ECRONICON OPEN ACCESS

EC CARDIOLOGY
Mini Review

Benefits and Risks of Sodium-Glucose Cotransporter-2 Inhibitors in Older Adults with Heart Failure with Preserved Ejection Fraction

Shigenori Ito*

Division of Cardiology, Sankuro Hospital, Toyota, Japan

***Corresponding Author:** Shigenori Ito, Division of Cardiology, Sankuro Hospital, Toyota, Japan.

Received: February 08, 2023; **Published:** February 28, 2023

Abstract

The incidence of heart failure with preserved ejection fraction (HFpEF), for which there is no established treatment, may increase with age. Recently, the sodium-glucose cotransporter-2 inhibitor (SGLT2i) has emerged as a promising drug not only for heart failure with reduced ejection fraction but also for HFpEF at any age independent of diabetes mellitus. Empagliflozin (empa) and dapagliflozin (dapa) have shown long-term cardiovascular benefits in large randomized controlled trials by comparing with controls. Empa and dapa have high SGLT2 selectivity of 5,000 and 1242 fold, respectively. The metabolic rate of empa is lower than that of the other SGLT2i, resulting in unchanged body mass in urine, which inhibits the SGLT2 receptor in the proximal convoluted tubule. Based on these mechanisms, empa and dapa may provide an additional effect to existing standard heart failure drugs through pleiotropic effects other than diuretic action. As it is often challenging to treat HFpEF in elderly patients due to worsening renal function by using loop diuretics, timely application of SGLT2i would reduce the dose of diuretics and provide benefit if side effects such as dehydration (especially when using diuretics), ketoacidosis, urinary tract/genital infections could be avoided.

Keywords: *Heart Failure with Preserved Ejection Fraction (HFpEF); Sodium-Glucose Cotransporter-2 Inhibitors; Older Adults; Elderly; Benefit; Risk; Diuretics*

Introduction

In recent years, the prevalence of heart failure (HF) has continued to increase with the aging of the population. The proportion of heart failure with preserved ejection fraction (HFpEF) is increasing. The incidence of HF during follow-up was more than doubled in the Cardiovascular Heart Study (mean age 73 years) compared with the Framingham Heart Study (mean age 58 years); the majority were heart failure with reduced ejection fraction (HFrEF) in the Framingham Heart Study, but 53% were HFpEF in the Cardiovascular Health Study [1]. Thus, the proportion of HFpEF may increase with age. The treatment option for HFpEF would become very important.

Characteristics of heart failure in older adults

In HF occurring in older adults, whether HFpEF or HFrEF, the multiple organ damage has the impact on subjective symptoms and prognosis that is greater than that of HF in younger patients. Therefore, it is necessary and important to recognize that it is not only the problem of aging itself that needs to be addressed during treatment. In particular, in the elderly with HF, there are many cases of atrial fibrillation (AF) and chronic kidney disease (CKD) that are related to treatment strategies. Results from the Jasper study, a registry of patients with HFpEF in Japan, showed that 77% had hypertension and 62% had AF in patients with an average age of 80 years. In this registry, the factors that exacerbated HF leading to hospitalization varied greatly depending on the presence or absence of AF [2]. In cases with sinus rhythm, increased afterload due to elevated blood pressure was a major factor, making hypertension management more im-

portant. On the other hand, in the group with AF, which accounted for more than half of the total cases, there was a tendency for repeated entry and exit due to inadequate water and salt restriction, arrhythmia, infection. rather than an increase in blood pressure. In this case, fluid control is important, suggesting the appropriate use of diuretics and mineralocorticoid antagonists [3]. In addition to treatments with proven effects on hard endpoints such as reduction in all-cause mortality and cardiovascular death, treatment to improve quality of life may also be necessary in the elderly. In HFpEF, various pathologies are complexly combined to produce diverse clinical forms [4]. Therefore, appropriate treatment is desired according to the condition and desires of each HF patient.

What are potential drugs for treatment of HFpEF?

