European Journal of Biomedical Research
Vol 3 | Issue 5 | December 2024
ISSN 2796-0056

RESEARCH ARTICLE

Triumph or Just Victory? Current Status of Sodium-Glucose Cotransporter-2 Inhibitors across Heart Failure Spectrum

Shigenori Ito*

ABSTRACT

In this review, I comment on the recently published review which focuses on sodium-glucose cotransporter-2 Inhibitor (SGLT2i) across the heart failure spectrum with chronic heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). Furthermore, it examines the usefulness of SGLT2i in various cardiac diseases such as acute heart failure, acute myocardial infarction, and arrhythmia (sudden cardiac death). This is promising for HFpEF, which has no available effective drugs to date. Many of the studies reported significantly superior primary and secondary endpoints in the SGLT2i group compared with the control group. SGLT2i is indicated for HFrEF and HFpEF as a class 1A recommendation, regardless of the presence of diabetes mellitus or left ventricular ejection fraction. Its effect on cardiovascular outcomes can be viewed as a *victory* in cardiac disease treatment. However, evidence supporting its use in elderly patients with chronic heart failure, who typically have reduced multiorgan reserves, remains scarce. SGLT2i may achieve a true "triumph" if it demonstrates benefit and safety that outweigh potential harm even in elderly patients with frailty, multimorbidity, and polypharmacy.

Keywords: Chronic kidney disease, Elderly, Multimorbidity, Sodium-glucose cotransporter-2 inhibitor.

Submitted: November 06, 2024

Published: December 02, 2024

10.24018/ejbiomed.2024.3.5.106

Division of Cardiology, Medical Corporation Sankyukai Sankuro Hospital, Japan.

Corresponding Author:
e-mail: shigeito918@gmail.com

1. Introduction

The indications for sodium-glucose cotransporter-2 inhibitor (SGLT2i) have gradually expanded [1]. It was initially used as a treatment for diabetes mellitus (DM) [2] and eventually applied in the management of various heart failure conditions [3] and chronic kidney disease (CKD) [4]. Large randomized controlled trials (RCTs) have demonstrated its long-term prognostic benefits and ability to inhibit disease progression. Several drugs belong to this class, with notable differences in their pharmacological characteristics owing to structural variations [5]. All 6 SGLT2i currently available on the market in Japan have a C-glucoside conjugate as their basic backbone, with a direct bond to carbon (C) to prevent hydrolysis. This C-glucoside conjugate is absorbed by the body and excreted in the urine, where D-glucose binds to SGLT2i, a sodium and glucose co-transporter in the proximal tubule. Modifications aimed at enhancing SGLT1/SGLT2 selectivity target aglycons and phloretin. The selectivity varied depending on the presence or absence of thiophene, a sulfur-containing five-membered ring compound. The selectivities of dapagliflozin (Dapa) and empagliflozin (Empa), which have sulfur-free five-membered ring phlorizins, were 1242 and 5000 times higher, respectively, than those of canagliflozin (Cana) (158 times) and ipragliflozin (Ipra) (254 times) [6]. The highly selective SGLT2i has a higher partition coefficient (logP) and a lower plasma protein binding rate [6]. In addition, Empa has poor degradation properties and a high urinary excretion rate in its unchanged form [5]. As described above, although Empa and Dapa may have structural and pharmacological advantages, which have been studied earlier to determine their usefulness in heart failure and cardiac-related conditions, the effect of differences in efficacy and mechanisms of action among SGLT2i drugs on their clinical usefulness is not fully understood.

2. Application of SGLT2I across a Wide Spectrum of Cardiac Diseases

In the review by Bhandari *et al*., which concisely summarized recent studies, primarily RCTs, the authors focused on chronic heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF), and the usefulness of SGLT2i in a wide spectrum of cardiac diseases, such as acute heart failure, acute myocardial infarction, and arrhythmias (sudden cardiac death) [3]. This is particularly beneficial for HFpEF, for which no effective drugs have been available for a long time [7], [8]. The SGLT2i discussed in this article primarily included Empa and Dapa, along with references to Cana and sotagliflozin (Sota). Many studies have shown that the primary and secondary endpoints were significantly superior in the SGLT2i group than in the control group. Notably, SGLT2i is indicated for HFrEF and HFpEF as a class 1A recommendation, regardless of the presence of DM or left ventricular ejection fraction [9], forming part of the four essential medications for heart failure.

