Advances in Clinical Medicine 临床医学进展, 2023, 13(12), 18976-18981
Published Online December 2023 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2023.13122669

Hans汉斯

SGLT1/SGLT2抑制剂在预防和治疗心力衰竭方面的价值判断

董兴梅[1*]，马利祥[2#]，汤秀英[2]

[1]承德医学院研究生学院，河北 承德
[2]秦皇岛市第一医院心血管内科，河北 秦皇岛

收稿日期：2023年11月11日；录用日期：2023年12月4日；发布日期：2023年12月13日

摘　要

心力衰竭是一种心脏疾病终末期表现出来的综合征，由于人口老龄化，心力衰竭患病率正在增加，估计占全球人口的1%至2%。此外，心力衰竭导致高死亡率和发病率，患者的生活质量通常较差。钠－葡萄糖转运体2抑制剂(SGLT2i)是一种新型的降糖药，然而目前已成为治疗心力衰竭的新兴药物，但其作用机制尚不清楚。越来越多关于SGLT2i的研究发现这些药可以诱导心脏代谢的变化而改善心功能，同时发现正常人或心血管病患者的心肌细胞表达SGLT1，却未见SGLT2表达。研究发现钠－葡萄糖转运体2(SGLT2)抑制剂可以抑制钠－葡萄糖转运体1 (SGLT1)，从而可能对心血管系统产生有益影响。本文就SGLT1/SGLT2抑制剂在预防和治疗心力衰竭方面的价值判断作一综述。

关键词

钠－葡萄糖转运体1抑制剂，钠－葡萄糖转运体2抑制剂，心力衰竭

Value Judgment of SGLT1/SGLT2 Inhibitors in the Prevention and Treatment of Heart Failure

Xingmei Dong[1*], Lixiang Ma[2#], Xiuying Tang[2]

[1]Graduate School of Chengde Medical University, Chengde Hebei
[2]Department of Cardiology, Qinhuangdao First Hospital, Qinhuangdao Hebei

Received: Nov. 11th, 2023; accepted: Dec. 4th, 2023; published: Dec. 13th, 2023

[*]第一作者。
[#]通讯作者。

文章引用: 董兴梅, 马利祥, 汤秀英. SGLT1/SGLT2 抑制剂在预防和治疗心力衰竭方面的价值判断[J]. 临床医学进展, 2023, 13(12): 18976-18981. DOI: 10.12677/acm.2023.13122669

Abstract

Heart failure is a syndrome that manifests in the end stage of heart disease. Due to population ageing, the prevalence of heart failure is increasing and is estimated to account for 1% to 2% of the global population. In addition, heart failure leads to high mortality and morbidity, and patients often have poor quality of life. Sodium-glucose transporter 2 inhibitor (SGLT2i) is a new type of hypoglycemic drug, but it has become an emerging drug for the treatment of heart failure, but its mechanism of action is still unclear. More and more studies on SGLT2i have found that these drugs can induce changes in cardiac metabolism and improve cardiac function. At the same time, it has been found that SGLT1 is expressed in cardiomyocytes of normal people or patients with cardiovascular disease, but SGLT2 is not expressed. Sodium-glucose transporter 2 (SGLT2) inhibitors have been found to inhibit sodium-glucose transporter 1 (SGLT1), which may have beneficial cardiovascular effects. This article reviews the value judgment of SGLT1/SGLT2 inhibitors in the prevention and treatment of heart failure.

Keywords

Sodium-Glucose Transporter 1 Inhibitor, Sodium-Glucose Transporter 2 Inhibitor, Heart Failure

1. 引言

钠葡萄糖共转运体抑制剂(SGLTi)已被证明能有效地预防 2 型糖尿病(T2DM)患者心力衰竭(HF)的发展，并可降低 HF 患者的心血管(CV)死亡率和 HF 住院率[1]。在欧洲医疗指南中，卡格列净、达格列净、恩格列净、索格列净均已被推荐用于心血管事件风险的 T2DM 患者，用以减少心力衰竭、主要心血管事件、终末期肾功能不全及心血管死亡的发生[2]。但 SGLT 抑制剂对 SGLT1 和 SGLT2 的相对抑制作用存在较大差异。与 SGLT1 相比，索格列净对 SGLT2 的选择性是 SGLT1 的 20 倍，而恩格列净对 SGLT2 的选择性是 2500 倍，达格列净对 SGLT2 的选择性是 1200 倍，卡格列净对 SGLT2 的选择性是 250 倍[3]。因此，索格列净在提供与恩格列净类似的程度的 SGLT2i 的同时，提供了更多的 SGLT1i。