To improve the symptoms of HF patients, diuretics are used in the first stage and are also used in HFpEF as class I drugs according to the guidelines [5,6]. Although loop diuretics can be used in the elderly, the decision to use them is difficult due to comorbidities such as CKD. Standard treatments for HFrEF have not been effective in patients with HFpEF. Angiotensin receptor neprilysin inhibitor [7-9], phosphodiesterase type 5 inhibitor [10,11] and intravascular ablation of the visceral nerve [12] had emerged as potential strategies for HFpEF. Recently, sodium-glucose cotransporter-2 inhibitor (SGLT2i) has also been considered promising for HFpEF by two randomized controlled trial (RCT)s [13,14]. SGLT2i gives an additional effect to existing standard drugs for HF [14-16], possibly by providing pleiotropic effects on the heart other than diuretic action [17].

Chemical structure, main working mechanism and pleiotropic effects of SGLT2i

There are some variabilities in the effects of SGLT2i due to differences in chemical structure [18]. All SGLT2i currently marketed in Japan are based on C-glycosidic binding derivatives [19] and their pharmacokinetics are stabilized by a structure that prevents hydrolysis in the intestinal tract. Among all SGLT2is, only empagliflozin (empa) and dapagliflozin (dapa) have insurance coverage for HF at this stage in Japan. The C-glycosidic binding derivative is absorbed into the body and then excreted in the urine where the D-glucose of SGLT2i binds to the SGLT2 receptor in the proximal convoluted tubule [18]. The selectivity of SGLT1/SGLT2 depends on the flotylene structure, which is an aglycone, and both empa and dapa have high SGLT2 selectivity of 5 000, 1242 times because they don't have thiophene [18]. The metabolic rate of the other SGLT2is is about 70%, but that of empa is only about 25%. This low metabolic rate increases unchanged body mass in urine leading to inhibition of the SGLT2 receptor in the proximal convoluted tubules (empa 21.3 - 22.9%, 1 - 2.8 μg/mL vs dapa 1.4%, 35 - 70 ng/mL) [20]. In addition to the indirect multifaceted effects on the heart, it has been suggested that unchanged bodies in the blood may have a direct effect on cardiomyocytes [17]. Further research on these effects must be awaited.

Comparison of two SGLT2i Covered by insurance for HF in Japan

In a meta-analysis of RCTs for HFpEF [13,14,16], long-term cardiovascular death and risk of rehospitalization for HF were not significantly different between the empa and dapa groups, which showed better outcomes than the control groups [15] independent of diabetes mellitus (DM). The baseline clinical characteristics of patients with HFpEF did not differ between the two RCTs. In the data using 10 mg/day for both drugs, there appears to be no superiority or inferiority between the two drug in efficacy. For empa, it seems necessary to confirm the efficacy and safety of 25 mg/day, which is approved by the insurance companies in Japan Regarding safety, the two RCTs [13,14] had different event definitions and could not be directly compared.

Benefits of SGLT2is in older adults

In large RCTs, the subjects were usually heterogeneous and did not specifically recruit older adults [13,14,16]. However, the age-based sub-analysis in one RCT showed that SGLT2i was equally effective in people aged 75 years and older [14]. In a cohort study (total of 47,343 diabetic subjects with a mean age of 73.1 ± 5.58 years), subjects were divided into four groups based on the presence or absence of car-

diovascular disease (CVD) and HF. After 2 years of follow-up, SGLT2i had the greatest reduction in hospitalization for HF in the group with HF and no CVD [hazard ratio, 0.48; 95% CI, 0.25 - 0.85]. This means that efficacy has been demonstrated in the elderly [21]. In addition to the reduction in major adverse cardiovascular events (MACE), the following effects of SGLT2i may be beneficial in older adults, as renal function declines with age.

Loop diuretic dose reduction

It has been shown that the dose of diuretics can be reduced when used in combination with SGLT2i [22,23]. Since loop diuretics tend to worsen renal function, especially in the elderly, this effect may be beneficial for the elderly.

Renal function

Several large studies have shown an effect of SGLT2i on improving renal function [24,25].

Hyperkalemia

In patients with DM associated with CKD, canagliflozin was shown to be less likely to cause hyperkalemia than placebo [26].

Other

It is speculated that the mechanism of action of reducing stromal volume compared to intravascular volume may reduce hospitalization for HF [27]. It is also beneficial in HF treatment to avoid neurohumoral responses caused by diuretics [24].

