Editorial

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SGLT2 Inhibitors and GLP-1 Agonists: A Beacon of Hope for Stroke Prevention in Diabetes

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Diabetes mellitus is a formidable risk factor for macrovascular diseases. In modern medicine, the past decade has seen the emergence of novel pharmacological agents, notably sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) agonists, which has heralded a new era in the management of heart failure, atherosclerotic cardiovascular disease (ASCVD), and chronic kidney disease [1]. Nevertheless, the role of these new drugs in stroke prevention remains unclear.

Among these advancements, thiazolidinediones (TZDs) have shown efficacy in secondary ischemic stroke prevention [2], while a subset of clinical trials has illuminated the promising potential of GLP-1 agonists. A pivotal meta-analysis of randomized controlled trials presented the efficacy and safety of GLP-1 receptor agonists (GLP-1RAs) in mitigating nonfatal stroke, all-cause or cardiovascular mortality, myocardial infarction, and major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus (T2DM) [3]. The REWIND trial further emphasized this narrative, revealing a significant downturn in MACEs with the inclusion of the GLP-1RA dulaglutide in the treatment regimen of individuals with T2DM, thus broadening the protective scope of GLP-1RAs beyond mere stroke risk reduction [4]. Subsequent reviews have corroborated the stroke-protective virtues of GLP-1RAs in the T2DM populace, amplifying their potential as anti-stroke agents even in non-diabetic scenarios [5]. Furthermore, the long-term administration and higher dosages of GLP-1RAs have been linked with a reduced incidence of hospitalization for ischemic stroke among Asian patients with T2DM without established ASCVDs [6].

Conversely, the efficacy of SGLT2 inhibitors in stroke prevention has been met with skepticism. Prevailing evidence suggests a lack of significant impact on stroke incidence among T2DM patients when juxtaposed with control groups across different SGLT2 inhibitors (canagliflozin, dapagliflozin, and empagliflozin), notwithstanding a noticeable racial disparity that suggests the need for further investigation [7]. Nevertheless, a possible protective effect against hemorrhagic stroke emerges from systematic review and meta-analysis, proposing a potential reduction in this stroke subtype's risk via SGLT2 inhibitors [8].

The findings presented by Kim et al. [9] in this issue via a systematic review and network meta-analysis suggest the stroke prevention capacity of SGLT2 inhibitors, marking a significant departure from prior studies. The inclusion of data on sotagliflozin, a dual SGLT1/2 inhibitor, in their analysis might explain this divergence. Recent clinical trials, including the SCORED and SOLOIST-WHF, have introduced mixed results, with sotagliflozin demonstrating a stroke-protective effect in the SCORED trial, which enrolled diabetic patients with chronic kidney disease [10].

It is hypothesized that sotagliflozin's dual-inhibition mechanism might foster superior glycemic control and attenuate total stroke risk compared to other SGLT2 inhibitors, albeit at the expense of heightened risk of diarrhea and volume depletion, as noted in the SCORED trial [11]. Furthermore, the presence of SGLT1 in the brain and its overexpression in areas of brain damage could contribute to ischemia and reperfusion injury, bolstering the argument for sotagliflozin's unique role in stroke

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prevention [12].

The Korean Diabetes Association has yet to provide specific guidelines on primary prevention for ischemic stroke [13], and the results of forthcoming large-scale clinical trials are highly anticipated. As the landscape of diabetes management continues to evolve, novel findings from these studies have the potential to reshape our understanding and approach to stroke prevention in diabetes.

CONFLICTS OF INTEREST

There are no potential conflicts of interest relevant to this article to report.

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