2. SGLT2i 在改善心功能方面的机制、作用及局限性

(一) 机制：SGLT2 是在近端肾小管中表达的高容量，低亲和力的葡萄糖转运蛋白，其负责正常人尿葡萄糖重吸收的约 97%和尿钠重吸收的 4%~5%，它的抑制作用导致葡萄糖排泄与钠排泄的增加。SGLT2i 已被证明对患有 T2DM 的高心血管风险患者，无 T2DM 的高心血管风险患者，以及患有心力衰竭但无 T2DM 的患者，其都可有效预防和治疗心力衰竭(包括 HFrEF 和 HFpEF) [1]。SGLT2i 可能通过影响肾脏与心肌的多种机制及代谢的改变发挥其有益作用。在肾脏方面，SGLT2i 引起渗透性利尿和尿钠排泄，但不激活肾素－血管紧张素系统(RAS)和交感神经系统。此外，SGLT2i 抑制钠－氢交换，激活去乙酰化酶，并诱导心肌细胞的自噬，所有这些机制都可能有利于减缓慢性肾脏疾病(CKD)和心力衰竭(HF)的进展[4]。

(二) 作用：

(1) SGLT2i 在改善血管功能方面的作用：血管平滑肌和内皮功能障碍在心力衰竭的病理生理学中起

关键作用[5] [6]。SGLT2 在心力衰竭患者中的存在增加了发病率和死亡率。SGLT2i 已被证明通过减弱内皮细胞活化，诱导直接血管松弛，减少与早期动脉粥样硬化发生相关的内皮细胞功能障碍和分子变化，降低动脉壁硬度，降低血管阻力[7] [8] [9] [10]。

(2) SGLT2i 在心脏功能方面的作用：SGLT2i 通过其利尿、改善动脉僵硬度、降压等作用减少心脏前后负荷，降低心室肥厚或重构的风险，减少左心室质量指数，改善收缩和/或舒张功能。一项动物研究结果表明 SGLT2i 可减少缺血 60 分钟后的梗死面积。这项研究的结果强调了 SGLT2i 在代谢正常受试者中的治疗潜力，发现在心脏缺血期间，SGLT2i 确实会影响心脏收缩功能，并延缓挛缩的发展[11] [12]。在缺血性损伤后，大多数研究报告也表明使用 SGLT2i 可对心脏功能有所改善[13] [14]。

(3) SGLT2i 在心脏重塑方面的作用：影响心力衰竭严重程度的重要影响之一是不良心脏重塑。其中包括心脏纤维化、心脏肥大、心肌炎症和心肌细胞死亡。一些实验和人体研究表明 SGLT2 抑制剂会对心脏重塑造成有益的影响[15] [16] [17] [18] [19]。

(三) 局限性：

然而，SGLT2i 有一些局限性。最近的一项荟萃分析显示，糖尿病患者使用 SGLT2i 可降低收缩压[20]。根据之前的流行病学观察及在高血压病患者中的随机试验，收缩压降低应该会减少患者中风的发生。不过，尽管应用了 SGLT2i 的 T2DM 患者的收缩压显著降低了约 3 mmHg，但是其与 T2DM 患者的非致死性和致死性卒中的减少没有呈现相关性[21] [22] [23]。在 SGLT2i 影响下，心肌梗死发病率的减少，可能继发于前负荷和心肌氧需求的减少。在缺血性心脏病患者中，前负荷和心肌氧需求的减少可以降低缺血和心肌梗死的风险[4]。因此，脑卒中发生率的降低和心肌梗死发生率的适当降低都可能表明 SGLT2i 缺乏主要的抗动脉粥样硬化或抗血栓作用[4]。