Disadvantages of SGLT2i in older adults

Older adults are at greater risk of drug-related adverse events than younger people because of increased multiple complications, polypharmacy, reduced functional status, accelerated muscle loss and geriatric syndromes, especially frailty [28]. Against this background, the use of SGLT2i in older diabetic adults with reduced muscle mass is disadvantageous. At this stage, its use in elderly HF patients is also controversial. The potential unanticipated risks of SGLT2i have been shown to include diabetic ketoacidosis (DKA), lower limb amputation (LLA), serious urinary tract infections, and genital infections [29-33]. A large population-based cohort study using Medicare data was conducted to compare the efficacy and safety of SGLT2i and glucagon like polypeptide 1 receptor agonist in elderly patients with type 2 DM. In this study, a total of 90,094 patients aged 66 years and older with type 2 DM (mean age 72 years) were followed for ~6 months [28]. The effect of SGLT2i was similar with MACE and hospitalization for HF being reduced by 3.2 per 1000 person-years with SGLT2i28). As a result of the safety evaluation, SGLT2i showed 0.7 more DKA events [risk difference (RD) 0.72 95% CI (0.02, 1.41)], 0.9 more LLA [RD 0.90 (95% CI 0.10, 1.70)], 57. 1 more genital infections [RD 57.08 (95% CI (53.45, 60.70)], and 7.1 fewer acute kidney injury events [RD -7.05 (95% CI -10.27, -3.83)] per 1, 000 person-years28). Dehydration (especially when using diuretics) and ketoacidosis are likely to occur, especially on the sick day of DM. Therefore, careful observation and timely discontinuation of SGLT2i would be mandatory when used in older adults with DM/HF. A therapeutic decision should be based on the patient's state of frailty: if SGLT2i treatment at a standard dose (10 mg/day) is recommended for robust patients; starting treatment at 5 mg/day for frail patients and then increasing the dose to 10 mg/day after 1 month; finally, for dependent patients, therapeutic abstinence in the absence of sufficient scientific evidence [34].

Conclusion

SGLT2i is a promising candidate for the treatment of HFpEF in older adults independent of DM, its application should be carefully decided considering both advantages and disadvantages of this drug based on age and clinical characteristics especially frailty in each patient.

Conflict of Interest

The author declares that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

Bibliography

1. Ho JE., *et al*. "Predicting heart failure with preserved and reduced ejection fraction: The international collaboration on heart failure subtypes". *Circulation-Heart Failure* (2016): 9.
2. Nagai T., *et al*. "Clinical characteristics, management, and outcomes of Japanese patients hospitalized for heart failure with preserved ejection fraction - a report from the Japanese heart failure syndrome with preserved ejection fraction (Jasper) registry". *Circulation Journal* 82 (2018): 1534-1545.
3. Pitt B., *et al*. "Spironolactone for heart failure with preserved ejection fraction". *The New England Journal of Medicine* 370 (2014): 1383-1392.
4. Lam CSP., *et al*. "Heart failure with preserved ejection fraction: From mechanisms to therapies". *European Heart Journal* 39 (2018): 2780-2792.
5. McDonagh TA., *et al*. "2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure". *European Heart Journal* 42 (2021): 3599-3726.
6. Heidenreich PA., *et al*. "2022 aha/acc/hfsa guideline for the management of heart failure: Executive summary: A report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines". *Journal of the American College of Cardiology* 79 (2022): 1757-1780.
7. Vaduganathan M., *et al*. "Prior heart failure hospitalization, clinical outcomes, and response to sacubitril/valsartan compared with valsartan in HFpEF". *Journal of the American College of Cardiology* 75 (2020): 245-254.
8. Solomon SD., *et al*. "Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction". *The New England Journal of Medicine* 381 (2019): 1609-1620.
9. Solomon SD., *et al*. "Sacubitril/valsartan across the spectrum of ejection fraction in heart failure". *Circulation* 141 (2020): 352-361.
10. Zhuang XD., *et al*. "PDE5 inhibitor sildenafil in the treatment of heart failure: A meta-analysis of randomized controlled trials". *International Journal of Cardiology* 172 (2014): 581-587.
11. Polsinelli VB and Shah SJ. "Advances in the pharmacotherapy of chronic heart failure with preserved ejection fraction: An ideal opportunity for precision medicine". *Expert Opinion on Pharmacotherapy* 18 (2017): 399-409.
12. Fudim M., *et al*. "Endovascular ablation of the right greater splanchnic nerve in heart failure with preserved ejection fraction: Early results of the rebalance-hf trial roll-in cohort". *European Journal of Heart Failure* 24 (2022): 1410-1414.
13. Anker SD., *et al*. "Empagliflozin in heart failure with a preserved ejection fraction". *The New England Journal of Medicine* 385 (2021): 1451-1461.

