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An Age of Sodium-Glucose Cotransporter-2 Inhibitor Priority: Are We Ready?

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Over the past decade, the use of dipeptidyl peptidase-4 (DPP-4) inhibitors in Korea has steadily increased, replacing sulfonylurea as the most commonly used add-on drug for metformin because of its low risk of hypoglycemia and its relatively better glucose-lowering effect among Asians [1,2]. However, DPP-4 inhibitors have not shown beneficial cardiovascular effects beyond safety in randomized controlled clinical trials among type 2 diabetes mellitus (T2DM) patients [3,4]. In contrast, followed by the striking results of the EMPA-REG OUTCOME study (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) [5], a series of clinical trials demonstrated the protective effects of sodium-glucose cotransporter-2 (SGLT2) inhibitors on cardiovascular and renal complications [6-8]. Thus, most updated treatment guidelines recommend SGLT2 inhibitors to be considered as the preferred choice for T2DM patients with atherosclerotic cardiovascular disease, heart failure, nephropathy, or multiple risk factors [9,10]; SGLT2 inhibitors are accordingly being used in an increasing number of Korean T2DM patients. Today, there is even a practical guide to help doctors who are not experts in T2DM treatment to prescribe SGLT2 inihibitors to protect against cardiovascular and kidney complications in T2DM patients with high cardiovascular risk [11]. Indeed, it is the age of SGLT2 inhibitors in T2DM drugs.

In *Diabetes & Metabolism Journal*, Hong et al. [12] investigated short-term effects of SGLT2 inhibitors in the real-world setting of one general hospital in Korea. Although the analysis was performed only in a 3-month retrospective design, they confirmed good glucose-lowering efficacy of SGLT2 inhibitors as an add-on drug (–0.94% of glycosylated hemoglobin [HbA1c] change) under various anti-diabetic drug combinations including quadruple therapy, consistent with a previous study [13]. In addition, when changed from other anti-diabetic drugs to SGLT2 inhibitors (switch therapy), an overall –0.42% HbA1c lowering effect was observed. This is slightly better than the results of previous meta-analysis in which SGLT2 inhibitors appeared minimally more potent than DPP-4 inhibitors [14]. Real-world evidence as used in this study has weaknesses and uses. Considering the selection bias, it is desirable to target many subjects in various clinical conditions from various institutions. The decision to select or change a certain medication might have been easier in situations in which clinicians expected the treatment to have more positive effects. For example, SGLT2 inhibitors would have been preferable in obese patients with renal or cardiovascular risk. Moreover, the consequences of switching therapy in this study might have included specific clinical situations, resulting in drug switches (e.g., side effects on existing drugs). Nevertheless, the results of switching therapy to SGLT2 inhibitors are interesting because doctors often experience clinical situations in which they want to change prescriptions to SGLT2 inhibitors for various reasons including glucose control. Moreover, switching therapy may be a relatively common use pattern in Korea, where insurance coverage is restricted by number of drug classes used.

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Suggested clinical parameters associated with better glucose-lowering effectiveness of SGLT2 inhibitors are higher baseline HbA1c, shorter diabetes duration, and higher estimated glomerular filtration rate [15,16]. Hong et al. [12] demonstrated that switching to SGLT2 inhibitors showed the same efficacy in weight loss, blood pressure reduction, and decrease in triglyceride level with a half reduction of HbA1c compared to add-on therapy in inadequately controlled T2DM patients. This confirms the glucose-independent mechanism of SGLT2 inhibitors in previous studies [5,15].

Current pharmacologic treatment strategies for T2DM emphasizes a patient-centered approach. To choose the appropriate anti-diabetic drugs, doctors must consider efficacy, safety, patient comorbidities, costs, and patient preferences. In this context, there are still many unanswered questions about the usefulness of SGLT2 inhibitors. The cardio-renal benefit of the SGLT2 inhibitor is significant, but it appeared to vary across the diabetes continuum [17]. Although SGLT2 inhibitors are strongly considered in T2DM patients with prior atherosclerotic cardiovascular disease or heart failure, it is not yet known whether SGLT2 inhibitors are effective or safe for those with recent acute coronary syndrome with decompensation or acute stroke, like those with past history of cardiovascular disease in stable condition. Further, it is not yet known whether SGLT2 inhibitors provide similar benefits if used in individuals not requiring additional glucose lowering on their current therapy. In addition, at what stage and what characteristics of diabetic nephropathy the SGLT2 inhibitors are most effective and safe, what happens in case of acute kidney injury, what the best combination regimen for SGLT2 inhibitors is to achieve the highest efficacy and safety in patients with T2DM, and whether SGLT2 inhibitors are safe for long-term use are not yet established. More research is needed to define a "personalized" target for patients with T2DM.