3. SGLT1i 在协助 SGLT2i 改善心功能方面的机制

SGLT1 是一种低容量，高亲和力的葡萄糖转运体，可将葡萄糖与钠离子一起吸收到细胞中，在正常人体中，它负责重吸收约 3%的尿葡萄糖[24]。SGLT2 受体和 SGLT1 受体在人体中有着不同的表达部位，与仅在肾近端肾小管细胞中表达的 SGLT2 转运蛋白相比，SGLT1 转运蛋白表现出更广泛的组织分布，SGLT1 由 SLC5A1 基因编码，该基因主要在胃肠道和肾脏中表达[25]。SGLT2 在健康或衰竭的心脏中均不表达，但是心脏会部分表达 SGLT1 [26]。抑制心脏中的 SGLT1 有可能降低心肌 Na^+和葡萄糖的摄取，并减少高血糖诱导的活性氧(ROS)的产生[27]。SGLT1 在缺血性预处理诱导的心脏保护中起关键作用[28]。SGLT1i 减少卒中和心肌梗死的潜在机制已经被回顾性研究过，在研究中同时发现了 GLP-1 的增加会导致血小板活化的降低以及动脉粥样硬化斑块稳定性的增加[29] [30]。然而，目前仍缺乏对 SGLT1i 机制的明确认识，以及 SGLT1 在各种组织中表达增加与合共病(如 HF 和 T2DM)的相关性，因此，我们有必要对 SGLT1i 进行进一步的研究分析。

4. SGLT1/2i 索格列净在临床中的应用

SGLT1/2i 索格列净应用在肾功能正常和中度肾功能不全患者中，会导致持续增加尿糖和短暂增加尿钠排泄，并影响与 SGLT2i 相似的一些其他机制。然而，由于 SGLT1 也在肠道中表达，因此即使在患有严重肾脏疾病的患者中，抑制 SGLT1 也会延迟葡萄糖的吸收。虽然降低血清葡萄糖在预防或治疗 2 型糖尿病的 HF 中似乎并不重要，但它可能对长期预防 2 型糖尿病的微血管影响(如视网膜病变和神经病变)很重要。SGLT1i 对 T2DM 和心力衰竭患者微生物组的影响尚未完全研究透彻，但该影响可能很重要，因为微生物组的改变与高血压和卒中风险相关性较大[30] [31] [32]。重要的是，SGLT1 已被证明，其在糖尿病心肌病患者中会增加[33]，同时 NADPH 氧化酶 2 同样会增加。因此，心肌缺血模型中，SGLT1

下调可减轻缺血/再灌注损伤[34]。孟德尔随机化研究发现，与 SGLT1 功能降低相关的错义变异与 HF 发病率的降低有关，这可能部分与 SGLT1i 对 GLP1 和 GIP 释放的影响相关，而 GLP1 和 GIP 都对食欲和体重减轻有影响。研究发现，与无腹部肥胖的 T2DM 患者和有腹部肥胖但无 T2DM 的 T2DM 患者相比，有 T2DM 和腹部肥胖的患者发生 HF 的风险更高，因此对预防心力衰竭可能具有重要意义[35]。

SGLT1/2i 索格列净有效降低了心力衰竭患者的心血管死亡率和心力衰竭(包括 HFrEF 和 HFpEF)住院率。在 SOLOIST 和 SCORED 试验[36] [37]中，SGLT1/2i 索格列净有效延缓了 T2DM 和 CKD 患者的心力衰竭(包括 HFrEF 和 HFpEF)进一步的发展。另外，SGLT1/2i 索格列净与 SGLT2i 相似，同样降低了非致命性和致命性卒中与非致命和致命心肌梗死 30%以上的发生率[37]。减少非致命性和致命性卒中以及非致命性和致命性心肌梗死相关的机制虽然仍有待确定，但是在很大程度上可能与 SGLT1i 对 GLP-1 的作用和肠道微生物组的改变有关[4]。重要的是，住院率增加、长期残疾、生活质量下降、死亡率增加和高额医疗保健费用均会导致 T2DM 患者的卒中风险增加[1] [2]。SGLT1 也被认为与血管性认知障碍有关，同时，SGLT1i 在小血管疾病认知障碍模型中改善脑血流量[38]。因为心衰患者发生认知障碍的风险增加，并且该认知障碍往往不能及时发现并采取相应的治疗[2]，所以 SGLT1i 在改善脑血流量的作用对小血管疾病患者的认知障碍上具有潜在的重要性。因为 SGLT1 在肠道中的表达，可以预测到应用 SGLT1i 的患者腹泻发生率将会增加约 2%~3%，除此以外，索格列净其他的相关不良反应与对 SGLT2 呈高选择性的 SGLTi 类药物(恩格列净、达格列净)相似[36] [37]。