Consequently, SGLT2i are recommended for use as soon as possible in all patients without contraindications [10], [11]. The effect of SGLT2i on cardiovascular outcomes, which achieved *victory* in the treatment of cardiac disease, cannot be solely attributed to the blockade of SGLT2i in the proximal renal tubules. The potential mechanisms may include systemic effects, such as increased vascular progenitor cells, increased erythropoietin, decreased blood pressure and sympathetic relaxation, increased ketone body metabolism, and direct effects on the myocardium [12]. SGLT2i with a high urinary excretion rates of unchanged forms might have an advantage in terms of its direct effects on the myocardium. This may explain the frequent use of Empa and Dapa in the studies included in this minireview [3]. When used in the treatment of heart failure and CKD, SGLT2i is only contraindicated in a few patients and has limited side effects [8], [13], [14]. SGLT2i is easier to use compared with the recently introduced angiotensin receptor-neprilysin inhibitor sacubitril/valsartan [15]. Its use carries a lower risk of hypotension or worsening renal failure and requires fewer volume adjustments. Overall, SGLT2i is a user-friendly and easy-to-administer medication, representing advancement in the ongoing effort to treat heart failure-related conditions.

3. Future Studies Expected to Attain Veni, Vidi, and Viri (Triumph)

Although CKD, frailty, and multimorbidity frequently complicate the treatment of heart failure and cardiovascular diseases, this review primarily addresses cardiac diseases without referencing recent studies that evaluated the effects of SGLT2i on populations with CKD, frailty, and multimorbidity [16]. SGLT2i appears to be promising in older adults from a practical perspective, given that the prevalence of heart failure increases with age [17] and has been termed a pandemic [18]. Heart failure in older adults is frequently associated with DM, HFpEF, CKD, atrial fibrillation, anemia, and cardiorenal anemia syndrome [19], [20]. Although long-term prognostic efficacy in CHF and CKD has already been reported, the prognostic efficacy of SGLT2i in older adults with multiple complications remains unclear and has not been addressed [3]. Several studies have predicted the efficacy of SGLT2i in these contexts.

A previous study demonstrated a reduction in the dose of loop diuretics among patients with heart failure treated with SGLT2i, which is particularly beneficial for elderly patients susceptible to renal impairment from using loop/thiazide diuretics [21]. In the EMPEROR-Preserved trial on HFpEF, which evaluated the effects of SGLT2i in patients with HFpEF, the initiation of diuretics and dose escalation were less likely, while diuretic de-escalation and discontinuation were more common [8]. A post hoc analysis of the EMPA-KIDNEY trial revealed that the SGLT2i group demonstrated superior outcomes compared with the placebo group, regardless of the presence of frailty, multimorbidity, and polypharmacy. SGLT2i treatment proved to be safer, well-tolerated, and effectively reduced cardiorenal and hospitalization risks, with the absolute benefits particularly pronounced in frail patients at high risk of hospitalization [16].

4. Conclusion

In elderly patients with chronic heart failure, who typically have reduced organ reserve, SGLT2i may achieve a true *triumph* when it provides benefit and safety that offset potential harm even in patients with frailty, multimorbidity, and polypharmacy.

Author Contributions

Shigenori Ito contributed to this study, designed the overall concept and outline of the manuscript, discussed and designed the manuscript followed by the writing, wrote and edited the manuscript, and reviewed the literature.

Conflict of Interest

Author declares that there is no conflict of interest regarding this manuscript.

References

[1] Zelniker TA, Braunwald E. Mechanisms of cardiorenal effects of sodium-glucose cotransporter 2 inhibitors: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;75:422–34. doi: 10.1016/j.jacc.2019.11.031. PMID 32000955.

[2] Tahrani AA, Barnett AH, Bailey CJ. SGLT inhibitors in management of diabetes. *Lancet Diabetes Endocrinol*. 2013;1:140–51. doi: 10.1016/s2213-8587(13)70050-0. PMID 24622320.

[3] Bhandari M, Pradhan A, Vishwakarma P, Abhishek Singh A, Sethi R. Sodium glucose cotransporter 2 inhibitors in the management of heart failure: veni, vidi, and vici. *World J Cardiol*. 2024;16:550–63. doi: 10.4330/wjc.v16.i10.550.

[4] Herrington WG, Staplin N, Wanner C, Green JB, Hauske SJ, Emberson JR, *et al.* Empagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2023;388:117–27. doi: 10.1056/NEJMoa2204233. PMID 36331190.

[5] Tahara A, Takasu T, Yokono M, Imamura M, Kurosaki E. Characterization and comparison of sodium-glucose cotransporter 2 inhibitors in pharmacokinetics, pharmacodynamics, and pharmacologic effects. *J Pharmacol Sci*. 2016;130:159–69. doi: 10.1016/j.jphs.2016.02.003. PMID 26970780.

