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EDITORIAL

Natriuresis, Diuresis, and Volume Changes in Diabetics With Heart Failure With Preserved Ejection Fraction: Impact of Sodium-Glucose Cotransporter 2 Inhibitors on Natriuretic Peptides

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Heart failure with preserved ejection fraction (HFpEF) has proved to be a challenge in diagnosing and managing because of heterogeneous phenotypes and greater number of comorbidities associated with it, including diabetes mellitus (DM). Treatment strategies targeted at high filling pressures, hypertension, and lifestyle changes have been effective in reducing the incidence of heart failure (HF) episodes but have a negligible impact on hard cardiovascular outcomes, possibly because of the interaction of comorbidities. In particular, DM in patients with HFpEF has been associated with increased risk for hospitalizations, reduced exercise capacity, left ventricular (LV) hypertrophy, and activation of profibrotic and vasoconstrictor pathways.[1] Consequently, there continues to be an unmet need in discovering therapies for HFpEF.

See Article by Ejiri et al.

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have proved to impact patients with HF by reducing hospitalizations and HF-related death, specifically for those with HF with reduced ejection fraction (EF).[2,3] However, limited data exist related to their impact on patients with HFpEF. A substudy from DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58) included detailed information on patients on the basis of LV EF. The results showed a reduction in cardiovascular death or HF hospitalization risk to a greater extent in those with HF with reduced EF compared with those with EF ≥45%.[4] The mechanisms explaining these findings are precursory, but it is postulated that the effects of natriuresis and diuresis alleviating volume removal leads to reduction in sympathetic and renin-angiotensin-aldosterone system activation with improvements in preload and afterload.[5] In DM individuals with HFpEF, LV diastolic dysfunction, LV hypertrophy, increased left atrial volume index, or LV mass index is highly prevalent, and the use of SGLT2i in small observational studies has had an impact on such structural changes and diastolic parameters.[6]

In this issue of the *Journal of the American Heart Association* (*JAHA*), Miyoshi et al[7] performed a prospective multicenter, open-label randomized control trial Management of Diabetic Patients with Chronic Heart Failure and Preserved Left Ventricular Ejection Fraction (MUSCAT-HF) on the effects of luseogliflozin (SGLT2i) versus voglibose (an α-glucosidase inhibitor), in patients with type 2 DM and HFpEF. The primary outcome assessed the difference in BNP (B-type natriuretic peptide) levels from baseline to

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12 weeks of treatment for both therapies. Secondary outcomes analyzed differences in ratio of early mitral inflow velocity/mitral annular early diastolic velocity, LV EF, body weight, and hemoglobin A1c. Adverse events included major adverse cardiovascular events. Although the study showed no significant difference noted after 12 weeks of treatment between both cohorts (mean BNP ratio at week 12 to baseline was 0.79 in the luseogliflozin group and 0.87 in the voglibose group), there was a noticeable decrease of BNP in lthe useogliflozin group compared to the vogliobose group (percentage change, –9.0% versus –1.9%; ratio of change with luseogliflozin versus voglibose, 0.93; 95% CI, 0.78–1.10; *P*=0.26). In addition, no significant difference was seen in the secondary outcomes or major adverse cardiovascular events. A few points are worth discussing related to the results of this trial:

1. Luseogliflozin is a selective SGLT2i with excellent glycated hemoglobin–reducing effects and a significant enhancer of urinary glucose excretion with a safe pharmacokinetic profile.[8] However, among the other SGLT2i, luseogliflozin has one of the shortest half-lives in plasma, with lower drug concentration in the kidney, lower plasma concentration in those with renal impairment, and shorter duration of effect in urinary glucose excretion when compared with other SGLT2i, categorizing luseogliflozin as an intermediate SGLT2i.[9] It is important to recognize the pharmacodynamic implications of these agents as their "pleiotropic" effects on cardiovascular outcomes may significantly differ in regard to potential cardiac remodeling benefits.
2. The study required a minimum of 190 patients to observe the ratio of BNP change rate (≥30%) between both groups at the end of the study; however, because of slow enrollment, the study was underpowered to observe such differences by screening only 173 subjects, of whom only 165 completed the study. This likely had an impact on the results showing widespread CIs in the analysis.
3. The entry criteria of the study consisted of patients with LV EF of ≥45% with current or previous HF symptoms and BNP concentration ≥35 pg/mL but excluding those with history of significant cardiovascular disease, including previous stroke and myocardial infarction. Most patients were >65 years of age, with younger patients in the luseogliflozin group, well-controlled DM (average hemoglobin A1c, 7%), New York Heart Association functional class II, with a lower median BNP concentration (63.7 pg/mL [Interquartile range: 46.8–115.8 pg/mL] in luseogliflozin group versus 75.1 pg/mL [Interquartile range: 42.4–120 pg/mL] in voglibose group), and only 59% having atherosclerotic cardiovascular disease. Perhaps the selection of patients with lower cardiovascular risk profile in the current study may have failed to demonstrate the desired outcome, denoting early intervention as a noble strategy but longer follow-up required to achieve demonstratable effects. In addition, the entry levels of BNP and the median concentration noted on baseline demographics showed that these patients did not have significant values of congestion. In a recent study of 666 older adults with prior symptomatic cardiovascular events, evaluating the effects of canagliflozin on cardiovascular markers, treatment with canagliflozin showed a delayed increase of serum NT-proBNP (N-terminal pro-B-type natriuretic peptide) starting at 26 weeks and continuing over the 2-year follow-up period, providing strong support on the cardiovascular benefits of these agents at longer treatment periods.[10] Similarly to results from the current study, the DEFINE-HF (Dapagliflozin Effect on Symptoms and Biomarkers in Patients With Heart Failure) trial, using dapagliflozin in patients with established HF with reduced EF with and without type 2 DM, showed that adjusted mean NT-proBNP values were not significantly reduced over 12 weeks. However, the authors did notice a clinically meaningful reduction (≥20%) in both BNP and NT-proBNP over the treatment period in those treated with dapagliflozin, with a pronounced improvement in HF symptoms, function, and quality of life.[11] Moreover, exploratory analysis from the DAPA-HF (Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction) trial confirms that longer-duration therapy with SGLT2i is needed to have a significant impact on natriuretic peptides, where reduction in NT-pro BNP was achieved until 8 months after being on dapagliflozin, independent of the DM status.[12]

Despite a lack of statistically significant difference found in the study by Miyoshi et al,[7] there was a percentage change of BNP over the 12-week period compared with voglibose, and perhaps a significant difference could have been noted if the cohort analyzed had more symptomatic HF, advanced atherosclerotic cardiovascular disease, or higher baseline BNP levels. As noted from prior SGLT2i trials in patients with HF with reduced EF, the absent changes in NT-proBNP do not play a role in the reduction of cardiovascular outcomes, including worsening HF or cardiovascular death. Perhaps more than the reduction in biomarker profile, SGLT2i exert their benefits from decreasing blood pressure attributable to improved vascular compliance from reduction in arterial wall stiffness and improved endothelial function; increased osmotic diuresis with preservation of renal function; and improvement in cardiac remodeling by reduction in LV mass attributable to reduction in

oxidative stress, fibrosis, and epicardial fat, all leading to increased ventricular metabolic efficiency. Notably in the current study, although changes in parameters of systolic and diastolic function were similar among both groups, there was greater reduction in left atrial volume index and LV mass index after luseogliflozin use. Such findings have been demonstrated in other studies, where significant reduction in LV mass index occurs after 6 months and possibly accounts for the impact on cardiovascular outcomes.[13]

The authors should be commended for taking the first steps toward finding alternative ways to manage patients with HFpEF, a task that has proved to be daunting, with many trials failing to show an impact on cardiovascular outcomes. Larger clinical trials with clearly defined phenotypes of HFpEF using the advantageous properties of SGLT2i will need to continue to make an indelible mark in the course of the disease of these patients. We are hopeful that the current clinical trials underway (PRESERVED-HF (Dapagliflozin in PRESERVED Ejection Fraction Heart Failure), DETERMINE-Preserved (Dapagliflozin Effect on Exercise Capacity Using a 6-minute Walk Test in Patients With Heart Failure With Preserved Ejection Fraction), DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure), EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction), and ERADICATE-HF (Ertugliflozin trial in Diabetes with Preserved or Reduced Ejection Fraction Mechanistic Evaluation in Heart Failure)) will provide a deeper clinical insight on the salutary effects of these medications.[14]

ARTICLE INFORMATION

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Disclosures

None.