因此，从目前可用的证据可以推测，SGLT1/2i 索格列净在预防 T2 DM 和 CKD 患者的心力衰竭以及降低 HFrEF 和 HFpEF 合并 T2DM 患者的心血管死亡率和 HHF 方面至少与对 SGLT2 呈高选择性的 SGLTi 类药物一样有效。SGLT1i 似乎增加了 SGLT2i 的益处，因为通过索格列净(SGLT1/2i)可以使 T2DM 患者的非致命性和致命性卒中以及非致命性和致命性心肌梗死的发病率减少百分之三十[37]; 尽管这一假说需要在大量的直接对比试验中得到进一步的证实，而且关于 SGLT1 在合并和不合并 T2DM 的心衰患者中的表达和功能仍有许多有待了解的地方，但从上面综述的证据来看，SGLT1i 确实增加了 SGLT2i 在预防和治疗心力衰竭方面的益处。

参考文献

[1] Herrington, W.G., Savarese, G., Haynes, R., Marx, N., Mellbin, L., Lund, L.H., *et al*. (2021) Cardiac, Renal, and Metabolic Effects of Sodium-Glucose Co-Transporter 2 Inhibitors: A Position Paper from the European Society of Cardiology Ad-Hoc Task Force on Sodium-Glucose Co-Transporter 2 Inhibitors. *European Journal of Heart Failure*, **23**, 1260-1275. https://doi.org/10.1002/ejhf.2286

[2] McDonagh, T.A., Metra, M., Adamo, M., Gardner, R.S., Baumbach, A., Böhm, M., *et al*. (2021) 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure. *European Heart Journal*, **42**, 3599-3726. https://doi.org/10.1093/eurheartj/ehab670

[3] Cinti, F., Moffa, S., Impronta, F., Cefalo, C.M., Sun, V.A., Sorice, G.P., Mezza, T. and Giaccari, A. (2017) Spotlight on Ertugliflozin and Its Potential in the Treatment of Type 2 Diabetes: Evidence to Date. *Drug Design, Development and Therapy*, **11**, 2905-2919. https://doi.org/10.2147/DDDT.S114932

[4] Pitt, B., Bhatt, D.L. and Metra, M. (2022) Does SGLT1 Inhibition Add to the Benefits of SGLT2 Inhibition in the Prevention and Treatment of Heart Failure? *European Heart Journal*, **43**, 4754-4757. https://doi.org/10.1093/eurheartj/ehac417

[5] Uthman, L., Homayr, A., Juni, R.P., Spin, E.L., Kerindongo, R., Boomsma, M., *et al*. (2019) Empagliflozin and Dapagliflozin Reduce ROS Generation and Restore NO Bioavailability in Tumor Necrosis Factor *α*-Stimulated Human Coronary Arterial Endothelial Cells. *Cellular Physiology and Biochemistry*, **53**, 865-886. https://doi.org/10.33594/000000178

[6] Endemann, D.H. and Schiffrin, E.L. (2004) Endothelial Dysfunction. *Journal of the American Society of Nephrology*, **15**, 1983-1992. https://doi.org/10.1097/01.ASN.0000132474.50966.DA

[7] Patel, A.R., Kuvin, J.T., Pandian, N.G., Smith, J.J., Udelson, J.E., Mendelsohn, M.E., Konstam, M.A. and Karas, R.H.