SGLT2 inhibitors increase the risks of urinary frequency, dehydration, genital infection, and rare diabetic ketoacidosis (DKA). Serum glucose in SGLT2 inhibitor-associated DKA is often lower than in traditional DKA because of increased renal clearance of glucose by the SGLT2 inhibitors, which can delay recognition by both the affected individual and clinician. Although the incidence is very low, one Korean study found that DKA patients using SGLT2 inhibitors needed longer ICU treatment than non-users [18]. Caution should be taken before initiating SGLT2 inhibitor therapy in individuals with a predisposition to hypovolemia or a history of urinary tract infection, those who have decreased insulin secretion capacity or borderline kidney function, or those who are taking concomitant diuretics or nephrotoxic medications. Patients may not mention the side effects unless the doctor informs them in advance or asks them during treatment. In retrospective data, there is a possibility that side effects were not recorded in detail and were thus underestimated in the medical chart. Indications of SGLT2 inhibitors are likely to gradually expand to patients without T2DM if they have heart failure or chronic kidney disease after completion of ongoing studies [19-22]. During the writing, it was announced that dapagliflozin had a protective effect against heart failure with reduced ejection fraction even in nondiabetic patients [23]. Optimal prescription of SGLT2 inhibitors requires full understanding of the benefits and risks. Better understanding is needed to achieve this goal.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Ko SH, Kim DJ, Park JH, Park CY, Jung CH, Kwon HS, Park JY, Song KH, Han K, Lee KU, Ko KS; Task Force Team for Diabetes Fact Sheet of the Korean Diabetes Association. Trends of antidiabetic drug use in adult type 2 diabetes in Korea in 2002-2013: nationwide population-based cohort study. Medicine (Baltimore) 2016;95:e4018.
2. Ko SH, Han K, Lee YH, Noh J, Park CY, Kim DJ, Jung CH, Lee KU, Ko KS, TaskForce Team for the Diabetes Fact Sheet of the Korean Diabetes A. Past and Current Status of Adult Type 2 Diabetes Mellitus Management in Korea: A National Health Insurance Service Database Analysis. Diabetes Metab J 2018; 42:93-100.
3. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Van de Werf F, Peterson ED, Holman RR; TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232-42.
4. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes.

N Engl J Med 2013;369:1327-35.
5. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.
6. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57.
7. Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295-306.
8. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347-57.
9. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2019. Diabetes Care 2019;42(Suppl 1):S90-102.
10. Kim MK, Ko SH, Kim BY, Kang ES, Noh J, Kim SK, Park SO, Hur KY, Chon S, Moon MK, Kim NH, Kim SY, Rhee SY, Lee KW, Kim JH, Rhee EJ, Chun S, Yu SH, Kim DJ, Kwon HS, Park KS; Committee of Clinical Practice Guidelines, Korean Diabetes Association. 2019 Clinical practice guidelines for type 2 diabetes mellitus in Korea. Diabetes Metab J 2019;43:398-406.
11. Vardeny O, Vaduganathan M. Practical guide to prescribing sodium-glucose cotransporter 2 inhibitors for cardiologists. JACC Heart Fail 2019;7:169-72.
12. Hong AR, Koo BK, Kim SW, Yi KH, Moon MK. Efficacy and safety of sodium-glucose cotransporter-2 inhibitors in Korean patients with type 2 diabetes mellitus in real-world clinical practice. Diabetes Metab J 2019;43:590-606.
13. Jeon HJ, Ku EJ, Oh TK. Dapagliflozin improves blood glucose in diabetes on triple oral hypoglycemic agents having inadequate glucose control. Diabetes Res Clin Pract 2018;142:188-94.
14. Wang Z, Sun J, Han R, Fan D, Dong X, Luan Z, Xiang R, Zhao M, Yang J. Efficacy and safety of sodium-glucose cotransporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors as monotherapy or add-on to metformin in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Obes Metab 2018;20:113-20.
15. Petrykiv S, Sjostrom CD, Greasley PJ, Xu J, Persson F, Heerspink HJL. Differential effects of dapagliflozin on cardiovascular risk factors at varying degrees of renal function. Clin J Am Soc Nephrol 2017;12:751-9.
16. Lee JY, Cho Y, Lee M, Kim YJ, Lee YH, Lee BW, Cha BS, Kang ES. Predictors of the therapeutic efficacy and consideration of the best combination therapy of sodium-glucose co-transporter 2 inhibitors. Diabetes Metab J 2019;43:158-73.
17. Verma S, Juni P, Mazer CD. Pump, pipes, and filter: do SGLT2 inhibitors cover it all? Lancet 2019;393:3-5.
18. Jeon JY, Kim SK, Kim KS, Song SO, Yun JS, Kim BY, Kim CH, Park SO, Hong S, Seo DH, Seo JA, Noh JH, Kim DJ; DKA Study Group of Gyeonin Branch of the Korean Diabetes Association. Clinical characteristics of diabetic ketoacidosis in users and non-users of SGLT2 inhibitors. Diabetes Metab 2019;45:453-7.
19. AstraZeneca: A study to evaluate the effect of dapagliflozin on renal outcomes and cardiovascular mortality in patients with chronic kidney disease (Dapa-CKD). Available from: https://clinicaltrials.gov/ct2/show/NCT03036150 (updated 2019 Oct 15).
20. Boehringer Ingelheim. EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced). Available from: https://clinicaltrials.gov/ct2/show/NCT03057977 (updated 2019 Oct 15).
21. Boehringer Ingelheim. EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved). Available from: https://clinicaltrials.gov/ct2/show/NCT03057951 (updated 2019 Oct 15).
22. Herrington WG, Preiss D, Haynes R, von Eynatten M, Staplin N, Hauske SJ, George JT, Green JB, Landray MJ, Baigent C, Wanner C. The potential for improving cardio-renal outcomes by sodium-glucose co-transporter-2 inhibition in people with chronic kidney disease: a rationale for the EMPA-KIDNEY study. Clin Kidney J 2018;11:749-61.
23. McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Belohlavek J, Bohm M, Chiang CE, Chopra VK, de Boer RA, Desai AS, Diez M, Drozdz J, Dukat A, Ge J, Howlett JG, Katova T,

Kitakaze M, Ljungman CEA, Merkely B, Nicolau JC, O'Meara E, Petrie MC, Vinh PN, Schou M, Tereshchenko S, Verma S, Held C, DeMets DL, Docherty KF, Jhund PS, Bengtsson O, Sjostrand M, Langkilde AM; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019 Sep 19 [Epub]. https://doi.org/10.1056/NEJMoa1911303.