REFERENCES

1. Lindman BR, Dávila-Román VG, Mann DL, McNulty S, Semigran MJ, Lewis GD, de las Fuentes L, Joseph SM, Vader J, Hernandez AF, et al. Cardiovascular phenotype in HFpEF patients with or without diabetes: a RELAX trial ancillary study. *J Am Coll Cardiol*. 2014;64:541–549.
2. Zinman B, Lachin JM, Inzucchi SE. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2016;374:1094.
3. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380:347–357.
4. Kato ET, Silverman MG, Mosenzon O, Zelniker TA, Cahn A, Furtado RHM, Kuder J, Murphy SA, Bhatt DL, Leiter LA, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. *Circulation*. 2019;139:2528–2536.
5. Verma S. Are the cardiorenal benefits of SGLT2 inhibitors due to inhibition of the sympathetic nervous system? *JACC Basic Transl Sci*. 2020;5:180–182.
6. Soga F, Tanaka H, Tatsumi K, Mochizuki Y, Sano H, Toki H, Matsumoto K, Shite J, Takaoka H, Doi T, et al. Impact of dapagliflozin on left ventricular diastolic function of patients with type 2 diabetic mellitus with chronic heart failure. *Cardiovasc Diabetol*. 2018;17:132.
7. Ejiri K, Miyoshi T, Kihara H, Hata Y, Nagano T, Takaishi A, Toda H, Nanba S, Nakamura Y, Akagi S, et al. Effect of luseogliflozin on heart failure with preserved ejection fraction in patients with diabetes mellitus. *J Am Heart Assoc*. 2020;9:e015103. DOI: 10.1161/JAHA.119.015103.
8. Samukawa Y, Haneda M, Seino Y, Sasaki T, Fukatsu A, Kubo Y, Sato Y, Sakai S. Pharmacokinetics and pharmacodynamics of luseogliflozin, a selective SGLT2 inhibitor, in Japanese patients with type 2 diabetes with mild to severe renal impairment. *Clin Pharmacol Drug Dev*. 2018;7:820–828.
9. 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;130:159–169.
10. Januzzi JL Jr, Butler J, Jarolim P, Sattar N, Vijapurkar U, Desai M, Davies MJ. Effects of canagliflozin on cardiovascular biomarkers in older adults with type 2 diabetes. *J Am Coll Cardiol*. 2017;70:704–712.
11. Nassif ME, Windsor SL, Tang F, Khariton Y, Husain M, Inzucchi SE, McGuire DK, Pitt B, Scirica BM, Austin B, et al. Dapagliflozin effects on biomarkers, symptoms, and functional status in patients with heart failure with reduced ejection fraction: the DEFINE-HF trial. *Circulation*. 2019;140:1463–1476.
12. Petrie MC, Verma S, Docherty KF, Inzucchi SE, Anand I, Belohlavek J, Böhm M, Chiang CE, Chopra VK, de Boer RA, et al. Effect of dapagliflozin on worsening heart failure and cardiovascular death in patients with heart failure with and without diabetes. *JAMA*. 2020;323:1353–1368.
13. Verma S, Mazer CD, Yan AT, Mason T, Garg V, Teoh H, Zuo F, Quan A, Farkouh ME, Fitchett DH, et al. Effect of empagliflozin on left ventricular mass in patients with type 2 diabetes mellitus and coronary artery disease: the EMPA-HEART CardioLink-6 randomized clinical trial. *Circulation*. 2019;140:1693–1702.
14. Lam CSP, Chandramouli C, Ahooja V, Verma S. SGLT-2 inhibitors in heart failure: current management, unmet needs, and therapeutic prospects. *J Am Heart Assoc*. 2019;8:e013389. DOI: 10.1161/JAHA.119.013389.