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COMMENT

Who benefits from the blood pressure-lowering effects of SGLT2 inhibitors in patients with type 2 diabetes mellitus and chronic kidney disease? — Obese or non-obese?

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Recently, the management of type 2 diabetes mellitus (T2DM) has been dramatically changed by new classes of glucose-lowering drugs. Especially, the emergence of sodium-glucose cotransporter-2 inhibitor (SGLT2i) can be cited as the primary factor for this change. SGLT2i blocks glucose reabsorption in the proximal tubules of the kidney and increases glucosuria, as well as blocking sodium resorption and leading to sodium excretion in the urine [1]. A recent series of mega-scale clinical trials for SGLT2i indicated cardioprotective effects of SGLT2i [2–4], and some SGLT2is have now become the first-line treatment for T2DM with comorbid atherosclerotic cardiovascular disease (ASCVD) and heart failure. Furthermore, several studies have reported a lowering effect of SGLT2i on blood pressure (BP) [5]. However, it is unclear which type of patients, especially obese or non-obese, may experience a greater antihypertensive effect with SGLT2i treatment.

The present study by Tsukamoto et al. [6] retrospectively evaluated 447 Japanese patients with T2DM and chronic kidney disease (CKD) treated with SGLT2i for at least 1 year. The primary outcome was achieving the target BP (<130/80 mmHg) after SGLT2i treatment. Consequently, the body mass index (BMI) <29.1 group had significantly lower systolic and diastolic BPs after SGLT2i treatment than the BMI ≥29.1 group. Baseline BMI was associated with the antihypertensive effects of SGLT2i. The present study is clinically significant as it demonstrates that the BP-lowering effect of SGLT2i is more effective in non-obese patients. Furthermore, conversely, this study could also be interpreted as indicating the limitations of the BP-lowering effect of SGLT2i in obese patients. From previous reports [7], it was believed that BP-lowering effect of SGLT2i were more effective in obese patients. However, sub-analyses based on obesity status were not extensively reported in previous cardiovascular outcome trials. The present study is a groundbreaking research that overturns previous reports in a cohort model with propensity score matching.

Although mechanisms underlying the BP-lowering effects of SGLT2i are unclear, SGLT2i presumably acts primarily by decreasing circulating plasma volume through osmotic and natriuretic diuresis in the early stages of administration and later by suppressing sympathetic nerve activity in the long term [8, 9]. In the present study, Tsukamoto et al. proposed insufficient improvement in insulin resistance or inhibition of sympathetic nervous system hyperactivation due to "residual risk of obesity" as a potential mechanism for the insufficient BP reduction in obese patients treated with SGLT2i (Fig. 1). Furthermore, exploring the potential impact of obstructive sleep apnea, which is highly prevalent in obese patients, would be of great interest in the BP-lowering effect of SGLT2i.

In addition, what is particularly interesting in this study is the degree of BP reduction achieved with SGLT2i. SGLT2i has shown modest but significant BP-lowering effects [10]. In individuals with elevated BP, SGLT2i lower systolic BP by 3–9 mmHg [5, 11]. The magnitude of BP lowering is consistent regardless of number of background BP-lowering agents and is also observed in individuals with treatment- resistant hypertension [12, 13]. In the present study, the overall systolic BP reduction was about 9–10 mmHg (about 12 mmHg in the lower BMI group). The authors attribute this greater systolic BP reduction to the inadequate blood pressure control in the study patients. However, conversely, these findings may suggest that in non-obese patients, the BP-lowering effect of SGLT2i is sufficient even as a monotherapy.

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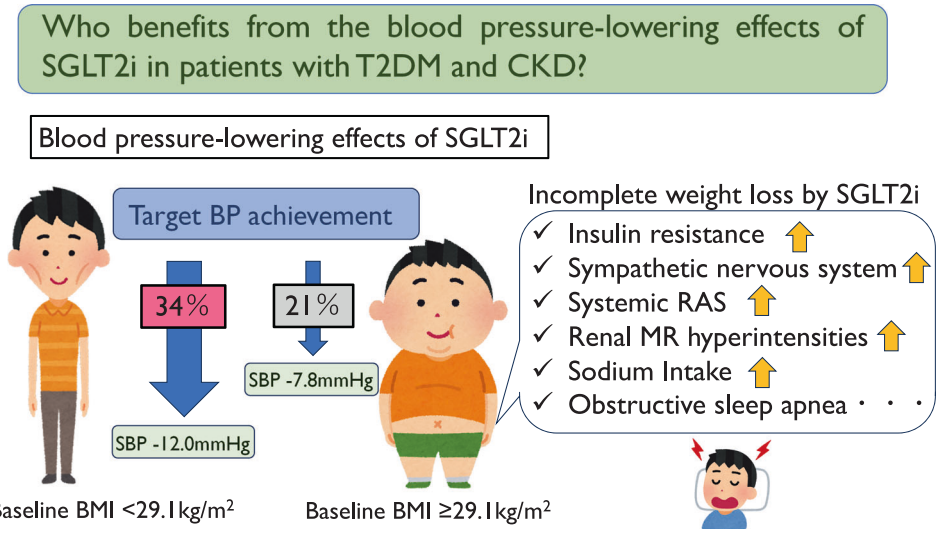