(2001) Heart Failure Etiology Affects Peripheral Vascular Endothelial Function after Cardiac Transplantation. *Journal of the American College of Cardiology*, **37**, 195-200. https://doi.org/10.1016/S0735-1097(00)01057-3

[8] Gaspari, T., Spizzo, I., Liu, H., Hu, Y., Simpson, R.W., Widdop, R.E. and Dear, A.E. (2018) Dapagliflozin Attenuates Human Vascular Endothelial Cell Activation and Induces Vasorelaxation: A Potential Mechanism for Inhibition of Atherogenesis. *Diabetes and Vascular Disease Research*, **15**, 64-73. https://doi.org/10.1177/1479164117733626

[9] Mancini, S.J., Boyd, D., Katwan, O.J., Strembitska, A., Almabrouk, T.A., Kennedy, S., Palmer, T.M. and Salt, I.P. (2018) Canagliflozin Inhibits Interleukin-1*β*-Stimulated Cytokine and Chemokine Secretion in Vascular Endothelial Cells by AMP-Activated Protein Kinase-Dependent and -Independent Mechanisms. *Scientific Reports*, **8**, Article No. 5276. https://doi.org/10.1038/s41598-018-23420-4

[10] Juni, R.P., Kuster, D.W.D., Goebel, M., Helmes, M., Musters, R.J.P., van der Velden, J., Koolwijk, P., Paulus, W.J. and van Hinsbergh, V.W.M. (2019) Cardiac Microvascular Endothelial Enhancement of Cardiomyocyte Function Is Impaired by Inflammation and Restored by Empagliflozin. *JACC*: *Basic to Translational Science*, **4**, 575-591. https://doi.org/10.1016/j.jacbts.2019.04.003

[11] Uthman, L., Nederlof, R., Eerbeek, O., Baartscheer, A., Schumacher, C., Buchholtz, N., Hollmann, M.W., Coronel, R., Weber, N.C. and Zuurbier, C.J. (2019) Delayed Ischaemic Contracture Onset by Empagliflozin Associates with NHE1 Inhibition and Is Dependent on Insulin in Isolated Mouse Hearts. *Cardiovascular Research*, **115**, 1533-1545. https://doi.org/10.1093/cvr/cvz004

[12] Baker, H.E., Kiel, A.M., Luebbe, S.T., Simon, B.R., Earl, C.C., Regmi, A., Roell, W.C., Mather, K.J., Tune, J.D. and Goodwill, A.G. (2019) Inhibition of Sodium-Glucose Cotransporter-2 Preserves Cardiac Function during Regional Myocardial Ischemia Independent of Alterations in Myocardial Substrate Utilization. *Basic Research in Cardiology*, **114**, Article No. 25. https://doi.org/10.1007/s00395-019-0733-2

[13] Philippaert, K., Kalyaanamoorthy, S., Fatehi, M., Long, W., Soni, S., Byrne, N.J., Barr, A., *et al*. (2021) Cardiac Late Sodium Channel Current Is a Molecular Target for the Sodium/Glucose Cotransporter 2 Inhibitor Empagliflozin. *Circulation*, **143**, 2188-2204. https://doi.org/10.1161/CIRCULATIONAHA.121.053350

[14] Azam, M.A., Chakraborty, P., Si, D., Du, B., Massé, S., Lai, P.F.H., Ha, A.C.T. and Nanthakumar, K. (2021) Anti-Arrhythmic and Inotropic Effects of Empagliflozin Following Myocardial Ischemia. *Life Sciences*, **276**, Article ID: 119440. https://doi.org/10.1016/j.lfs.2021.119440

[15] Lambers Heerspink, H.J., de Zeeuw, D., Wie, L., Leslie, B. and List, J. (2013) Dapagliflozin a Glucose-Regulating Drug with Diuretic Properties in Subjects with Type 2 Diabetes. *Diabetes, Obesity and Metabolism*, **15**, 853-862. https://doi.org/10.1111/dom.12127

[16] Connelly, K.A., Zhang, Y., Visram, A., Advani, A., Batchu, S.N., Desjardins, J.F., Thai, K. and Gilbert, R.E. (2019) Empagliflozin Improves Diastolic Function in a Nondiabetic Rodent Model of Heart Failure with Preserved Ejection Fraction. *JACC*: *Basic to Translational Science*, **4**, 27-37. https://doi.org/10.1016/j.jacbts.2018.11.010