[6] Suganuma M. Class effects and drug effects of SGLT2 inihibitors. *Heart View*. 2021;25:1130–6 in Japanaese.
[7] Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, *et al.* Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. *N Engl J Med*. 2022;387:1089–98. doi: 10.1056/NEJMoa2206286. PMID 36027570.
[8] Butler J, Usman MS, Filippatos G, Ferreira JP, Böhm M, Brueckmann M, *et al.* Safety and efficacy of empagliflozin and diuretic use in patients with heart failure and preserved ejection fraction: a post hoc analysis of the EMPEROR-Preserved Trial. *JAMA Cardiol*. 2023;8:640–9. doi: 10.1001/jamacardio.2023.1090. PMID 37223933.
[9] Marx N, Federici M, Schütt K, Müller-Wieland D, Ajjan RA, Antunes MJ, *et al.* ESC guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J*. 2023;44:4043–140. doi: 10.1093/eurheartj/ehad192. PMID 37622663.
[10] Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al.* AHS/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation*. 2022;145:e895–1032. doi: 10.1161/cir.0000000000001063. PMID 35363499.
[11] Kittleson MM, Panjrath GS, Amancherla K, Davis LL, Deswal A, Dixon D, *et al.* ACC expert consensus decision pathway on management of heart failure with preserved ejection fraction: a report of the American College of Cardiology solution set oversight committee. *J Am Coll Cardiol*. 2023;81:1835–78. doi: 10.1016/j.jacc.2023.03.393. PMID 37137593.
[12] Lopaschuk GD, Verma S. Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors: a state-of-the-art review. *JACC Basic Transl Sci*. 2020;5:632–44. doi: 10.1016/j.jacbts.2020.02.004. PMID 32613148.
[13] Yen FS, Hwu CM, Liu JS, Wu YL, Chong K, Hsu CC. Sodium-glucose cotransporter-2 inhibitors and the risk for dialysis and cardiovascular disease in patients with stage 5 chronic kidney disease. *Ann Intern Med*. 2024;177:693–700. doi: 10.7326/m23-1874. PMID 38684099.
[14] Younes AM, Salem M, Maraey A, Nomigolzar S, Sewell K, Khalil M, *et al.* Safety outcomes of SGLT2i in the heart failure trials: a systematic review and meta-analysis. *Int J Cardiol*. 2022;366:51–6. doi: 10.1016/j.ijcard.2022.06.059. PMID 35777490.
[15] Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, *et al.* Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med*. 2019;381:1609–20. doi: 10.1056/NEJMoa1908655. PMID 31475794.
[16] Mayne KJ, Sardell RJ, Staplin N, Judge PK, Zhu D, Sammons E, *et al.* Frailty, multimorbidity and polypharmacy: exploratory analyses of the effects of empagliflozin from the empa-kidney trial. *Clin J Am Soc Nephrol*. 2024;19:1119–29. doi: 10.2215/cjn.0000000000000498. PMID 38949880.
[17] Pollack R, Cahn A. SGLT2 inhibitors and safety in older patients. *Heart Fail Clin*. 2022;18:635–43. doi: 10.1016/j.hfc.2022.03.002. PMID 36216492.
[18] Shimokawa H, Miura M, Nochioka K, Sakata Y. Heart failure as a general pandemic in Asia. *Eur J Heart Fail*. 2015;17:884–92. doi: 10.1002/ejhf.319. PMID 26222508.
[19] Silverberg DS, Wexler D, Iaina A, Steinbruch S, Wollman Y, Schwartz D. Anemia, chronic renal disease and congestive heart failure–the cardio renal anemia syndrome: the need for cooperation between cardiologists and nephrologists. *Int Urol Nephrol*. 2006;38:295–310. doi: 10.1007/s11255-006-0064-8. PMID 16868702.
[20] Ito S, Kato S. Impact of cardiorenal anaemia syndrome on clinical features in eederly outpatients with chronic heart failure: a Japanese community hospital experience. *Eur J Med Health Sci*. 2024;6:7–13. doi: 10.24018/ejmed.2024.6.2.2038.
[21] Shirakabe A, Matsushita M, Kiuchi K, Okazaki H, Inami T, Takayasu T, *et al.* Empagliflozin administration can decrease the dose of loop diuretics and prevent the exacerbation of renal tubular injury in patients with compensated heart failure complicated by diabetes. *Circ Rep*. 2020;2:565–75. doi: 10.1253/circrep.CR-20-0041. PMID 33693182.