14. Peikert A., *et al*. "Efficacy and safety of dapagliflozin in heart failure with mildly reduced or preserved ejection fraction according to age: The Deliver trial". *Circulation: Heart Failure* 15 (2022): e010080.

15. Vaduganathan M., *et al*. "SGLT2 inhibitors in patients with heart failure: A comprehensive meta-analysis of five randomised controlled trials". *Lancet* 400 (2022): 757-767.

16. Solomon SD., *et al*. "Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction". *The New England Journal of Medicine* 387 (2022): 1089-1098.

17. Lopaschuk GD and Verma S. "Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors: A state-of-the-art review". *JACC: Basic to Translational Science* 5 (2020): 632-644.

18. Suganuma M. "Class effects and drug effects of sglt2 inhibitors". *Heart View* 25 (2021): 1130-1136. (in Japanese)

19. Tahrani AA., *et al*. "SGLT inhibitors in management of diabetes". *The Lancet Diabetes and Endocrinology* 1 (2013): 140-151.

20. Tahara A., *et al*. "Characterization and comparison of sodium-glucose cotransporter 2 inhibitors in pharmacokinetics, pharmacodynamics, and pharmacologic effects". *Journal of Pharmacological Sciences* 130 (2016): 159-169.

21. Htoo PT., *et al*. "Cardiovascular effectiveness of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists in older patients in routine clinical care with or without history of atherosclerotic cardiovascular diseases or heart failure". *Journal of the American Heart Association* 11 (2022): e022376.

22. Masuda T., *et al*. "Sglt2 inhibitor and loop diuretic induce different vasopressin and fluid homeostatic responses in nondiabetic rats". *American Journal of Physiology-Renal Physiology* 323 (2022): F361-F369.

23. Shirakabe A., *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". *Circulation Reports* 2 (2020): 565-575.

24. Griffin M., *et al*. "Empagliflozin in heart failure: Diuretic and cardiorenal effects". *Circulation* 142 (2020): 1028-1039.

25. Mordi NA., *et al*. "Renal and cardiovascular effects of SGLT2 inhibition in combination with loop diuretics in patients with type 2 diabetes and chronic heart failure: The RECEDE-CHF trial". *Circulation* 142 (2020): 1713-1724.

26. Neuen BL., *et al*. "Effects of canagliflozin on serum potassium in people with diabetes and chronic kidney disease: The CREDENCE trial". *European Heart Journal* 42 (2021): 4891-4901.

27. Hallow KM., *et al*. "Why do SGLT2 inhibitors reduce heart failure hospitalization? A differential volume regulation hypothesis". *Diabetes, Obesity and Metabolism* 20 (2018): 479-487.

28. Patorno E., *et al*. "Comparative effectiveness and safety of sodium-glucose cotransporter 2 inhibitors versus glucagon-like peptide 1 receptor agonists in older adults". *Diabetes Care* 44 (2021): 826-835.

29. Taylor SI., *et al*. "SGLT2 inhibitors may predispose to ketoacidosis". *The Journal of Clinical Endocrinology and Metabolism* 100 (2015): 2849-2852.

30. Blau JE., *et al*. "Ketoacidosis associated with SGLT2 inhibitor treatment: Analysis of fears data". *Diabetes/Metabolism Research and Reviews* (2017): 33.

31. Fadini GP and Avogaro A. "SGLT2 inhibitors and amputations in the US FDA adverse event reporting system". *The Lancet Diabetes and Endocrinology* 5 (2017): 680-681.

32. Dave CV., *et al*. "Sodium-glucose cotransporter-2 inhibitors and the risk for severe urinary tract infections: A population-based cohort study". *Annals of Internal Medicine* 171 (2019): 248-256.

33. Heyward J., *et al*. "Association between sodium-glucose cotransporter 2 (SGLT2) inhibitors and lower extremity amputation: A systematic review and meta-analysis". *PLoS One* 15 (2020): e0234065.

34. Cleary D., *et al*. "[Treatment of congestive heart failure in older persons and SGLT2 inhibitors - having your patient's best interests at heart]". *Revue Médicale Suisse* 18 (2022): 2057-2062.

Volume 10 Issue 3 March 2023