[17] Byrne, N.J., Parajuli, N., Levasseur, J.L., Boisvenue, J., Beker, D.L., Masson, G., Fedak, P.W.M., Verma, S. and Dyck, J.R.B. (2017) Empagliflozin Prevents Worsening of Cardiac Function in an Experimental Model of Pressure Overload-Induced Heart Failure. *JACC*: *Basic to Translational Science*, **2**, 347-354. https://doi.org/10.1016/j.jacbts.2017.07.003

[18] Shi, L., Zhu, D., Wang, S., Jiang, A. and Li, F. (2019) Dapagliflozin Attenuates Cardiac Remodeling in Mice Model of Cardiac Pressure Overload. *American Journal of Hypertension*, **32**, 452-459. https://doi.org/10.1093/ajh/hpz016

[19] Verma, S., Garg, A., Yan, A.T., Gupta, A.K., Al-Omran, M., Sabongui, A., Teoh, H., Mazer, C.D. and Connelly, K.A. (2016) Effect of Empagliflozin on Left Ventricular Mass and Diastolic Function in Individuals with Diabetes: An Important Clue to the EMPA-REG OUTCOME Trial? *Diabetes Care*, **39**, e212-e213. https://doi.org/10.2337/dc16-1312

[20] Tsapas, A., Karagiannis, T., Kakotrichi, P., Avgerinos, I., Mantsiou, C., Tousinas, G., Manolopoulos, A., Liakos, A., Malandris, K., Matthews, D.R. and Bekiari, E. (2021) Comparative Efficacy of Glucose-Lowering Medications on Body Weight and Blood Pressure in Patients with Type 2 Diabetes: A Systematic Review and Network Meta-Analysis. *Diabetes, Obesity and Metabolism*, **23**, 2116-2124. https://doi.org/10.1111/dom.14451

[21] McGuire, D.K., Shih, W.J., Cosentino, F., Charbonnel, B., Cherney, D.Z.I., Dagogo-Jack, S., Pratley, R., Greenberg, M., Wang, S., Huyck, S., Gantz, I., Terra, S.G., Masiukiewicz, U. and Cannon, C.P. (2021) Association of SGLT2 Inhibitors with Cardiovascular and Kidney Outcomes in Patients with Type 2 Diabetes: A Meta-Analysis. *JAMA Cardiology*, **6**, 148-158. https://doi.org/10.1001/jamacardio.2020.4511

[22] Zheng, C., Lin, M., Chen, Y., Xu, H., Yan, L. and Dai, H. (2021) Effects of Sodium-Glucose Cotransporter Type 2 Inhibitors on Cardiovascular, Renal, and Safety Outcomes in Patients with Cardiovascular Disease: A Meta-Analysis of Randomized Controlled Trials. *Cardiovascular Diabetology*, **20**, Article No. 83. https://doi.org/10.1186/s12933-021-01272-z

[23] Gilbert, R.E. and Connelly, K.A. (2019) Reduction in the Incidence of Myocardial Infarction with Sodium-Glucose Linked Cotransporter-2 Inhibitors: Evident and Plausible. *Cardiovascular Diabetology*, **18**, Article No. 6.

https://doi.org/10.1186/s12933-019-0812-6

[24] Wright, E.M., Loo, D.D. and Hirayama, B.A. (2011) Biology of Human Sodium Glucose Transporters. *Physiological Reviews*, **91**, 733-794. https://doi.org/10.1152/physrev.00055.2009

[25] Uhlén, M., Fagerberg, L., Hallström, B.M., Lindskog, C., Oksvold, P., Mardinoglu, A., *et al*. (2015) Proteomics. Tissue-Based Map of the Human Proteome. *Science*, **347**, Article ID: 1260419. https://doi.org/10.1126/science.1260419

[26] Tsimihodimos, V., Filippas-Ntekouan, S. and Elisaf, M. (2018) SGLT1 Inhibition: Pros and Cons. *European Journal of Pharmacology*, **838**, 153-156. https://doi.org/10.1016/j.ejphar.2018.09.019

[27] Bell, R.M. and Yellon, D.M. (2018) SGLT2 Inhibitors: Hypotheses on the Mechanism of Cardiovascular Protection. *The Lancet Diabetes & Endocrinology*, **6**, 435-437. https://doi.org/10.1016/S2213-8587(17)30314-5

