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Editorial

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Benefits of SGLT2 Inhibitor: Preventing Heart Failure and Beyond

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Main cause of death and the costliest complications in diabetic patients are highly associated with cardiovascular disease. Specifically, type 2 diabetes mellitus (T2DM) is a risk factor for developing heart failure (HF).

Sodium glucose cotransporter 2 (SGLT2) inhibitors have emerged as oral anti-diabetic drugs that reduce cardiovascular death or major adverse events in patients with diabetes. In the non-diabetic context, dapagliflozin and phlorizin did not reduce the infarct size; however, they attenuated oxidative stress and cardiac fibrosis after myocardial infarction (MI).[1] Moreover, Canagliflozin Cardiovascular Assessment Study (CANVAS) also reported that canagliflozin reduced HF hospitalizations compared to placebo and the reductions in HF hospitalizations were more pronounced in patients with a history of HF.[2]

Pre-specified secondary analysis of Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOM) showed that empagliflozin reduced new-onset HF and hospitalization with HF.[3] In a rat metabolic syndrome model with pre-diabetes, empagliflozin reduced cardiac hypertrophy and fibrosis.[4] In the EMPA-HEART CardioLink-6 study, treatment with empagliflozin resulted in a great reduction in cardiac mass and increased left ventricular ejection fraction.[5] Moreover, empagliflozin was also shown to improve diastolic function and ameliorate cardiac hypertrophy and fibrosis in a mouse model with obesity.[6] Recently, empagliflozin was reported to improve cardiac function in non-diabetic rats with left ventricular dysfunction after MI. Empagliflozin attenuated myocardial oxidative stress by reductions in advanced oxidation protein product and nicotinamide adenine dinucleotide phosphate oxidase 2, therefore, cardiac fibrosis and oxidative damage to mitochondrial DNA were reduced.[7] These overall studies implicated that empagliflozin effectively attenuated left ventricular remodeling in patients with T2DM with HF.

How can inhibition of SGLT2 lead to such a striking cardioprotective effects in HF? The mechanisms of SGLT2 inhibitors contain inhibiting renal glucose reabsorption, improving insulin sensitivity and beta cell function. One of the possible explanations is that empagliflozin increases the plasma concentration of ketone bodies, which may improve efficiency of myocardial energy metabolism, and increases cardiac uptake of ketone bodies in HF patients compared with controls.[8] Ketone bodies such as acetoacetate

and β-hydroxybutyrate (βOHB) are alternative energy substrate in ischemic myocardium. Intriguingly, βOHB upregulates oxidative stress resistance factors, including forkhead box O3a (FOXO3a). In a pressure-overloaded HF mouse model, βOHB was elevated in response to oxidative stress in cardiomyocytes. Furthermore, βOHB upregulated superoxide dismutase 2 (SOD2) and catalase, both of which are targets of FOXO3a, and could contribute to cardioprotective effects.[9]

In this issue of the *Korean Circulation Journal*, Oh et al.[10] observed the cardioprotective effect of empagliflozin in both acute and chronic doxorubicin-induced HF models. More importantly, βOHB, increased in the blood by empagliflozin treatment, was identified as a critical mediator to reduce cardiomyocyte apoptosis, suppress the generation of intracellular reactive oxygen species, and improve mitochondrial function.[10] A recent study demonstrated the modulation of circulating ketone levels may represent a novel therapeutic for treatment of HF. In HF patients, application of βOHB exerted beneficial cardiac effects in a dose-dependent manner without safety issues.[11]

The understanding of how SGLT2 inhibitor might work is critical for future acceptance by clinicians to consider patients with high risk of developing HF. Overall, this novel avenue of research may set a new direction to SGLT2 inhibitor for promoting reverse remodeling in the failing heart.

REFERENCES

1. Lee TM, Chang NC, Lin SZ. Dapagliflozin, a selective SGLT2 Inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. *Free Radic Biol Med* 2017;104:298-310.
PUBMED | CROSSREF
2. Mahaffey KW, Neal B, Perkovic V, et al. Canagliflozin for primary and secondary prevention of cardiovascular events: results from the CANVAS program (Canagliflozin Cardiovascular Assessment Study). *Circulation* 2018;137:323-34.
PUBMED | CROSSREF
3. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;373:2117-28.
PUBMED | CROSSREF
4. Kusaka H, Koibuchi N, Hasegawa Y, Ogawa H, Kim-Mitsuyama S. Empagliflozin lessened cardiac injury and reduced visceral adipocyte hypertrophy in prediabetic rats with metabolic syndrome. *Cardiovasc Diabetol* 2016;15:157.
PUBMED | CROSSREF
5. Verma S, Mazer CD, Yan AT, 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;140:1693-702.
PUBMED | CROSSREF
6. Habibi J, Aroor AR, Sowers JR, et al. Sodium glucose transporter 2 (SGLT2) inhibition with empagliflozin improves cardiac diastolic function in a female rodent model of diabetes. *Cardiovasc Diabetol* 2017;16:9.
PUBMED | CROSSREF
7. Yurista SR, Silljé HH, Oberdorf-Maass SU, et al. Sodium-glucose co-transporter 2 inhibition with empagliflozin improves cardiac function in non-diabetic rats with left ventricular dysfunction after myocardial infarction. *Eur J Heart Fail* 2019;21:862-73.
PUBMED | CROSSREF
8. Voros G, Ector J, Garweg C, et al. Increased cardiac uptake of ketone bodies and free fatty acids in human heart failure and hypertrophic left ventricular remodeling. *Circ Heart Fail* 2018;11:e004953.
PUBMED | CROSSREF

https://doi.org/10.4070/kcj.2019.0287

9. Nagao M, Toh R, Irino Y, et al. β-Hydroxybutyrate elevation as a compensatory response against oxidative stress in cardiomyocytes. *Biochem Biophys Res Commun* 2016;475:322-8.
PUBMED | CROSSREF
10. Oh CM, Cho S, Jang JY, et al. Cardioprotective Potential of an SGLT2 Inhibitor Against Doxorubicin-Induced Heart Failure. *Korean Circ J* 2019;49:1183-95.
PUBMED | CROSSREF
11. Nielsen R, Møller N, Gormsen LC, et al. Cardiovascular effects of treatment with the ketone body 3-hydroxybutyrate in chronic heart failure patients. *Circulation* 2019;139:2129-41.
PUBMED | CROSSREF