Korean Circ J. 2024 Sep;54(9):562-564
https://doi.org/10.4070/kcj.2024.0214
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Editorial

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SGLT2 Inhibitor, an Agent for Diabetes, Heart, Kidney... and Stroke

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▸ See the article "Cardiovascular Outcomes of Sodium-Glucose Cotransporter-2 Inhibitors Therapy in Patients With Type 2 Diabetes Mellitus and Chronic Kidney Disease: A Systematic Review and Updated Meta-Analysis" in volume 54 on page 549.

Received: Jul 1, 2024
Accepted: Jul 24, 2024
Published online: Jul 25, 2024

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Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest
The authors have no financial conflicts of interest.

The prevalence of chronic kidney disease (CKD) is steadily increasing in many developed countries, but in South Korea, it is growing at a faster rate compared to others. CKD affects 360.3 cases per million individuals in South Korea, making it the third highest prevalence globally. Diabetes mellitus (DM) is one of the leading causes of CKD, and both DM and CKD are well-established risk factors for cardiovascular disease.[1] Given the heightened cardiovascular morbidity and mortality among CKD patients, it is crucial to mitigate cardiovascular risk in this population.[2]

Sodium-glucose co-transporter-2 (SGLT2) inhibitor is a medication known for effectively lowering glucose levels and reducing cardiovascular mortality - transforming clinical practices for DM, heart failure (HF), and CKD.[3] For diabetes patients, the cardioprotective benefit of SGLT2 inhibitors have led the American Diabetes Association to recommend SGLT2 inhibitors as first-line therapy for type 2 DM (T2DM) patients with established atherosclerotic cardiovascular disease (ASCVD) or at high risk for ASCVD, regardless of their hemoglobin A1C level or use of metformin.[4] In HF patients, SGLT2 inhibitor have demonstrated significant reductions in HF-related hospitalization, cardiovascular mortality, and improvement in HF symptoms, physical function, and quality of life. Consequently, the European Society of Cardiology recommends SGLT2 inhibitors as a first-line medication for HF irrespective of left ventricular ejection fraction.[5] In CKD patients, SGLT2 inhibitors have shown benefits in reducing the risk of kidney disease progression, serious hyperkalemia, lowering blood pressure, and decreasing serum uric acid levels. Initially recommended for CKD patients with T2DM, they are now recommended for all CKD patients regardless of the degree of albuminuria or presence of T2DM according to the Kidney Disease: Improving Global Outcomes guideline.[2]

In the latest issue of *Korean Circulation Journal*, Felix et al.[6] reported the effects of SGLT2 inhibitors on cardiovascular outcomes in patients with T2DM and CKD. Their analysis included data from 9 randomized controlled trials, including EMPA-KIDNEY, DAPA-CKD and SCORED. Primary endpoints examined were all-cause mortality, cardiovascular mortality, stroke, myocardial infarction, and major adverse cardiovascular events (MACE). Patients treated with SGLT2 inhibitor showed significant reductions in all-cause mortality (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.79–0.97; p=0.010), cardiovascular mortality (HR, 0.82; 95% CI, 0.72–0.94; p=0.005), myocardial infarction (HR, 0.78; 95% CI, 0.67–0.91;

Data Sharing Statement
The data generated in this study is available from the corresponding author upon reasonable request.

Author Contributions
Conceptualization: Yang T, Oh J; Supervision: Oh J; Writing - original draft: Yang T, Oh J; Writing - review & editing: Oh J, Lee J.

The contents of the report are the author's own views and do not necessarily reflect the views of the *Korean Circulation Journal*.

p=0.001), MACE (HR, 0.85; 95% CI, 0.77–0.94; p=0.002), and stroke (HR, 0.76; 95% CI, 0.59–0.97; p=0.03) compared to patients who received a placebo. Subgroup analysis further revealed that patients with an estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m^2 who used SGLT2 inhibitors had a significantly lower incidence of stroke (HR, 0.50; 95% CI, 0.31–0.79; p=0.003), whereas those with elevated eGFR (45–59 mL/min/1.73m^2) did not experience the same benefit (HR, 0.92; 95% CI, 0.66–1.28; p=0.61).[6]

While the impact of SGLT2 inhibitors on cardiovascular outcomes is generally robust, their effect on stroke remains controversial. Early studies suggested a possible association between SGLT2 inhibitors, elevated hematocrit levels, and an increased incidence of stroke. These findings raised concerns that SGLT2 inhibitors might elevate blood viscosity, potentially leading stroke. However, despite these concerns, subsequent research has demonstrated that SGLT2 inhibitors reduce cardiovascular mortality, blood pressure, and serum glucose levels, leading to a phenomenon referred as the "stroke paradox."[7]

There is increasing evidence supporting the potential beneficial impact of SGLT2 inhibitors on stroke. A recent meta-analysis found no significant difference in overall prevalence of stroke with SGLT2. Furthermore, subtype analysis revealed a protective effect against hemorrhagic stroke.[8] Observational data also suggest a reduced prevalence of stroke in patients with diabetes and atrial fibrillation who are treated with SGLT2 inhibitors.[9] The increase in hematocrit observed in individuals taking SGLT2 inhibitors is believed to result from the drug's diuretic and hematopoietic effects, which are considered beneficial for patients with CKD.[10] The findings from Felix et al.[6] further support the positive trends observed in recent studies on stroke and SGLT2 inhibitors.

The SGLT2 inhibitor offers numerous advantages that physicians should weigh when considering treatment options for their patients. Specifically, the beneficial effect of SGLT2 inhibitors on stroke highlighted in this study may provide additional evidence to cardiologists, neurologists, endocrinologists, primary care physicians, and other clinicians managing patients with stroke or those at high risk of stroke.

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