[28] Kanwal, A., Nizami, H.L., Mallapudi, S., Putcha, U.K., Mohan, G.K. and Banerjee, S.K. (2016) Inhibition of SGLT1 Abrogates Preconditioning-Induced Cardioprotection against Ischemia-Reperfusion Injury. *Biochemical and Biophysical Research Communications*, **472**, 392-398. https://doi.org/10.1016/j.bbrc.2016.02.016

[29] Cefalo, C.M.A., Cinti, F., Moffa, S., Impronta, F., Sorice, G.P., Mezza, T., Pontecorvi, A. and Giaccari, A. (2019) Sotagliflozin, the First Dual SGLT Inhibitor: Current Outlook and Perspectives. *Cardiovascular Diabetology*, **18**, Article No. 20. https://doi.org/10.1186/s12933-019-0828-y

[30] Pitt, B. and Bhatt, D.L. (2021) Does SGLT1 Inhibition Add Benefit to SGLT2 Inhibition in Type 2 Diabetes? *Circulation*, **144**, 4-6. https://doi.org/10.1161/CIRCULATIONAHA.121.054442

[31] Pitt, B., Steg, G., Leiter, L.A. and Bhatt, D.L. (2022) The Role of Combined SGLT1/SGLT2 Inhibition in Reducing the Incidence of Stroke and Myocardial Infarction in Patients with Type 2 Diabetes Mellitus. *Cardiovascular Drugs and Therapy*, **36**, 561-567. https://doi.org/10.1007/s10557-021-07291-y

[32] Lee, Y.T., Mohd Ismail, N.I. and Wei, L.K. (2021) Microbiome and Ischemic Stroke: A Systematic Review. *PLOS ONE*, **16**, e0245038. https://doi.org/10.1371/journal.pone.0245038

[33] Lin, N., Lin, H., Yang, Q., Lu, W., Sun, Z., Sun, S., Meng, L., Chi, J. and Guo, H. (2021) SGLT1 Inhibition Attenuates Apoptosis in Diabetic Cardiomyopathy via the JNK and p38 Pathway. *Frontiers in Pharmacology*, **11**, Article ID: 598353. https://doi.org/10.3389/fphar.2020.598353

[34] Li, Z., Agrawal, V., Ramratnam, M., Sharma, R.K., D'Auria, S., Sincoular, A., Jakubiak, M., Music, M.L., Kutschke, W.J., Huang, X.N., Gifford, L. and Ahmad, F. (2019) Cardiac Sodium-Dependent Glucose Cotransporter 1 Is a Novel Mediator of Ischaemia/Reperfusion Injury. *Cardiovascular Research*, **115**, 1646-1658. https://doi.org/10.1093/cvr/cvz037

[35] Seidelmann, S.B., Feofanova, E., Yu, B., Franceschini, N., Claggett, B., Kuokkanen, M., *et al*. (2018) Genetic Variants in SGLT1, Glucose Tolerance, and Cardiometabolic Risk. *Journal of the American College of Cardiology*, **72**, 1763-1773. https://doi.org/10.1016/j.jacc.2018.07.061

[36] Bhatt, D.L., Szarek, M., Steg, P.G., Cannon, C.P., Leiter, L.A., McGuire, D.K., *et al*. (2021) Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *The New England Journal of Medicine*, **384**, 117-128. https://doi.org/10.1056/NEJMoa2030183

[37] Bhatt, D.L., Szarek, M., Pitt, B., Cannon, C.P., Leiter, L.A., McGuire, D.K., *et al*. (2021) Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. *The New England Journal of Medicine*, **384**, 129-139. https://doi.org/10.1056/NEJMoa2030186

[38] Ishida, N., Saito, M., Sato, S., Tezuka, Y., Sanbe, A., Taira, E. and Hirose, M. (2021) Mizagliflozin, a Selective SGLT1 Inhibitor, Improves Vascular Cognitive Impairment in a Mouse Model of Small Vessel Disease. *Pharmacology Research & Perspectives*, **9**, e00869. https://doi.org/10.1002/prp2.869