Fig. 1 Blood pressure-lowering effect of SGLT2i stratified by BMI categories. SGLT2i sodium-glucose cotransporter-2 inhibitor, T2DM type 2 diabetes mellitus, BP blood pressure, CKD chronic kidney disease, BMI body mass index, RAS renin-angiotensin system, MR mineralocorticoid receptor, SBP systolic blood pressure

Finally, as mentioned by the authors in the Discussion, if we assume that the mechanism underlying the inadequate BP reduction in obese patients treated with SGLT2i is attributed to "residual obesity" and increased sodium intake, then, there is a possibility that additional administration of glucagon-like peptide-1 receptor agonist (GLP-1RA) or angiotensin receptor-neprilysin inhibitors (ARNI) may be effective. In future research, studies investigating the combination therapy of GLP-1RA or ARNI for obese patients with insufficient BP reduction by SGLT2i are anticipated.

Compliance with ethical standards

Conflict of interest KS received funds from Omron Health Care Ltd, Asahi Calpis Wellness Ltd, Teijin Pharma Ltd, Fukuda Lifetec Ltd.

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References

1. Kim Y, Babu AR. Clinical potential of sodium-glucose cotransporter 2 inhibitors in the management of type 2 diabetes. Diabetes Metab Syndr Obes. 2012;5:313–27.
2. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. EMPA-REG OUTCOME investigators: empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–28.
3. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. CANVAS program collaborative group: canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377:644–57.
4. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380:347–57.
5. Kario K, Okada K, Kato M, Nishizawa M, Yoshida T, Asano T, et al. 24-Hour blood pressurelowering effect of an SGLT-2 inhibitor in patients with diabetes and uncontrolled nocturnal hypertension: results from the randomized, placebo-controlled SACRA study. Circulation. 2018;139:2089–97.
6. Tsukamoto S, Kobayashi K, Toyoda M, Hatori N, Kanaoka T, Wakui H, et al. Pretreatment body mass index affects achievement of target blood pressure with sodium-glucose cotransporter 2 inhibitors in patients with type 2 diabetes mellitus and chronic kidney disease. Hypertens Res. 2023. https://doi.org/10.1038/s41440-023-01464-y.
7. Sakai S, Kaku K, Seino Y, Inagaki N, Haneda M, Sasaki T, et al. Efficacy and safety of the SGLT2 inhibitor luseogliflozin in japanese patients with type 2 diabetes mellitus stratified according to baseline body mass index: pooled analysis of data from 52-week phase III trials. Clin Ther. 2016;38:843–62.
8. van Ruiten CC, Smits MM, Kok MD, Serné EH, van Raalte DH, Kramer M, et al. Mechanisms underlying the blood pressure lowering effects of dapagliflozin, exenatide, and their combination in people with type 2 diabetes: a secondary analysis of a randomized trial. Cardiovasc Diabetol. 2022;21:63.
9. Shiina K, Tomiyama H, Tanaka A, Imai T, Hisauchi I, Taguchi I, et al. Canagliflozin independently reduced plasma volume from conventional diuretics in patients with type 2 diabetes and chronic heart failure: a subanalysis of the CANDLE trial. Hypertens Res. 2023;46:495–506.
10. Tanaka A, Node K. Hypertension in diabetes care: emerging roles of recent hypoglycemic agents. Hypertens Res. 2021;44:897–905.
11. Heerspink HJL, Perkins BA, Fitchett DH, Husain M, Cherney DZI. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. Circulation. 2016;134:752–72.
12. Ye N, Jardine MJ, Oshima M, Hockham C, Heerspink HJ, Agarwal R, et al. Blood pressure effects of canagliflozin and clinical outcomes in type 2 diabetes and chronic kidney disease: insights from the CREDENCE trial. Circulation. 2021;143:1735–49.
13. Ferreira JP, Fitchett D, Ofstad AP, Kraus BJ, Wanner C, Zwiener I, et al. Empagliflozin for patients with presumed resistant hypertension: a post hoc analysis of the EMPA-REG OUTCOME trial. Am J Hypertens. 2020;33:1092–101.