Editorial

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Cardiovascular Safety of SGLT2 Inhibitors Compared to DPP4 Inhibitors and Sulfonylureas as the Second-Line of Therapy in T2DM Using Large, Real-World Clinical Data in Korea

Kyuho Kim[1], Sung Hee Choi[1,2]

[1]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam,
[2]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

After approval of the first sodium glucose cotransporter 2 (SGLT2) inhibitors in 2013, SGLT2 inhibitors have been spotlighted due to their cardiovascular and renal benefits according to many randomized controlled trials (RCTs) [1-4]. Most updated guidelines recommended SLGT2 inhibitors as the preferred option for patients with established atherosclerotic cardiovascular disease (ASCVD) or indicators of high ASCVD risk, heart failure (HF), and chronic kidney disease (CKD) [5,6]. Based on positive results from the landmark trials (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure [DAPA-HF] [7] and The Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction [EMPEROR-Reduced] [8]), dapagliflozin and empagliflozin were approved for reducing the risk of CV death and hospitalization in patients with heart failure with reduced ejection fraction (HFrEF), both with and without type 2 diabetes mellitus [9]. Still, metformin is the first-line therapy for type 2 diabetes mellitus according to most guidelines, unless there are contraindications. For patients without established ASCVD, indicators of high ASCVD risk, HF, or CKD, the choice of a second-line therapy to add to metformin is not yet prioritized with solid evidence, but rather by considering many clinical profiles of individual patients [6].

Jeon et al. [10] reported the cardiovascular safety of SGLT2 inhibitors compared to dipeptidyl peptidase-4 (DPP-4) inhibitors and sulfonylureas (SU) in a large real-world Korean cohort using National Health Insurance Service data [10]. They showed that SGLT2 inhibitors as a second-line therapy were associated with decreased risk of hospitalization for heart failure (HHF; –22%) and HHF plus all-cause mortality (–21%) compared with DPP-4 inhibitors; SGLT2 inhibitors are also associated with decreased risk of HHF (–34%), all-cause mortality (–40%), myocardial infarction (MI; –35%), stroke (–26%), and modified major adverse cardiovascular events (MACEs; all-cause mortality, MI, and stroke; –31%) compared with SU after the propensity score matching method. The study population included those lower than 20% of the established cardiovascular disease at baseline; thus, the enrolled subjects with metformin failure in this study for second-line therapy might be at low risk for developing MACE. In other words, they suggested that beneficial effects of SGLT2 inhibitors on cardiovascular composite outcomes might be expected in general populations of patients with type 2 diabetes mellitus.

SGLT2 inhibitors as an add-on to metformin monotherapy showed similar glucose lowering efficacy compared with SU and DPP-4 inhibitors. In a previous head-to-head trial, empagliflozin as an add-on to metformin monotherapy showed non-inferior efficacy at week 52 (relative glycosylated hemo-

Corresponding author: Sung Hee Choi https://orcid.org/0000-0003-0740-8116
Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea
E-mail: shchoimd@gmail.com

globin [HbA1c] reduction; –0.07%), superior efficacy at week 104 (relative HbA1c reduction; –0.11%), and a low risk of hypoglycemia (2%) compared with glimepiride (24%) [11]. Dapagliflozin and canagliflozin showed non-inferior efficacy compared with glipizide and glimepiride, respectively [12,13]. Meanwhile, as an add-on to metformin monotherapy, canagliflozin 100 and 300 mg showed non-inferior efficacy, and canagliflozin 300 mg showed superior efficacy compared with sitagliptin (relative HbA1c reduction; –0.15%) at week 52 [14]. An indirect meta-analysis comparison of dapagliflozin as an add-on to metformin monotherapy demonstrated similar HbA1c control compared with DPP-4 inhibitors after 1 year of treatment [15].

Considering the low risk of hypoglycemia, weight benefits, cardiovascular and renal benefits, and similar glucose-lowering efficacy compared with other oral hypoglycemic agents [16], it is reasonable to give priority to SGLT2 inhibitors as a second-line therapy after metformin monotherapy in patients with type 2 diabetes mellitus in the future, in particular over ASCVD or CKD predominates.

CONFLICTS OF INTEREST

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

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