Engl J Med, 2017, 377(21): 2099. DOI: 10.1056/NEJMc1712572.

[33] Kosiborod M, Cavender MA, Fu AZ, *et al*. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors *versus* other glucose-lowering drugs: the CVD-REAL study (comparative effectiveness of cardiovascular outcomes in new users of sodium-glucose cotransporter-2 inhibitors)[J]. Circulation, 2017, 136(3): 249-259. DOI: 10.1161/circulationaha.117.029190.

[34] Franco C, Roberto L, Antonio N. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes[J]. N Engl J Med, 2017, 376(9): 890-892. DOI: 10.1056/NEJMc1615712.

[35] Pfeffer MA, Claggett B, Diaz R, *et al*. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome[J]. N Engl J Med, 2015, 373(23): 2247-2257. DOI: 10.1056/NEJMoa1509225.

[36] Holman RR, Bethel MA, Mentz RJ, *et al*. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes[J]. N Engl J Med, 2017, 377(13): 1228-1239. DOI: 10.1056/NEJMoa1612917.

[37] Marso SP, Daniels GH, Brown-Frandsen K, *et al*. Liraglutide and cardiovascular outcomes in type 2 diabetes[J]. N Engl J Med, 2016, 375(4): 311-322. DOI: 10.1056/NEJMoa1603827.

[38] Masoudi FA, Inzucchi SE, Wang YF, *et al*. Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: an observational study[J]. Circulation, 2005, 111(5): 583-590. DOI: 10.1161/01.IR.0000154542.13412.B1.

[39] Andersson C, Olesen JB, Hansen PR, *et al*. Metformin treatment is associated with a low risk of mortality in diabetic patients with heart failure: a retrospective nationwide cohort study[J]. Diabetologia, 2010, 53(12): 2546-2553. DOI: 10.1007/s00125-010-1906-6.

[40] Eurich DT, Weir DL, Majumdar SR, *et al*. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34000 patients[J]. Circ Heart Fail, 2013, 6(3): 395-402. DOI: 10.1161/circheartfailure.112.000162.

[41] Fadini GP, Avogaro A, Esposti LD, *et al*. Risk of hospitalization for heart failure in patients with type 2 diabetes newly treated with DPP-4 inhibitors or other oral glucose-lowering medications: a retrospective registry study on 127 555 patients from the Nationwide OsMed Health-DB Database[J]. Eur Heart J, 2015, 36(36): 2454-2462. DOI: 10.1093/eurheartj/ehv301.

(编辑: 郑真真)